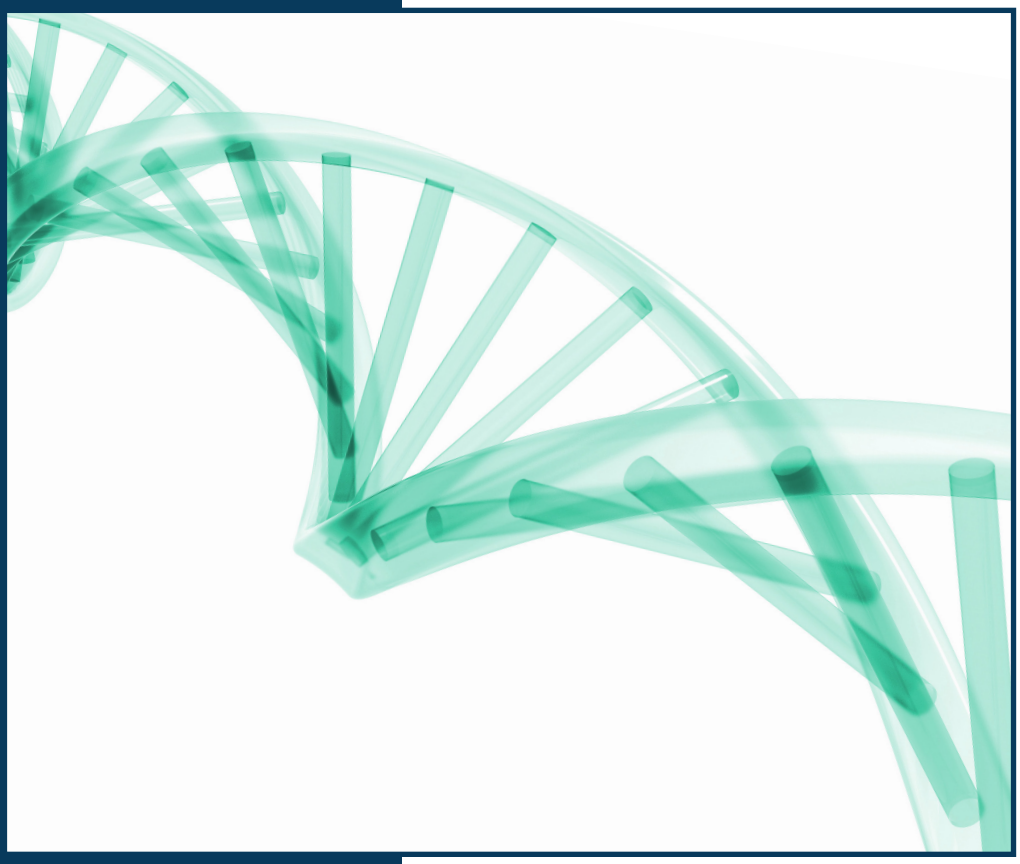
THE SCIENCE & CLINICAL APPLICATION OF NUTRIGENOMIC GENETICS

Empowering Medical Providers with Genetic Solutions.

worldlink MEDICAL

THE ACADEMY OF PREVENTIVE & INNOVATIVE MEDICINE



April 26, 2019 | Salt Lake City, UT

Joint Providers:
The Foundation
For Care Management
& Worldlink Medical

Credits:
8 AMA PRA Category 1 Credits™
8 Nursing Contact Hours (8 Pharmacologic Hours)
8 Contact Hours Pharmacy Credit *(Knowledge based)

COURSE SYLLABUS

The Science and Clinical Application of Nutrigenomic Genetics

April 26 - 27, 2019
Salt Lake City, UT

Nutrigenomic Guided Precision Nutrition for Maximizing Health and Recovery Today will focus on an enhanced scientific and rational means to optimize nutrition and improve recovery potential with respect to an individual's specific genotype. This overview will provide a genetic guided Precision Nutritional algorithm for most disease states that will eliminate the guesswork regarding "necessary" supplementation while reducing potential clinical liability for the practitioner. Participants will accomplish the following objectives

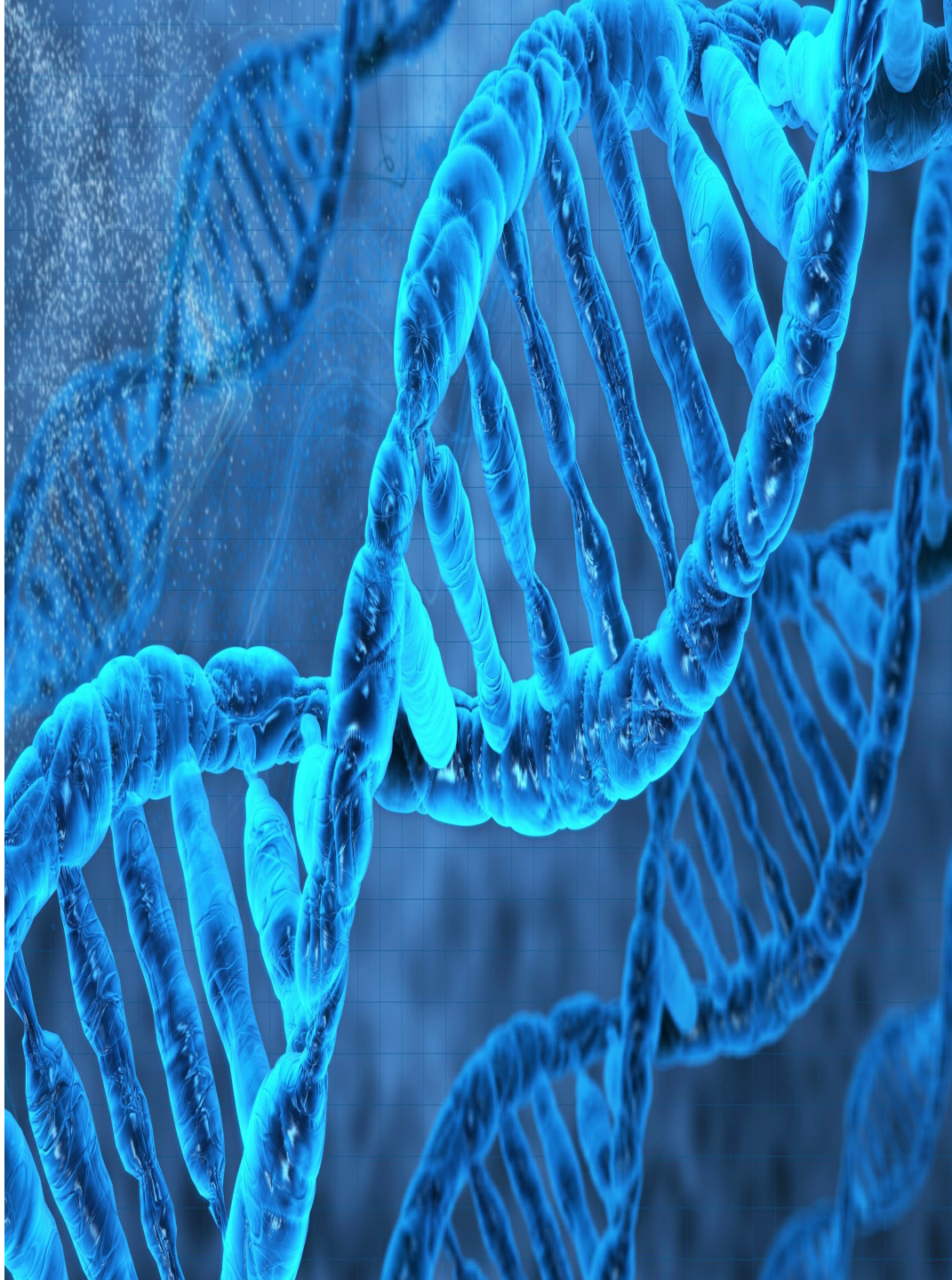
7:00 - 8:00 AM	Registration
8:00 - 10:00 AM	**Genetic Tools: Introduction to Biochemistry and Science Around Nutrigenomic Testing** Presenter: Kendal Stewart, MD
10:00 -10:15 AM	Break
10:15 AM - 11:00 AM	**Case #8: Homozygous C677T MTHFR & other Genetic Errors** Presenter: Dan Purser, MD
11:00 - 12:00 PM	**Foundational Biochemistry** The Complete Methylation Pathway Mitochondrial Respiration Immune Function and In-Depth Cytokine Modulation Presenter: Kendal Stewart, MD
12:00 - 1:00 PM	**Lunch**
1:00 - 2:00 PM	**Foundational Biochemistry (cont.)** The Complete Methylation Pathway Mitochondrial Respiration Immune Function and In-Depth Cytokine Modulation Presenter: Kendal Stewart, MD
2:00 - 3:45 PM	**Foundational Biochemistry** Neurotransmitter Production and Bioavailability 3 Phases of Detoxification: Pathways of Transmethylation, Acetylation, Phosphorylation and Glutathione Conjugation Hormone Productions and Breakdown

	Autophagy and mTOR Regulation Presenter: Dr. Kendal Stewart
3:45 - 4:00 PM	Break
4:00- 5:00 PM	**Genes Related to Nutritional Deficiencies and Health Problems** Presenter: Dr. Kendal Stewart
5:00 - 5:30 PM	Q&A with Dr. Stewart
5:30 - 6:30 PM	Reception

Nutrigenomic Guided Precision Supplementation for Maximizing Health and Recovery

Kendal Stewart, MD

Neurotology / Skull Base Surgery
Neuro-Immune Specialist
Chairman and CMO
Neuro-Sensory Center of Austin
GX Sciences



Disclosure

Dr. Stewart is the Chief Medical Officer for GX Sciences

Food for Thought

"The goal of a physician should be to find health because anyone can find disease"

Andrew Taylor Still, MD, DO
(1828-1917)

What is Unique About Genetic Guided Precision Nutritional Supplementation?

- The body possesses a unique ability to heal itself from most injuries or disease states
- Unfortunately, the physiology of the body involves complex biochemical interactions that are found at the cellular level
- Until recently, health professionals were unable to ascertain cellular level deficiencies due to an inability to "see" the intra-cellular chemistry
- Health Professionals were limited to blood testing and supplementation based on plasma levels which don't necessarily correlate with intracellular concentrations of nutrients
- Genetic Guided Nutritional Supplementation specifically addresses the unique biochemical deficiencies based on an the individuals unique genetic make-up.
- The focus of Precision Nutrition is to provide the ideal intracellular environment to **maximize "healing" and possible "cure"** for the underlying disease process.

Are your patients taking supplements?
Yes!

- **Industry Statistics:**
  - In 2004 - $20 billion Industry
  - In 2018 - $132 billion Industry
  - By 2024 - $284 billion Industry
  - 170 million adults in U.S. take supplements
  - 3 out of 4 patients over 55 take supplements daily
  - Most of their education is online or through commercials
  - >70% of the supplements taken provide no biological effect for the patient
  - 90% of supplements are “food grade” meaning no FDA oversight or purity standards
  - Most supplements produced in Asia.
  - Some supplements can be dangerous for the patient if not monitored.

- **Physicians must become educated on supplements and understand the biochemistry that relates to specific supplements.**

Key Events in the Emergence of Genetics

Human Genome Project (HGP):

•Completed in 2003
•HGP gave us the ability to sequence and map the human genome
•Enabled researchers to understand genetic factors in disease and learn how differences in genes affect the body's response to medications

1000 Genomes Project:

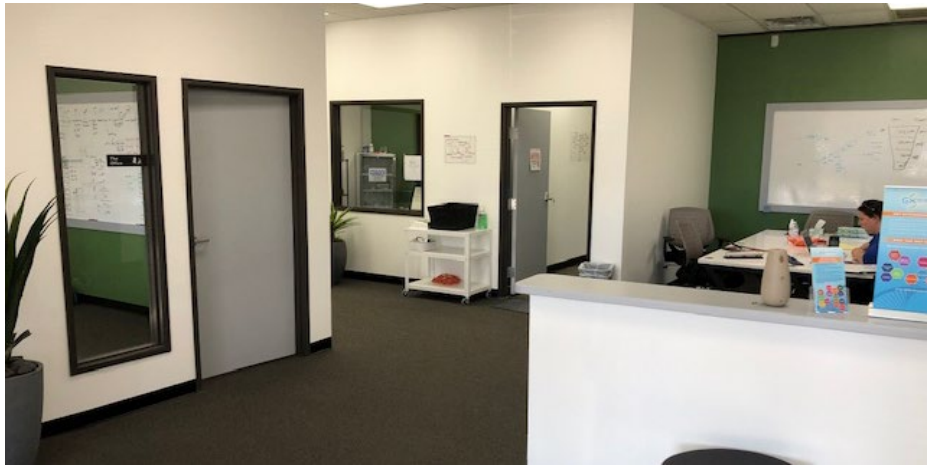
- Launched in 2008
- Establish a detailed catalog of human genetic variation and the normal sequence for each of the genes within the human genome
- In October, 2012, the sequencing of 1,092 genomes was announced

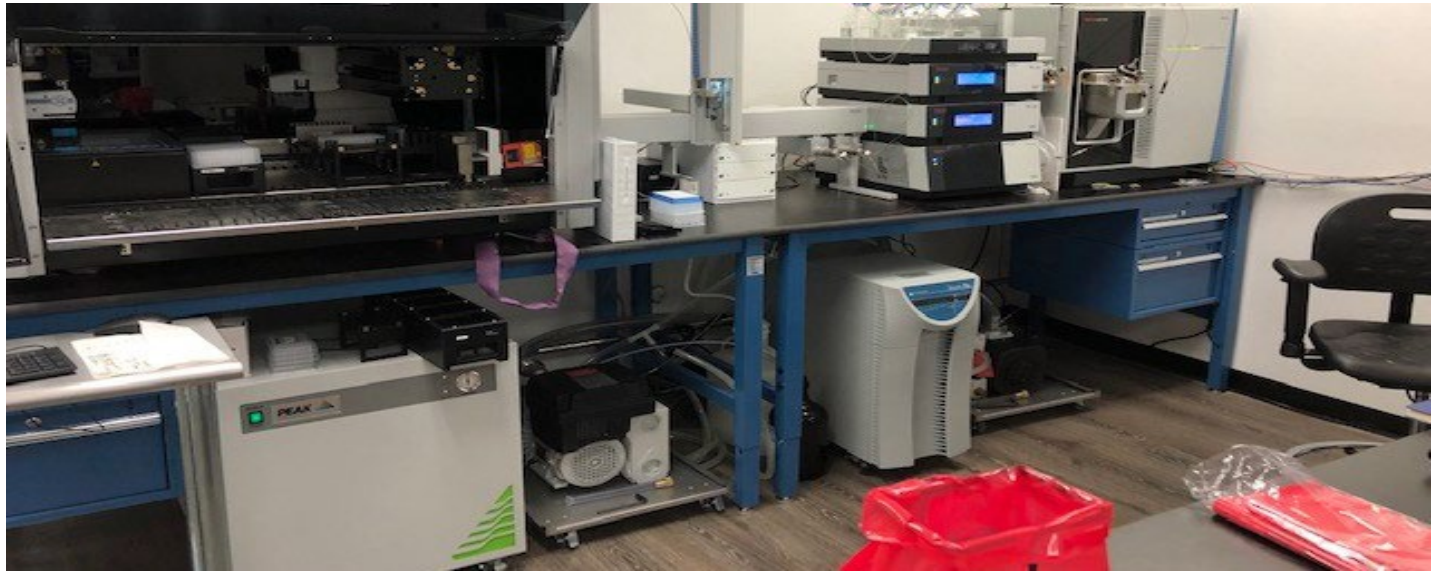
Advances in Genomic Instrumentation

Recent advances in Quantitative PCR and Next Generation Sequencing (NGS) have lowered the cost and improved access of genetic testing. (2014)

3 Major Forms of Genetic Testing?

- **Exome Sequencing**
  - Correlation of genetics with medical disease and risk analysis
  - More focused on disease identification, drug development, cancer risk and infantile screening
- **Pharmacogenomics**
  - Pharmacokinetics
    - Body's impact on drug
  - Pharmacodynamics
    - Drugs impact on body
- **Nutrigenomics**
  - The study of correlating gene expression and genetic differences (SNPs) with a drug or nutrient's absorption, metabolism, elimination or biological effects
  - **Must have therapeutic option for consideration**

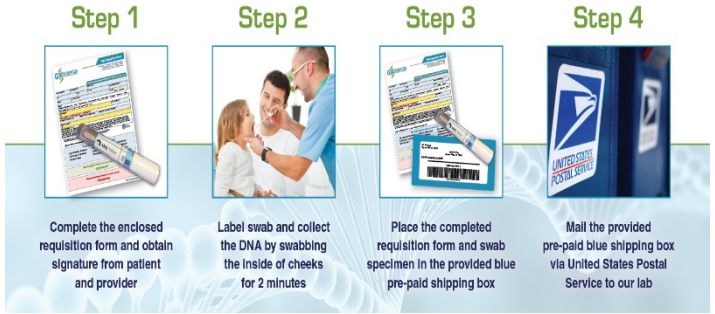




Genetics Lab
Austin, TX

Laboratory Workflow

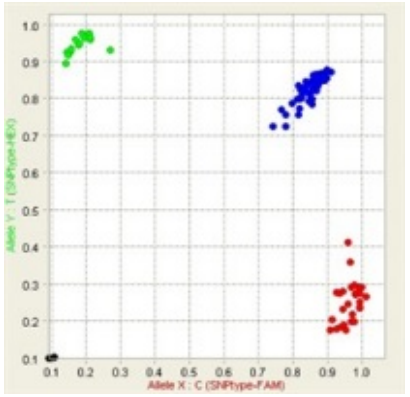
Obtaining Sample



Sample receiving & DNA extraction

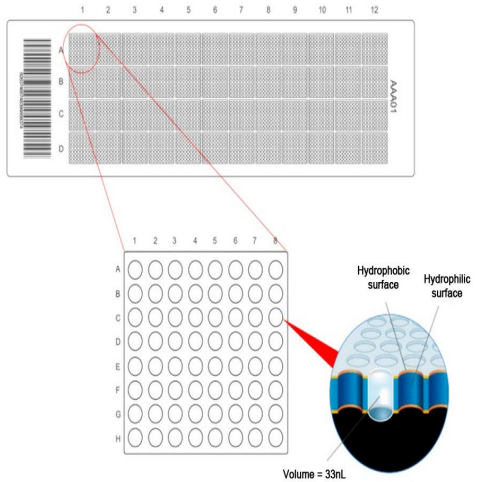
Liquid Handling

Testing Platform

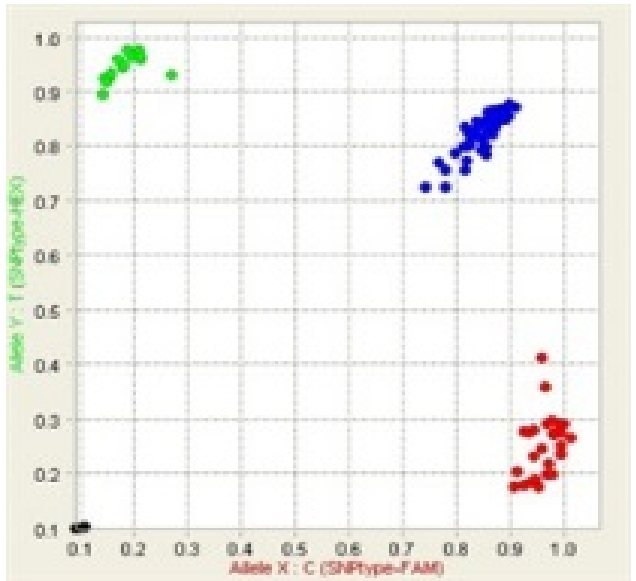


Analyze Data

Individualized Precision Medicine

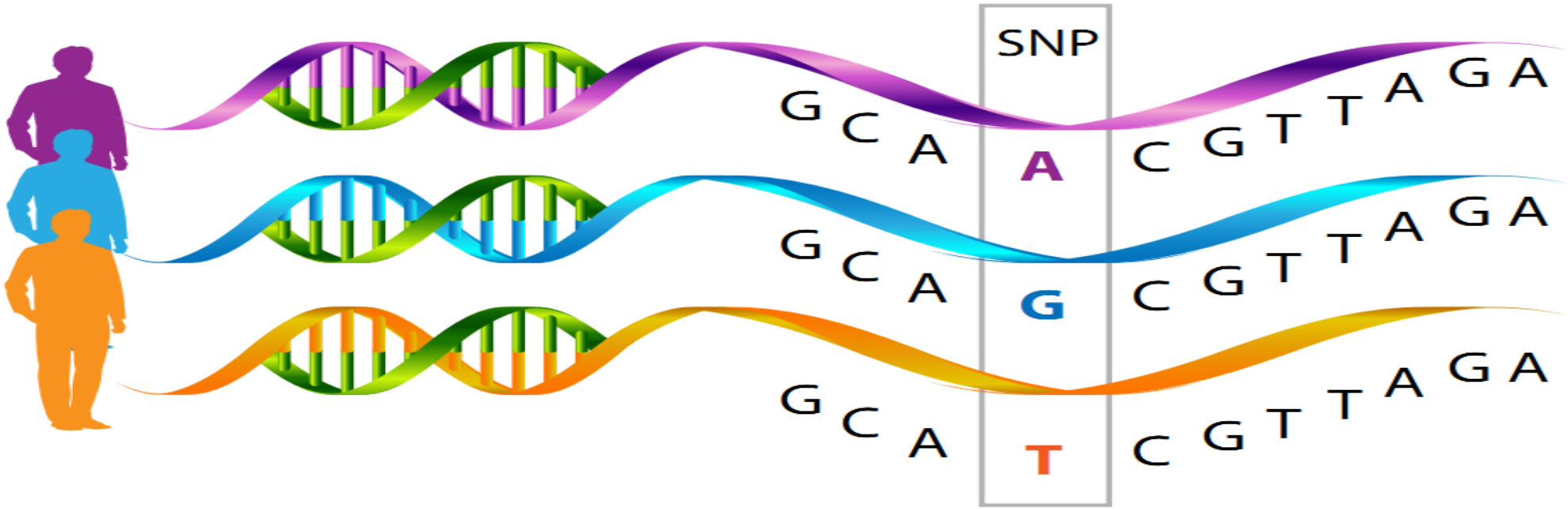


Best in Class
Real Time PCR



What is a Single Nucleotide Polymorphism ?

A **single nucleotide polymorphism**, or **SNP,** is a genetic variation in a single nucleotide that occurs at a specific position in the genome where each variation is present to some appreciable degree within a population (>1%)



Single Nucleotide Polymorphisms (SNPs)

- Most Simple form of polymorphism
- 90% of all DNA polymorphisms
- Occur 1 per every 1000 base pairs
- Not uniformly distributes
- >1,000,000 SNPs identified
- Occur as:
    - Synonymous (silent mutation
    - Non-synonymous (missense or nonsense mutation)

Minor Allele Frequency

Minor allele frequency (MAF) refers to the frequency at which the second most common allele occurs in a given population. SNPs with a minor allele frequency of 0.05 (5%) or greater were targeted by the HapMap project. MAF is widely used in population genetics studies because it provides information to differentiate between common and rare variants in the population.

Example: MAF: 0.15

If a SNP allele frequency is 0.15 in a population of 100 people:

Total number of alleles for each SNP: 100 * 2 = 200 (each individual has two alleles)

Total number of alleles for your SNP with a MAF of 0.15: 200 * 0.15 = 30

The minor allele is present 30 times in your population of 200.

However, you don't know the distribution of heterozygote and homozygote.

Allele Subtypes

- **Wild Type (-/-)**
  - Dominant allele in population
  - Encoded protein is usually functional and made in proper amount

- **Heterozygous (+/-)**
  - One copy of polymorphed gene
  - One copy of wild type gene
  - May confer weakness or up-regulation of function
  - Half of proteins are mutated form

- **Homozygous (+/+)**
  - Two copies of polymorphed gene
  - May confer weakness or up-regulation of function

- **X linked**
  - Traits only seen on X chromosome
  - Males have trait conferred only by mother

Why do we care about SNPs ?

- Many **single nucleotide polymorphisms** lead to appreciable differences in enzyme or protein function.
- Some SNPs can confer **increased or decreased activity of a particular enzyme.**
- **Polymorphisms and their subsequent effect can predict risk of specific conditions and lead to targeted and individualized treatments, lower patient risk and decreased liability.**

Definition of Nutrigenomics

Nutrigenomics is a branch of genetics focused on an genomic sequencing and its' effects on identifying and understanding **molecular-level interactions between nutrients and their subsequent bio-actives** on health and recovery.

Nutrigenomics studies the genetic variation, or Single Nucleotide Polymorphisms (SNPs), of an individual person and the **biochemical effects on a nutrient's absorption, delivery, metabolism, elimination or biological action.**

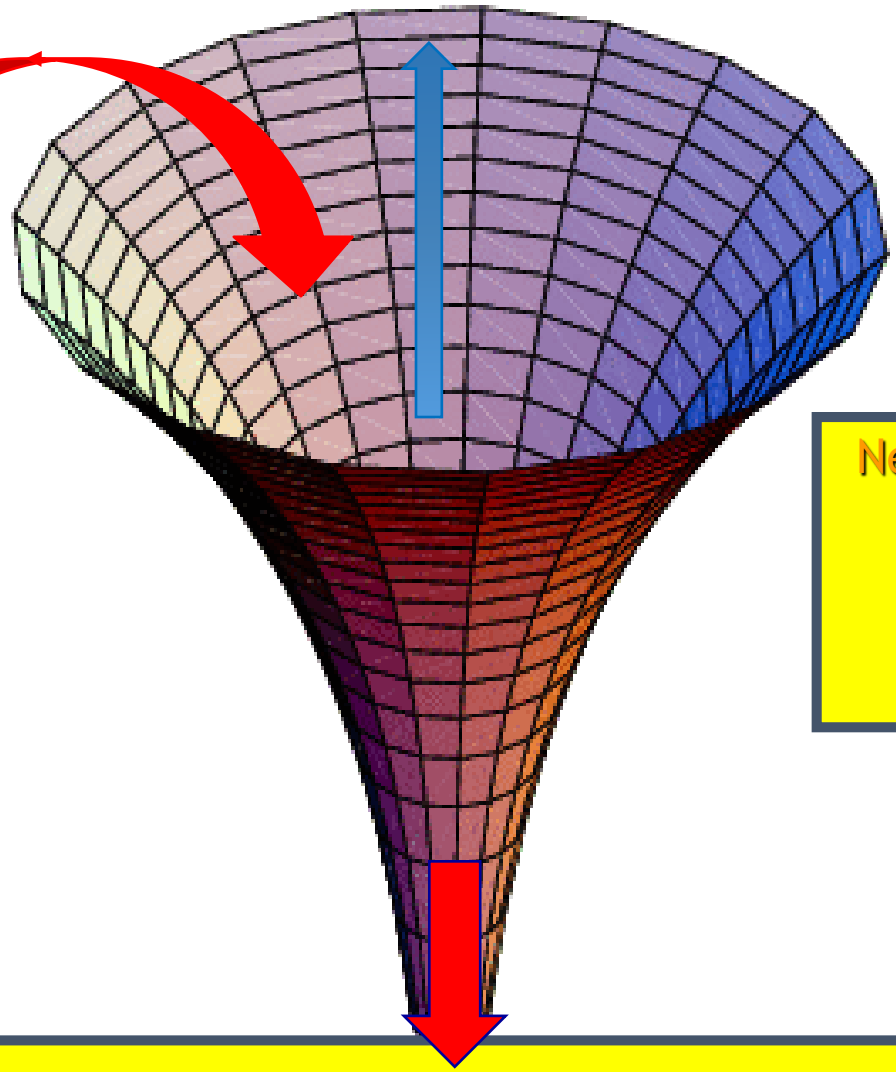
Nutrigenomics' purpose is to provide an **enhanced scientific and rational means to optimize nutrition with respect to an individual's genotype.**

What is Unique About Genetic Guided Precision Nutritional Supplementation?

- The body possesses a unique ability to heal itself from most injuries or disease states
- Unfortunately, the physiology of the body involves complex biochemical interactions that are found at the cellular level
- Until recently, health professionals were unable to ascertain cellular level deficiencies due to an inability to “see” the intra-cellular chemistry
- Health Professionals were limited to blood testing and supplementation based on plasma levels which don’t necessarily correlate with intracellular concentrations of nutrients
- Genetic Guided Nutritional Supplementation specifically addresses the unique biochemical deficiencies based on an the individuals unique genetic make-up and allows the practitioner to focus on providing an ideal intracellular environment focused on recovery potential.

Genetic Predisposition

Immune / Methylation / Mitochondrial / Autophagy / Detoxification



Triggering event(s)

Oxidative Stress:

- Vaccines (live viral)
- Severe Infections
- Environmental Toxins
- Dietary
- Allergies
- Trauma
- Surgery
- Emotional
- Growth

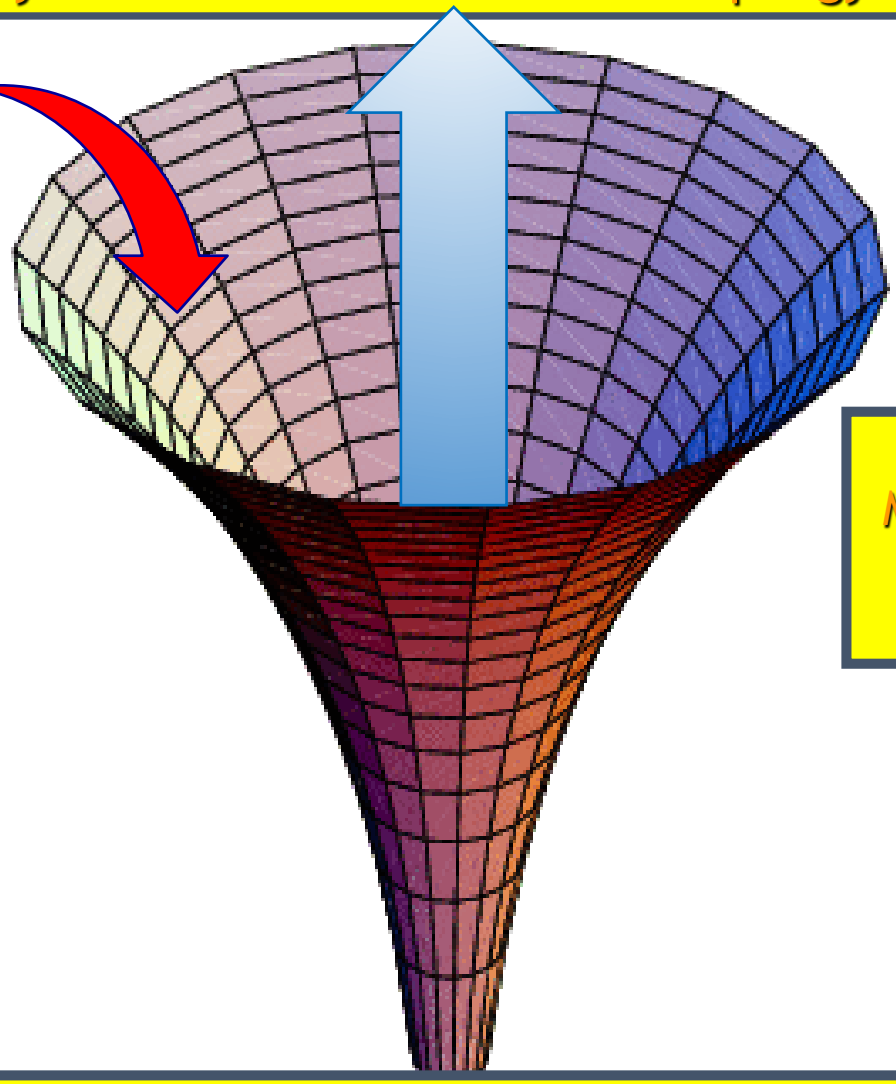
Neurologic and Immunologic Syndromes are simply oxidative stressors with inadequate recovery potential

Propagation of Disorder:

(Inability to resolve the metabolic deficiency / inflammatory state)

Overcome Genetic Weakness

Immune / Methylation / Mitochondrial / Autophagy / Detoxification



Triggering event(s)

Oxidative Stress:

- Vaccines (live viral)
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- Emotional
- Growth

Recovery Involves Minimizing Oxidative Stress and Maximizing Recovery Potential

Propagation of Disorder:

(an inability to resolve the metabolic deficiency / inflammatory state)

What areas does Nutrigenomic testing cover?

- Inflammation Indicators
- Autophagy
- Methylation
- Neurotransmitter Production and Bioavailability
- Mitochondrial Function
- Detoxification of Chemicals and Bio-actives
- Health Precautions

The Goal of Genetic-Guided Personalized Precision Medicine

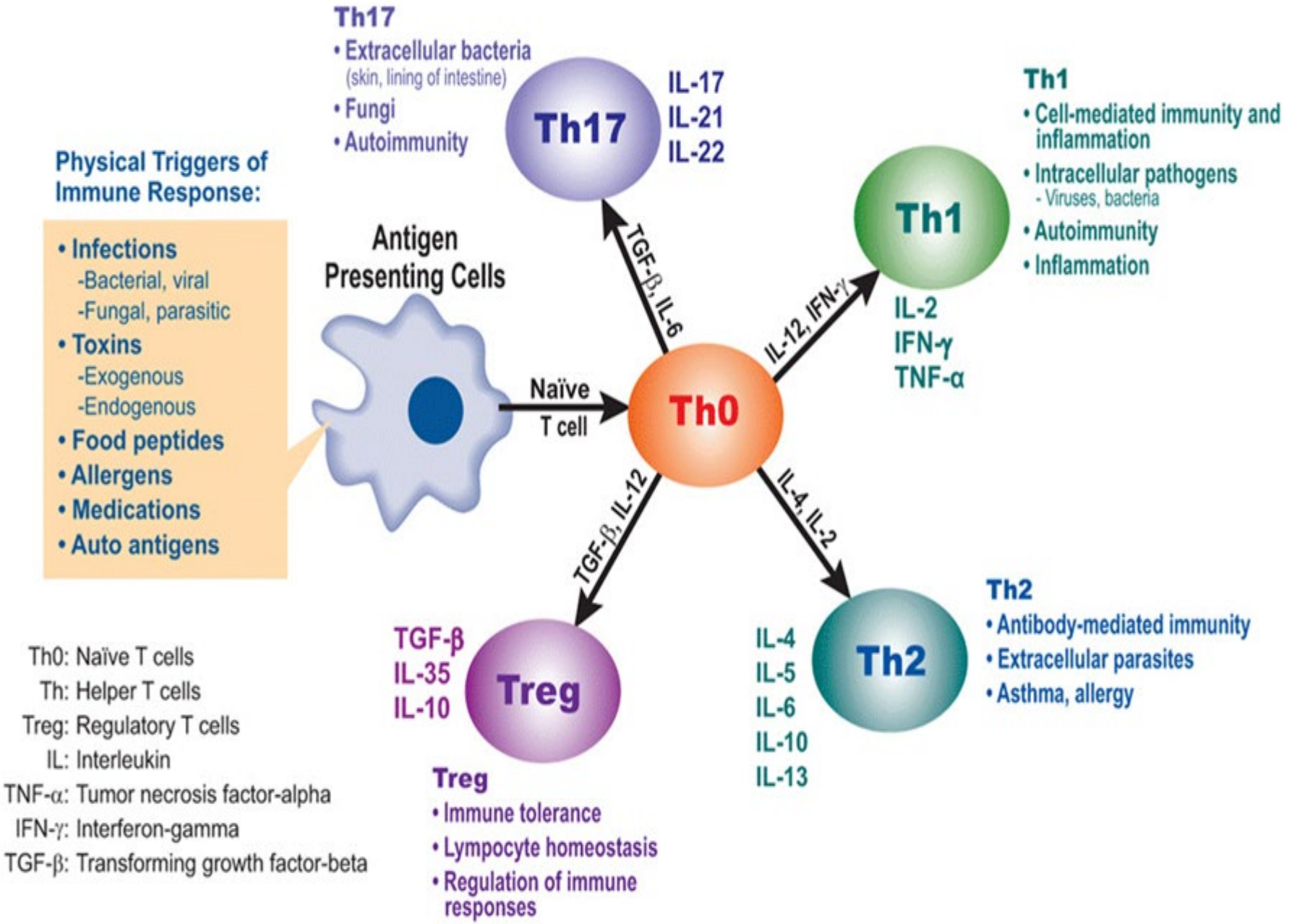
The **Right** Supplement/s in
The **Right** Amount for
The **Right** Indication for
The **Right** Patient at
The **Right** Time

Biochemistry Review

Inflammation Cellular

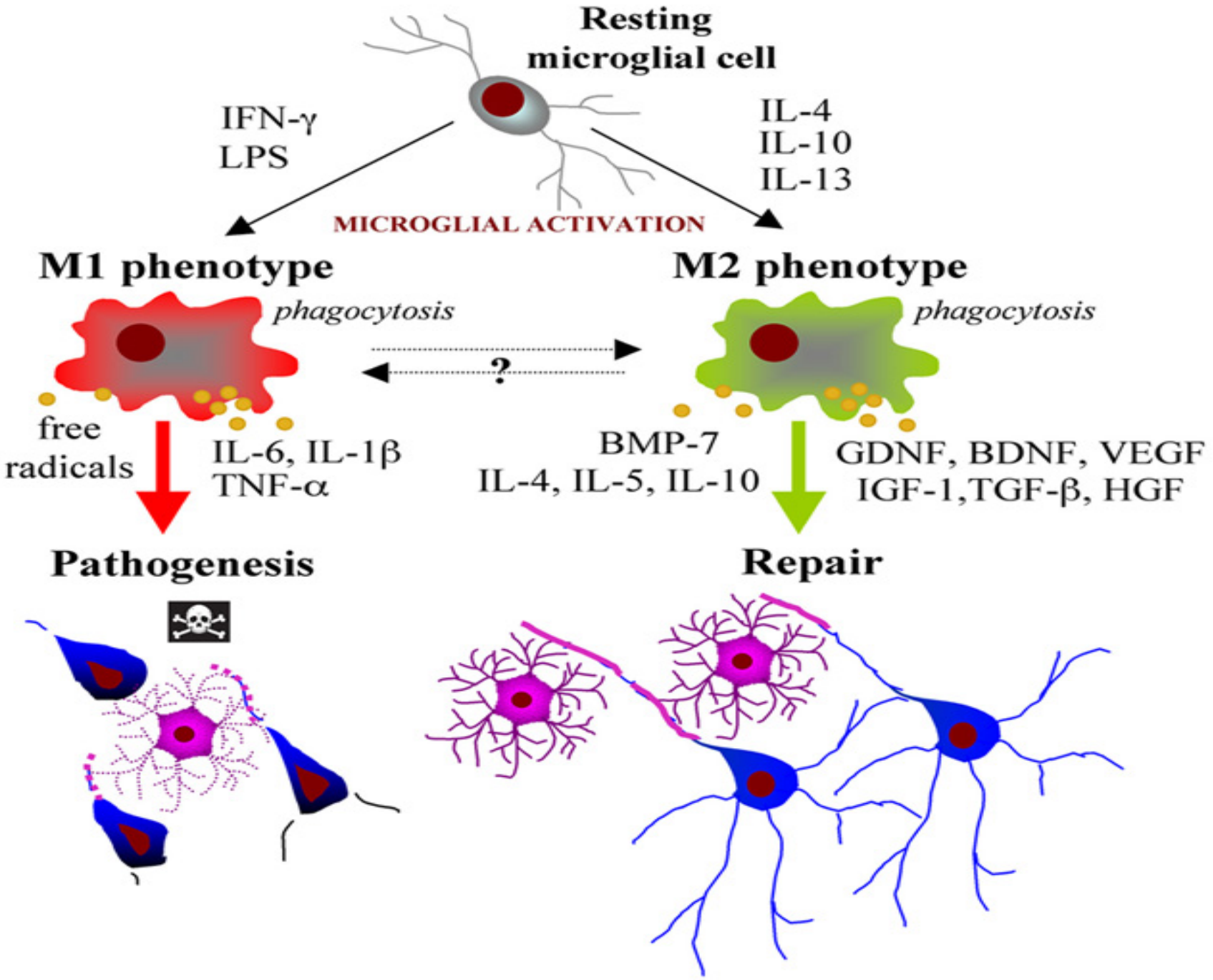
What cells are affected?

T cells



What cells are affected?

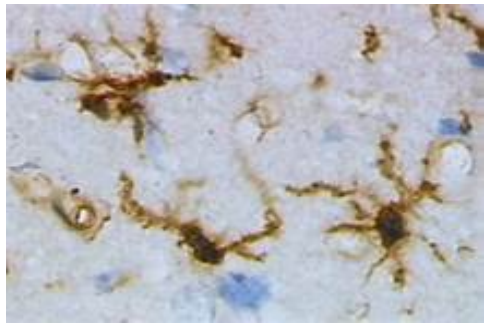
Microglia

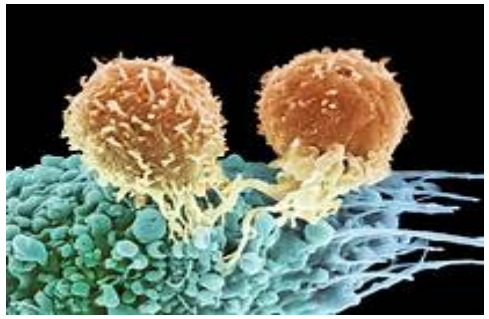


Microglial / T Cell Activation

"ON" Switches

*C3**
*CD14**
IL2
IL4
*IL5**
*IL6**
IL13
IL23R
IL2RA





"OFF" Switches

TNF
TRAF1
CTLA4
STAT4
SOCS-1

Therefore, individuals who develop Neuro-inflammation have more aggressive microglial activation to inflammatory stimuli (i.e. vaccination, infection, trauma, toxic exposure) than the general population due to inherited genetic polymorphisms of immune modulation.

"On Switches"

- ***C3 (Complement Component 3) (MAF: .45)***
  - *Member of the Innate Immune System*
  - *Controls phagocytosis, inflammation and membrane attack*

- ***CD14 (Cluster of Differentiation 14) (MAF: .47)***
  - *Member of the Innate Immune System*
  - *Receptor for bacterial polysaccharides*
  - *Increased risk of gut inflammation, Alzheimer's, chronic infections, pre-eclampsia, cardiovascular*

- ***IL-5 (Interleukin 5) (MAF: .45)***
  - *Mostly produced by TH2 and mast cells*
  - *Polymorphism codes for aggressive allergic reactivity*
  - *Strongly associated with allergies, asthma and eosinophilia*

"On Switches"

- ***IL2 (Interleukin 2) (MAF: .27)***
  - *Controls proliferation of T and B cells*
  - *Polymorphism codes for explosive allergic response to inflammatory stimuli*
  - *Correlated to severe allergies, cancer risk and bowel inflammation*

- ***IL4 (Interleukin 4) (MAF: .47)***
  - *Produced by activated T cells*
  - *Modifies the STAT system*
  - *Polymorphism produces a robust inflammatory response to allergic stimuli*
  - *can be associated with severe asthma, allergies, chronic sinusitis, migraines and IBS*

- ***IL-13 (Interleukin 13)(MAF: .25)***
  - *Mostly produced by TH2 cells*
  - *Polymorphism codes for aggressive allergic inflammation*
  - *Strongly associated with reactive airway disease*

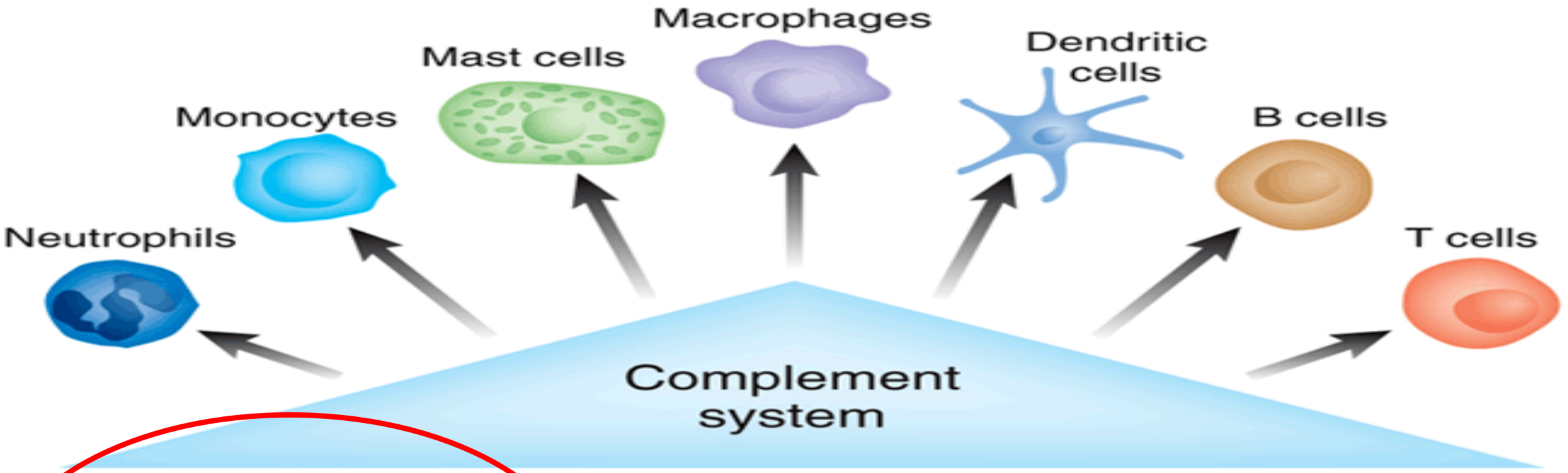
"On Switches"

- ***IL-6 (Interleukin 6) (MAF: .14)***
  - *Mostly produced by monocytes*
  - *Increased risk of general inflammation and IBS*
  - *Polymorphism may respond to JAK-STAT inhibitors*

- ***IL23R (Interleukin 23 Receptor) (MAF: .03)***
  - *Highly associated with the JAK2 system*
  - *Associated with higher risk of Crohn's and Graves' Disease*
  - *Polymorphism may respond clinically to JAK- STAT inhibitors*

- ***IL2RA (Interleukin 2 Receptor Alpha) (MAF: .09)***
  - *Increased risk of inflammation, Higher Risk of Multiple Sclerosis if with CTLA-4, Type 1 Diabetes*
  - *Patient may respond well to Daclizumab*
  - *Need high level of D3*

C3 Polymorphism “up-regulation”



Innate immunity

Opsonization
Lysis of pathogens
Chemotaxis
Inflammation
Cell activation

Disposal system

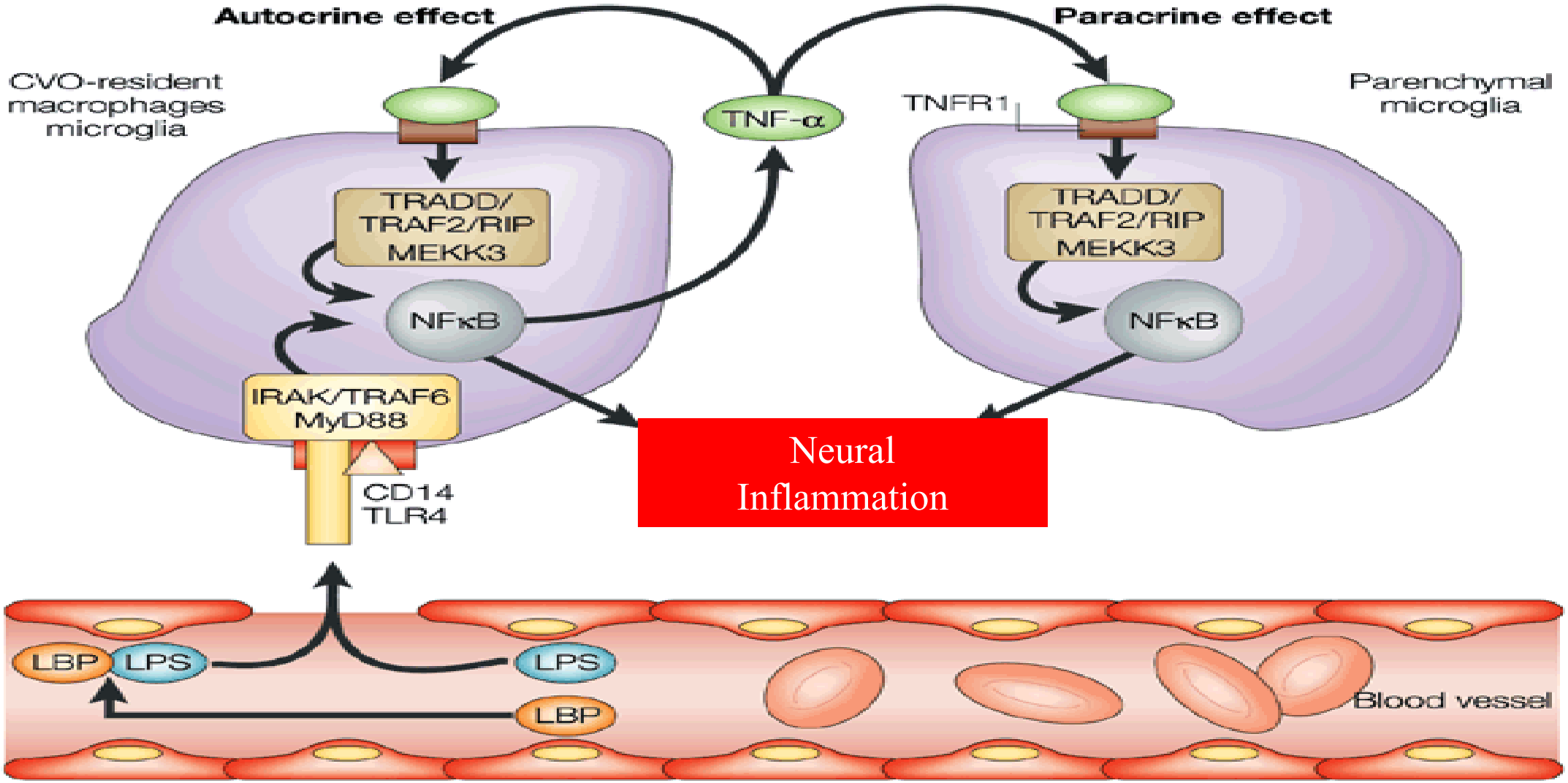
Clearance of immune complexes and apoptotic cells

Adaptive immunity

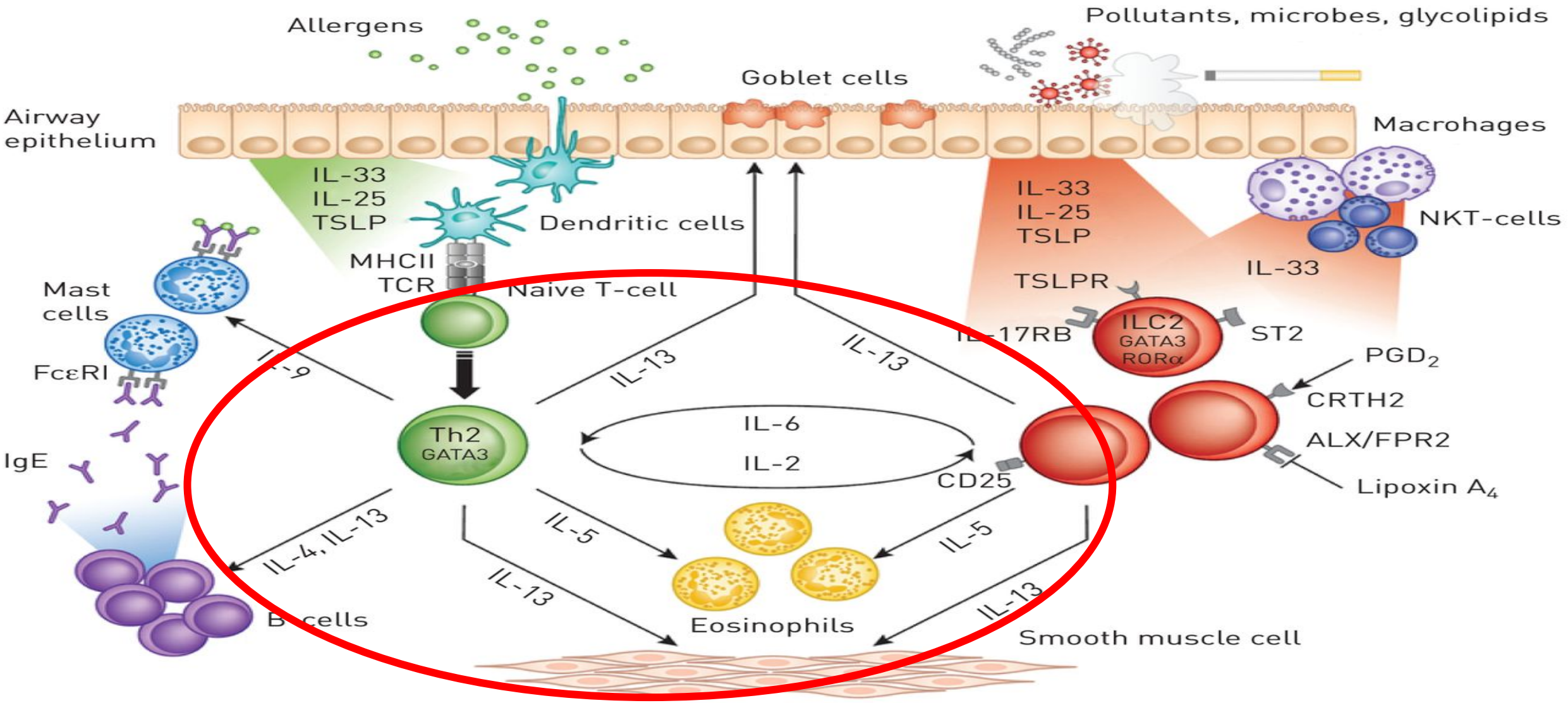
Augmentation of antibody response
Promotion of T-cell response
Elimination of self-reactive B cells
Enhancement of immunologic memory

Katie Ris-Vicari

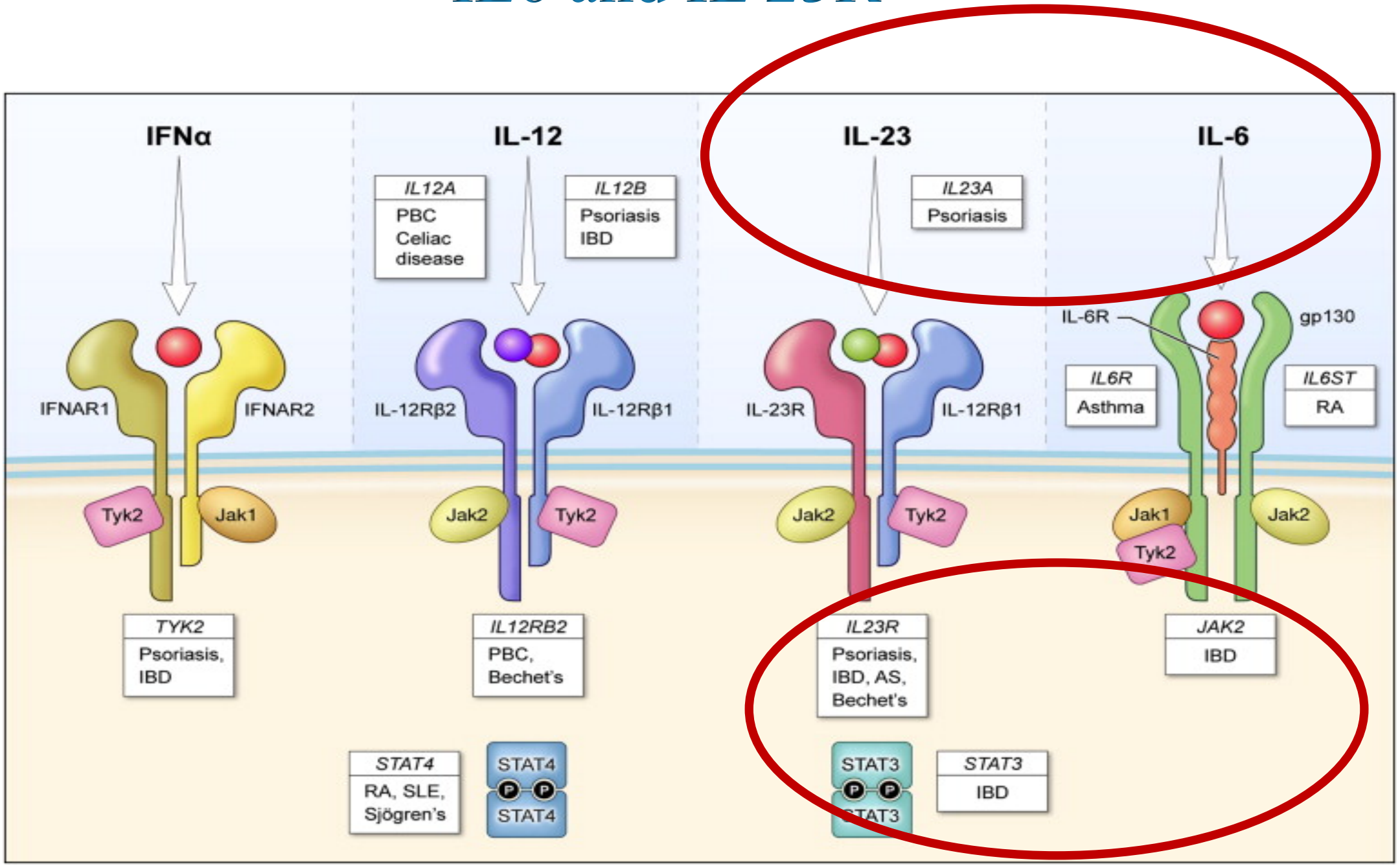
CD14 Polymorphism “up regulation”



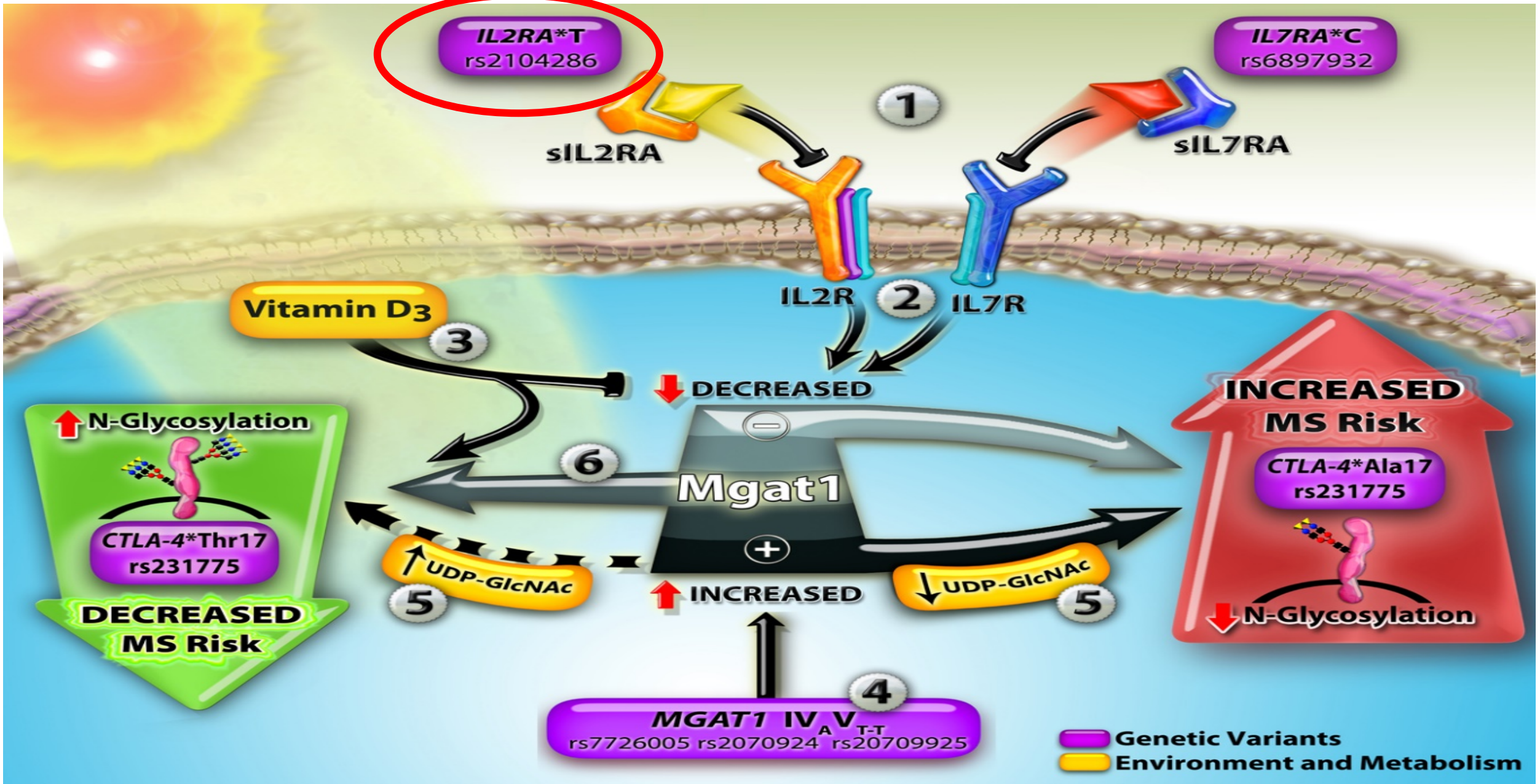
IL4 / IL5 / IL6 / IL13 Polymorphism



IL6 and IL 23R



IL2RA Polymorphism

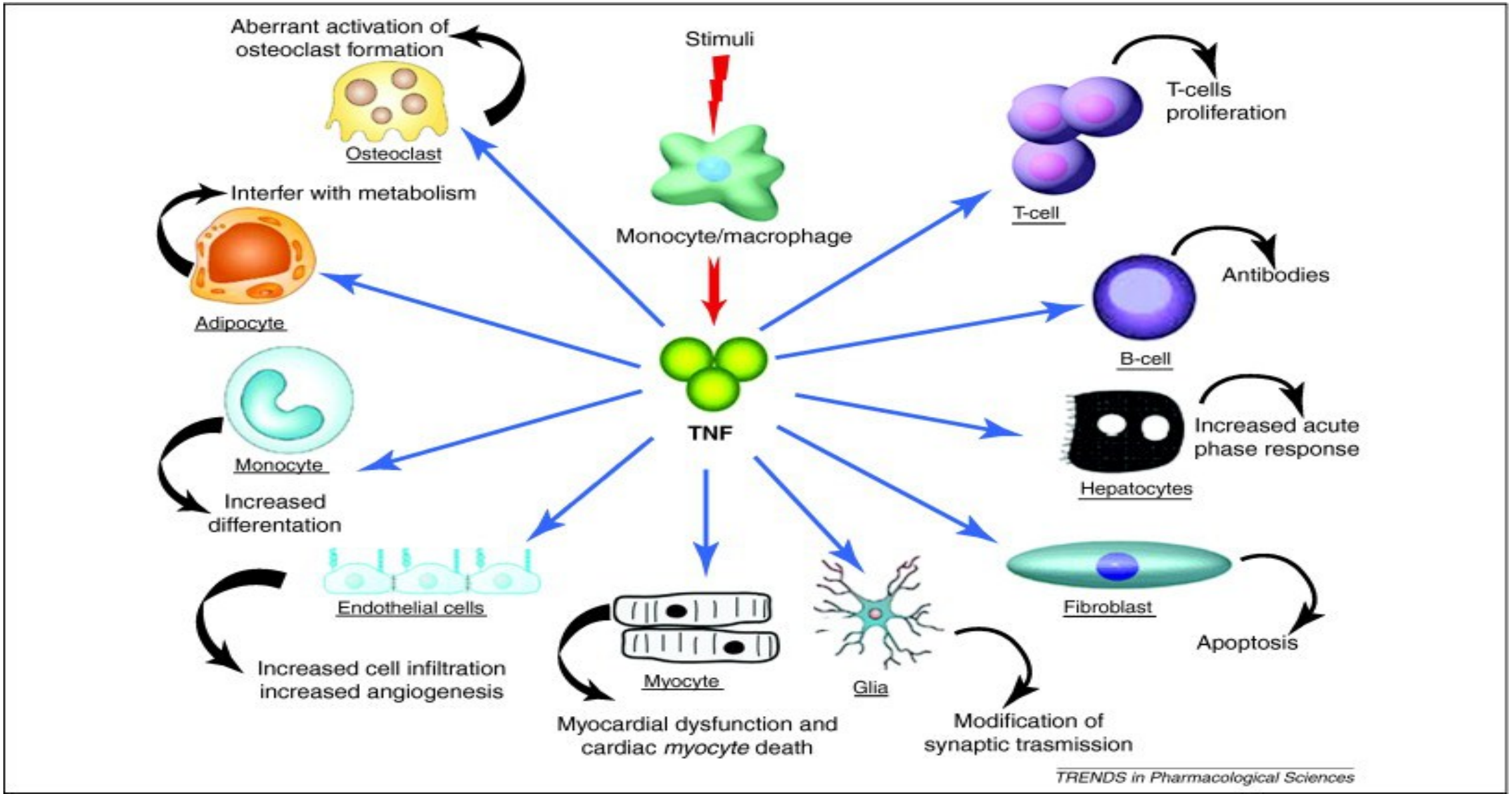


Immune Inflammatory Cellular SNP's "Off Switches"

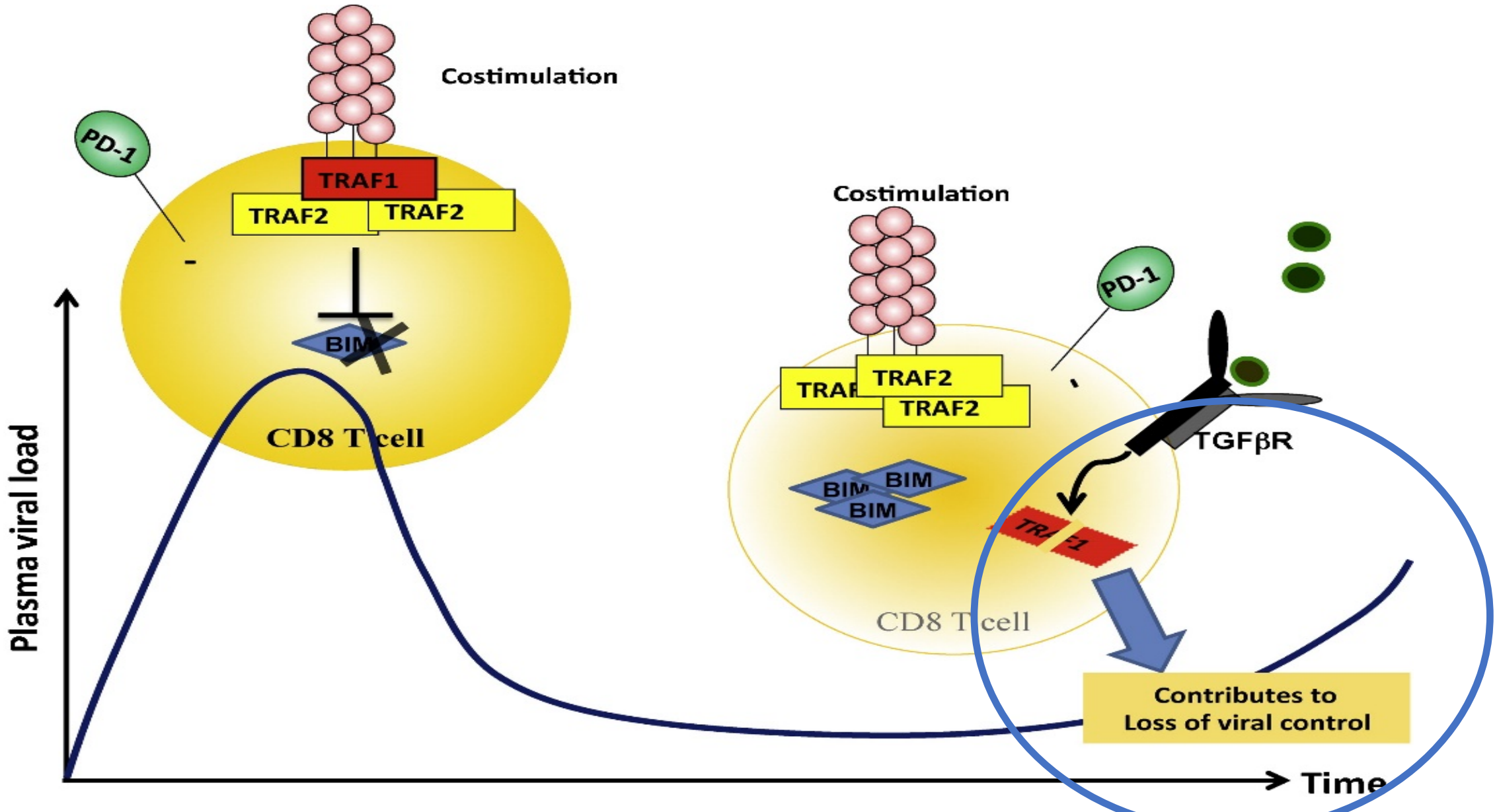
- ***TNF (Tumor Necrosis Factor) (MAF: .10)***
  - *Cytokine responsible for B and T cell activation*
  - *Polymorphism results in aggressive T cell overactivation*

- ***TRAF1 (TNF Receptor Activation Factor 1) (MAF: .46)***
  - *Mostly produced by T cells*
  - *Functions as off switch for TLR and JK*
  - *Can be induced by Epstein Barr infection*

Polymorphism = Increased Aggression



TRAF1 (TNF Receptor Factor Activation Factor 1)



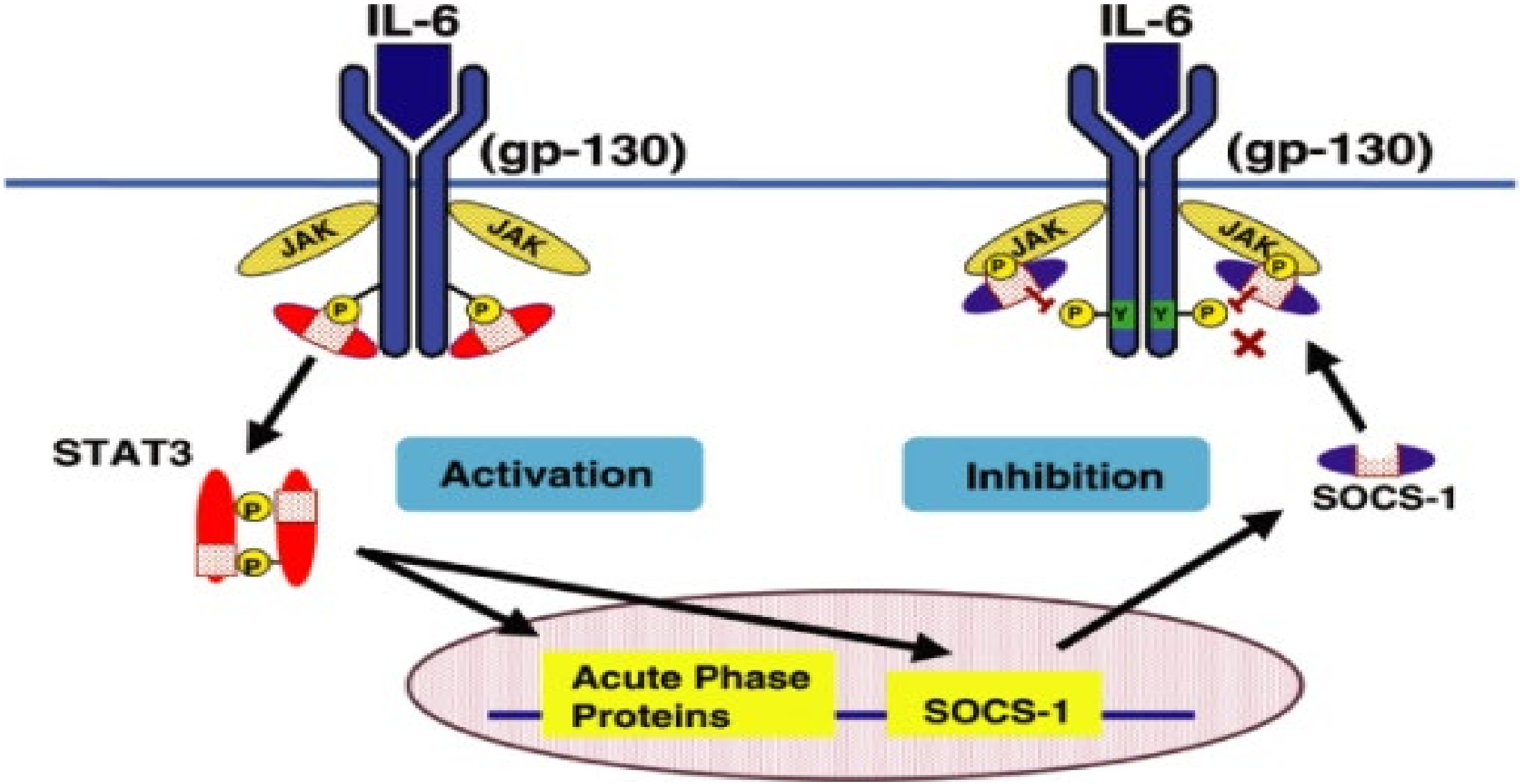
Immune Inflammatory Cellular SNPs "Off Switches"

- ***SOCS-1 (Suppressor of Cytokine Signaling 1) (MAF: .39)***
  - *Member of the STAT family*
  - *Polymorphism codes for aggressive inflammation*
  - *May respond well to JAK-STAT inhibitors*

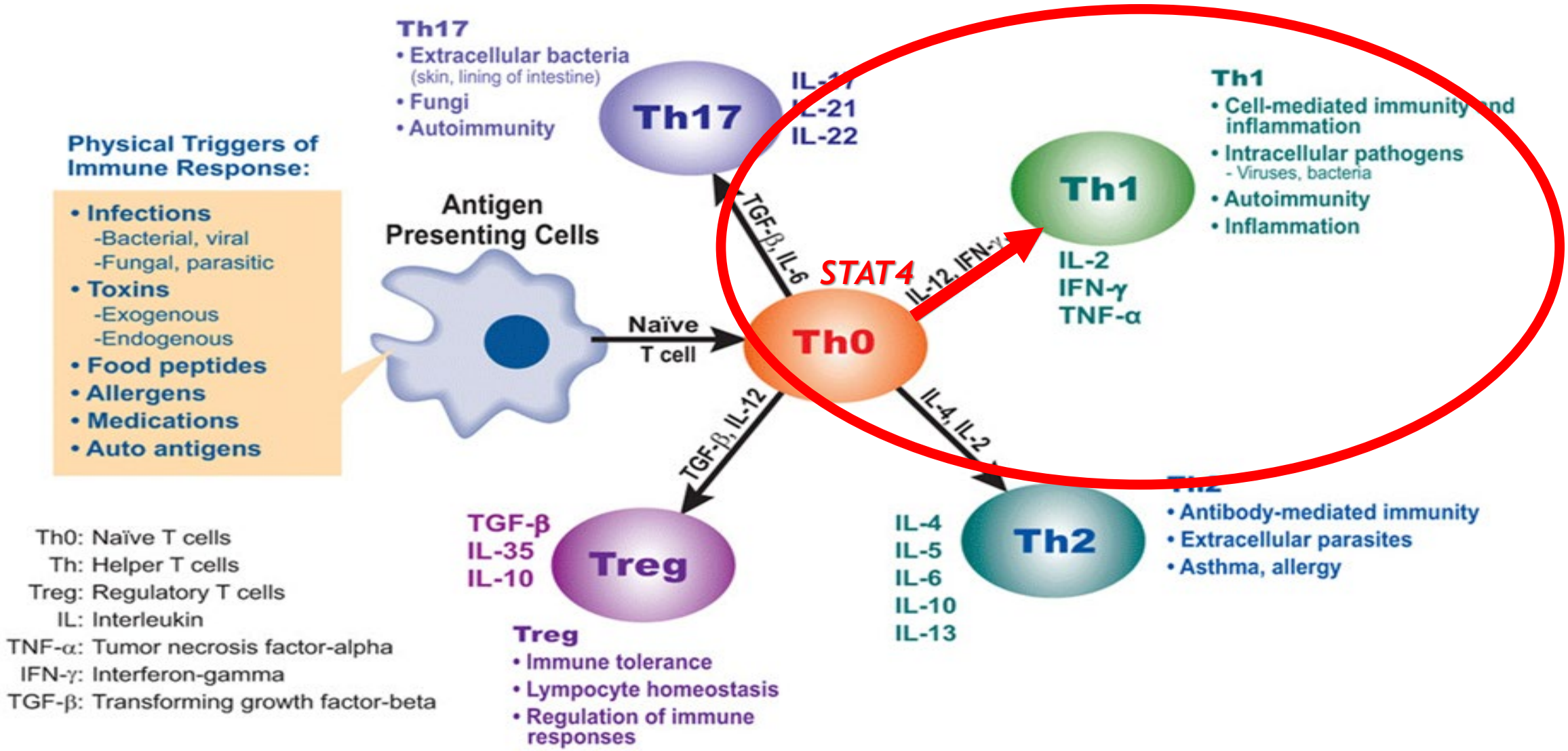
- ***STAT4 (Signal Transducer and Activator 4)(MAF: .26)***
  - *Codes for protein that activates TH1 from naïve CD4*
  - *Polymorphism codes for overtly aggressive inflammatory aggression*
  - *May respond well to JAK-STAT inhibitors*

- ***CTLA4 (Cytotoxic T Lymphocyte Associated Protein 4) (MAF: .43)***
  - *Functions as an "off switch" or immune down regulator*
  - *Polymorphism allows for severe chronic inflammation*

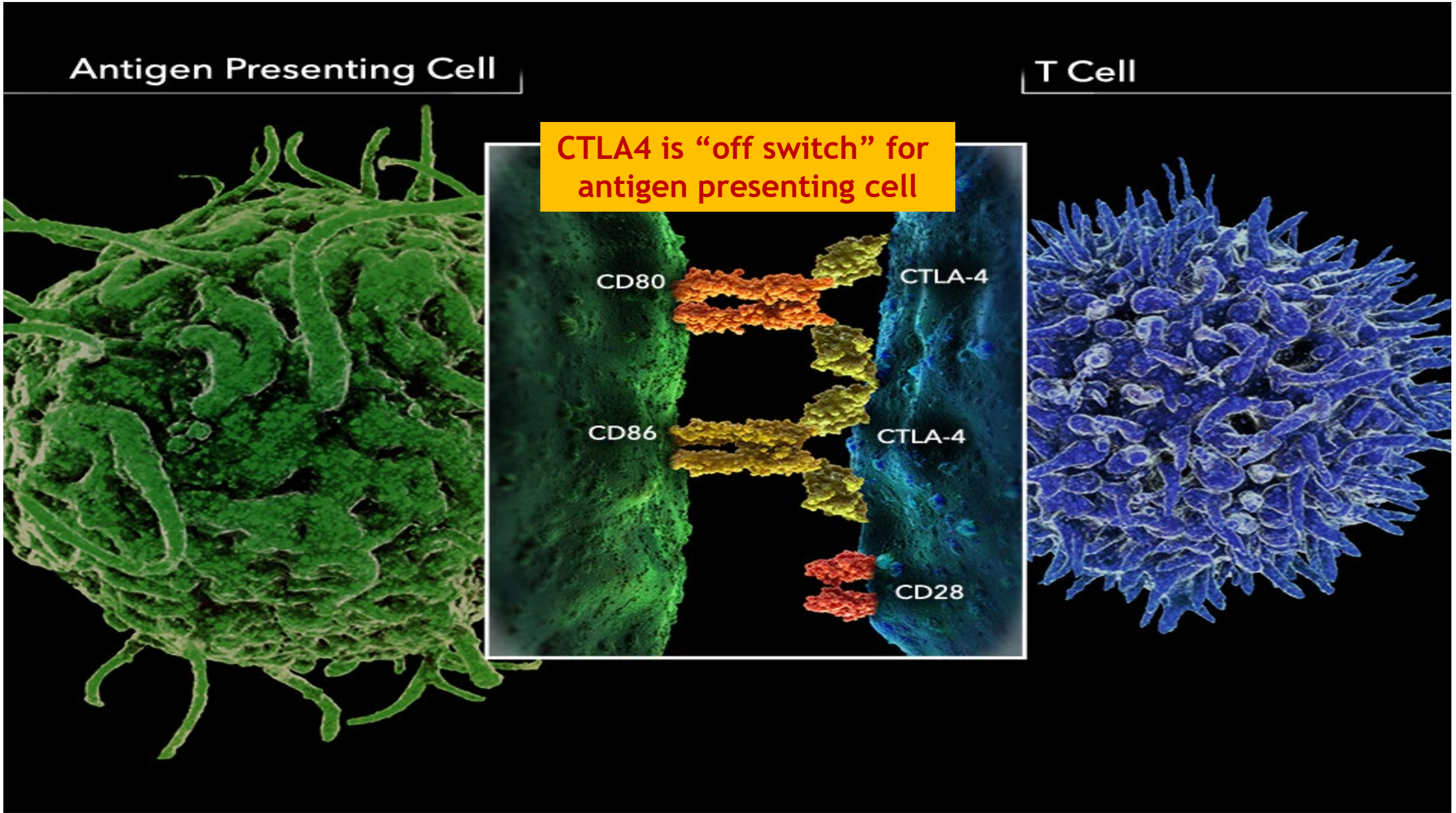
SOCS-1 (Suppressor of Cytokine Signaling)



STAT4 (Signal Transducer and Activator 4) Polymorphism



CTLA4 (Cytotoxic T Cell Protein 4)

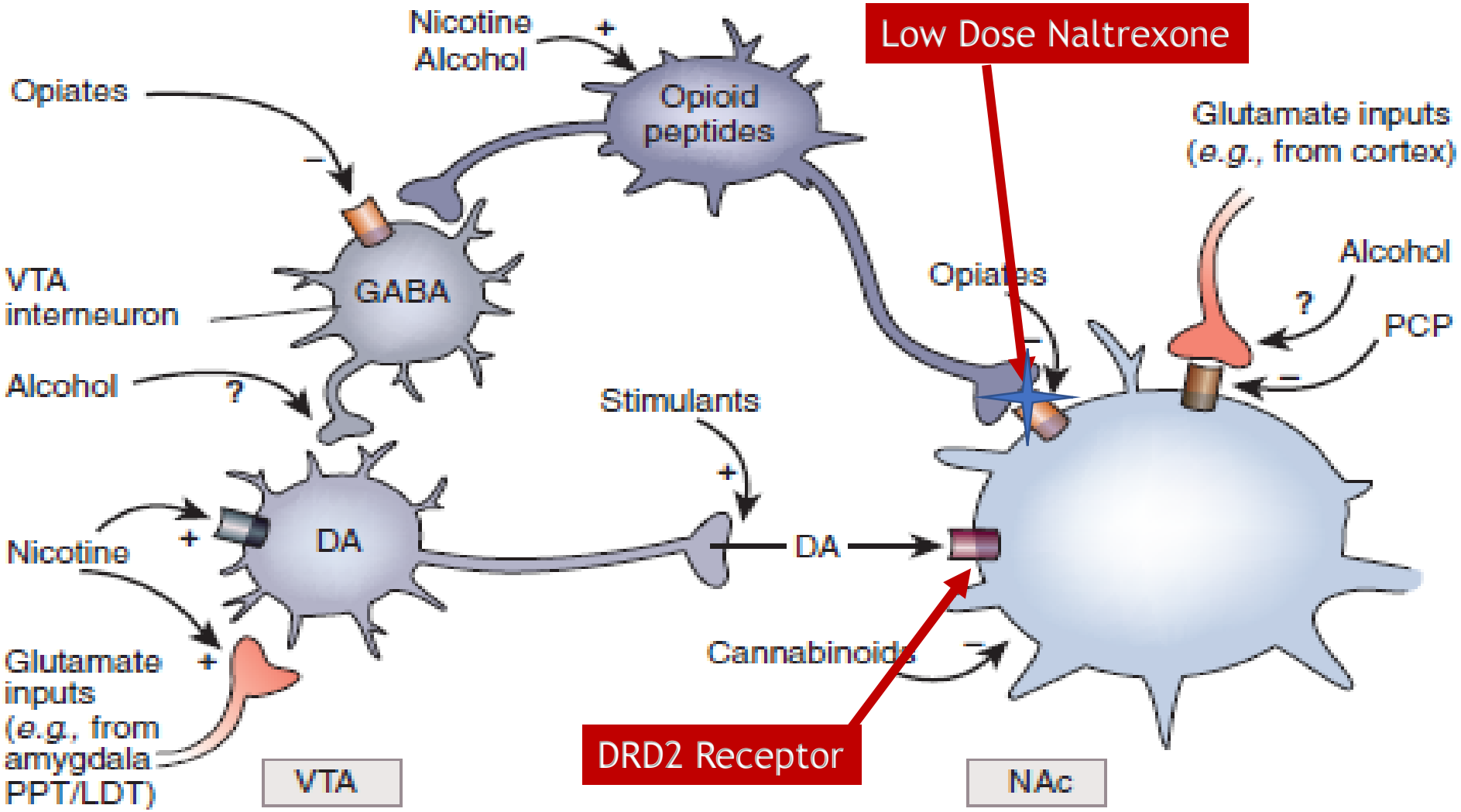


Important Immune Enzymes

- ***DRD2 (Dopamine Receptor D2) (MAF: .23)***
  - Higher response rate to Low Dose Naltrexone

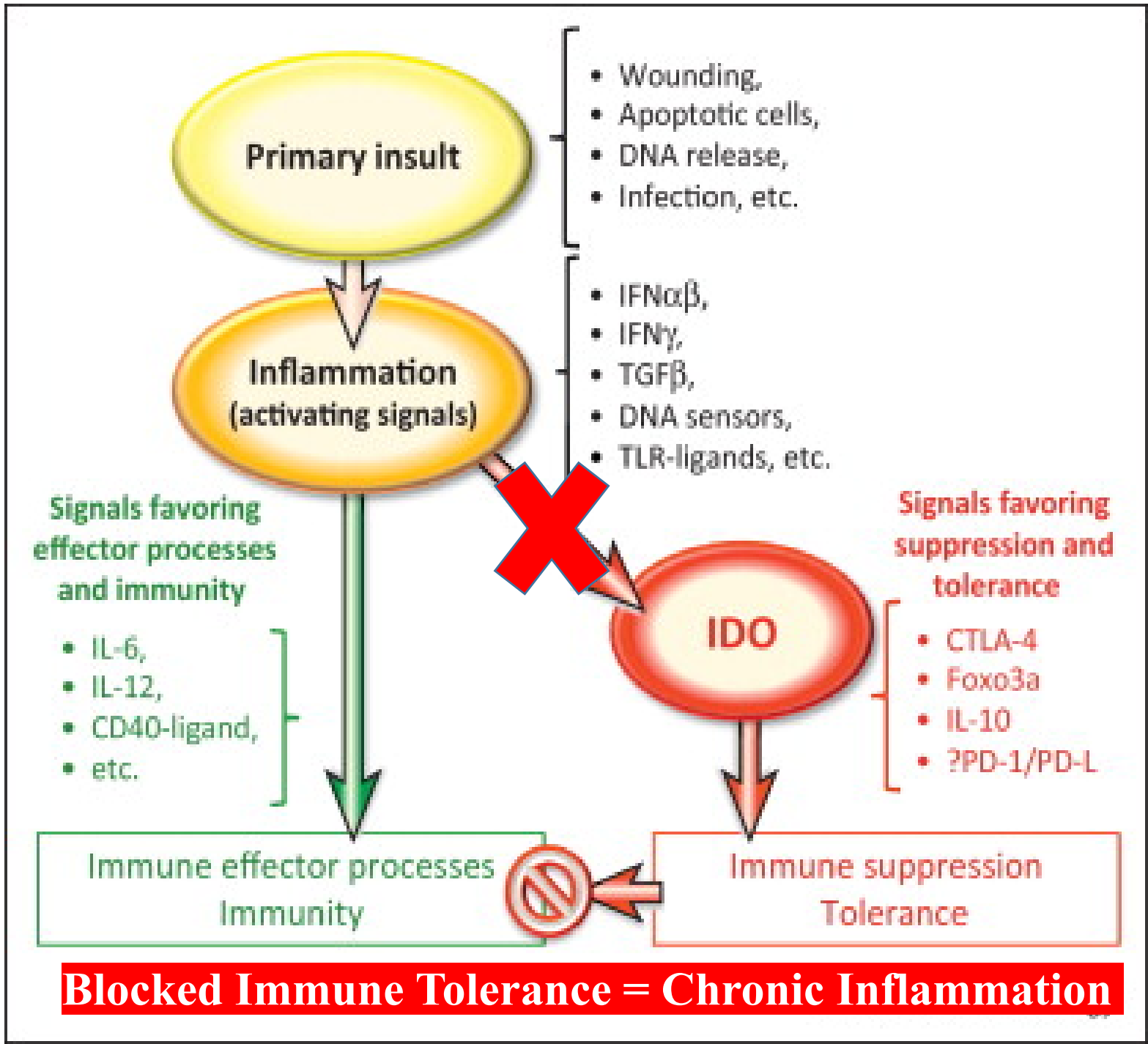
- ***IDO1(Indolamine Dioxygenase) (MAF: .45)***
  - Control conversion of tryptophan to kynurenine
  - Polymorphism leads to buildup or tryptophan which lead to T reg (CD8) cell depletion
  - Polymorphism weakens immune tolerance and can lead to difficulty with infection, pregnancy, transplantation, autoimmunity, and neoplasia
  - Treatment: Beta Glucans, Andrographalide, Astralagus

DRD2 (Dopamine Receptor D2)



Ann Thomson

IDO1
Indolamine 2,3-Dioxygenase 1

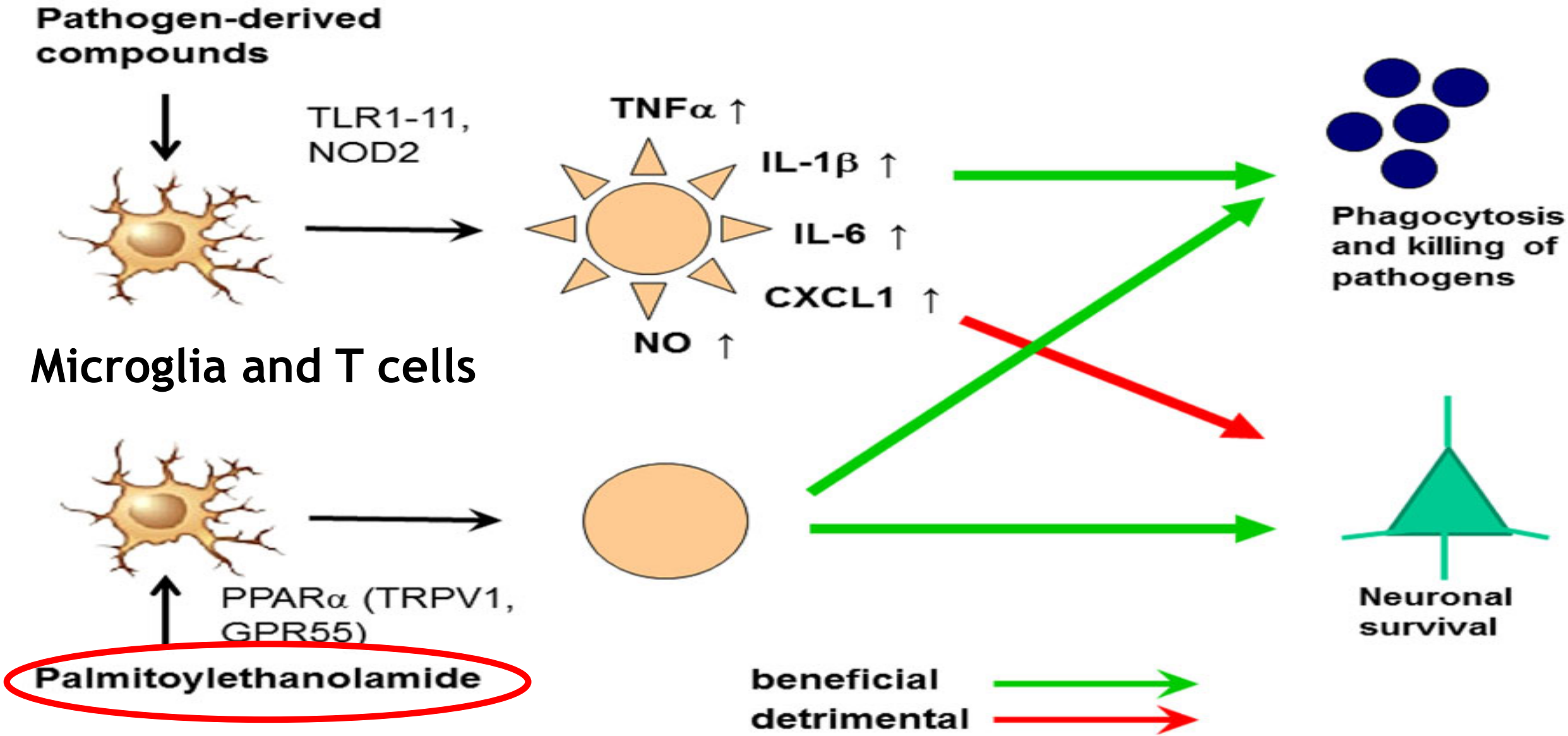


Treatment Inflammation Cellular

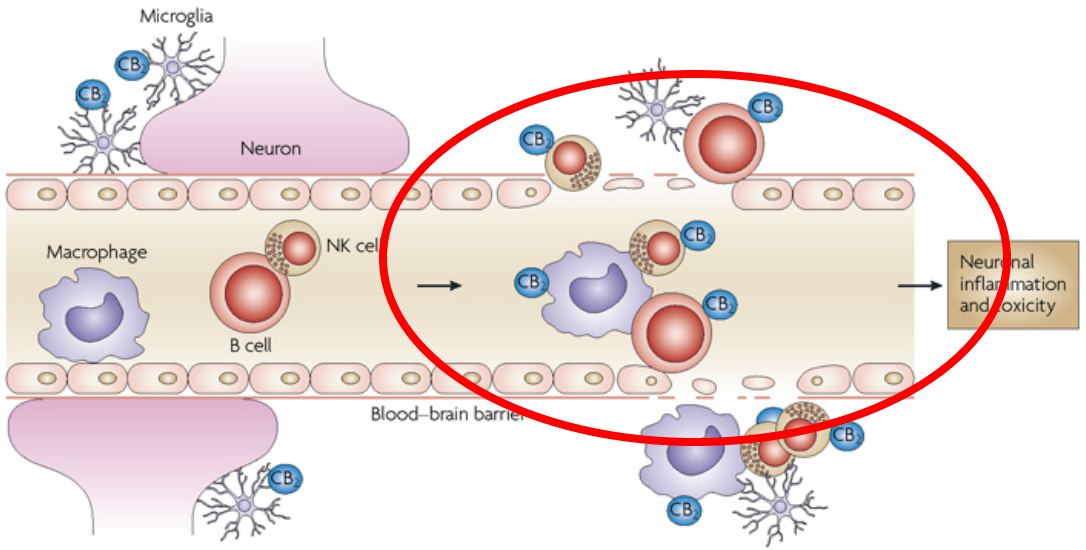
Treatment should be targeted at alternative "off switch" or down-regulator

- **Cannabidiol (CBD) oil**
- **Low Dose Naltrexone (LDN) capsules or lotion**
- **Palmitoylethinolamide (PEA)**
- **Beta Glucans (probiotic or mushroom based)**
- **Omega 3 Fatty Acids**
- **Bio-identical steroids (Pregnenolone, Progesterone, Testosterone)**
- **Curcuminoids (COX Modifier) and Resveratrol (IL1B Modifier)**

Inflammation Cellular - PEA

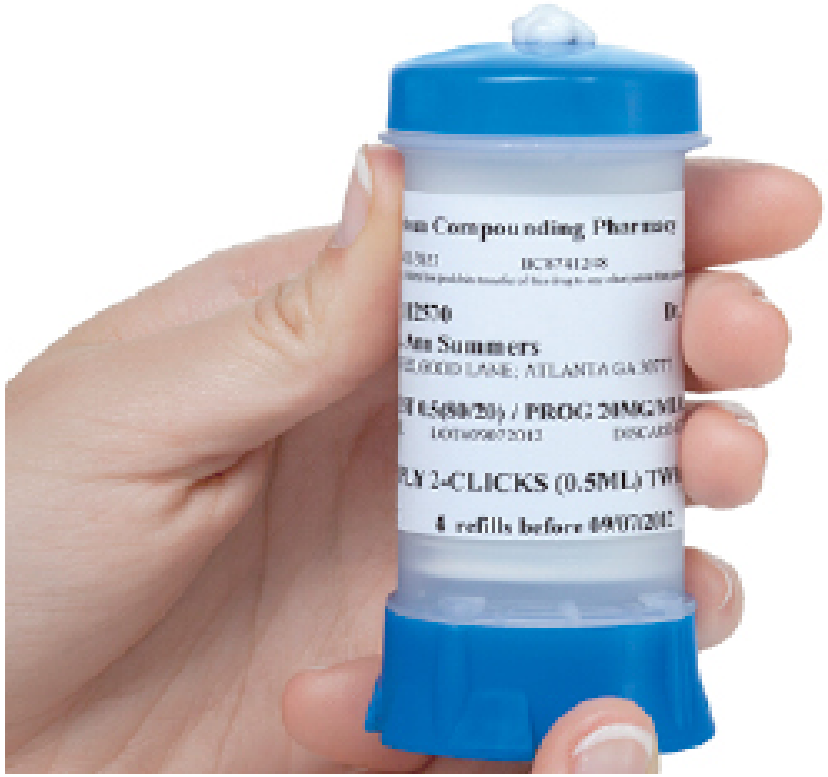


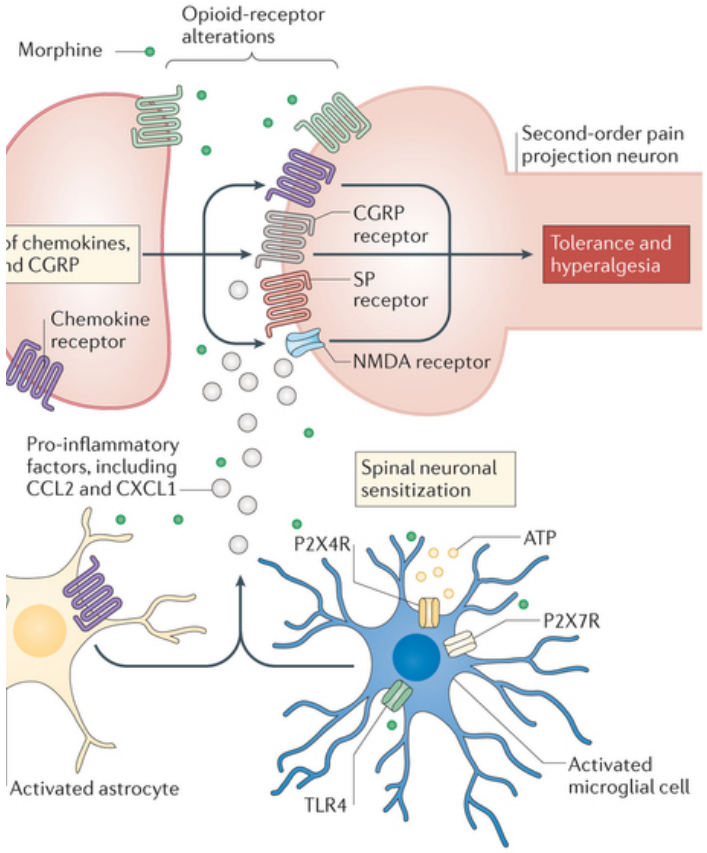
Inflammation Cellular
Cannabidiol and Neuro-Inflammation



Nature Reviews | Drug Discovery

Inflammation Cellular Treatment
Low Dose Naltrexone Lotion





Nature Reviews | Neuroscience

Inflammation Cellular: Palmitoylethanolamide

Indication:

- STAT4, CTLA4, TNF, multiple "ON" SNPs
- Aggressive Inflammation
- Chronic Pain / ADD / Depression / Cognitive / Anxiety / Seizures

MOA: Binds to cannabinoid G protein and enhances anandamide (endocannabinoid) activity

Does not bind directly to CB1 or CB2 receptors

Objective: **PEA** is a **Nuclear Factor Agonist** that is:

- **Peroxisome Proliferator Alpha Agonist**
- **Anti-inflammatory**
- **Anti-convulsant**
- **Neuro-protective**
- **Anti-nocioceptive**

Inflammation Cellular
Beta Glucans and Immune Modulation

Genes and Symptoms:

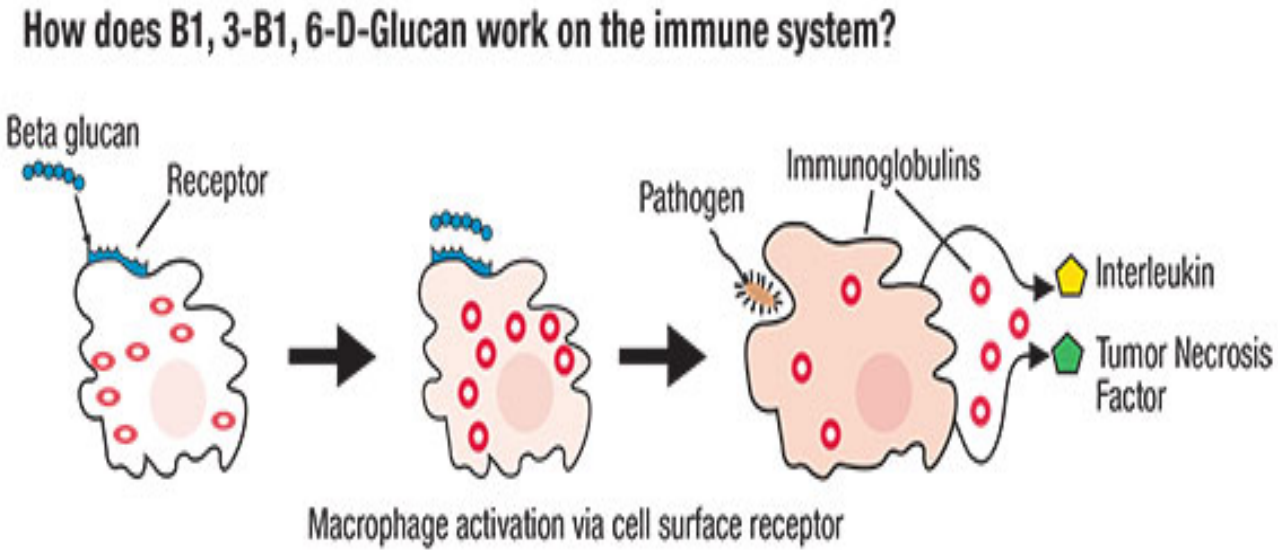
- STAT4, CTLA4, TNF, IL13, IL6, IL5
- Low T cell counts

Objective: Beta Glucans can:

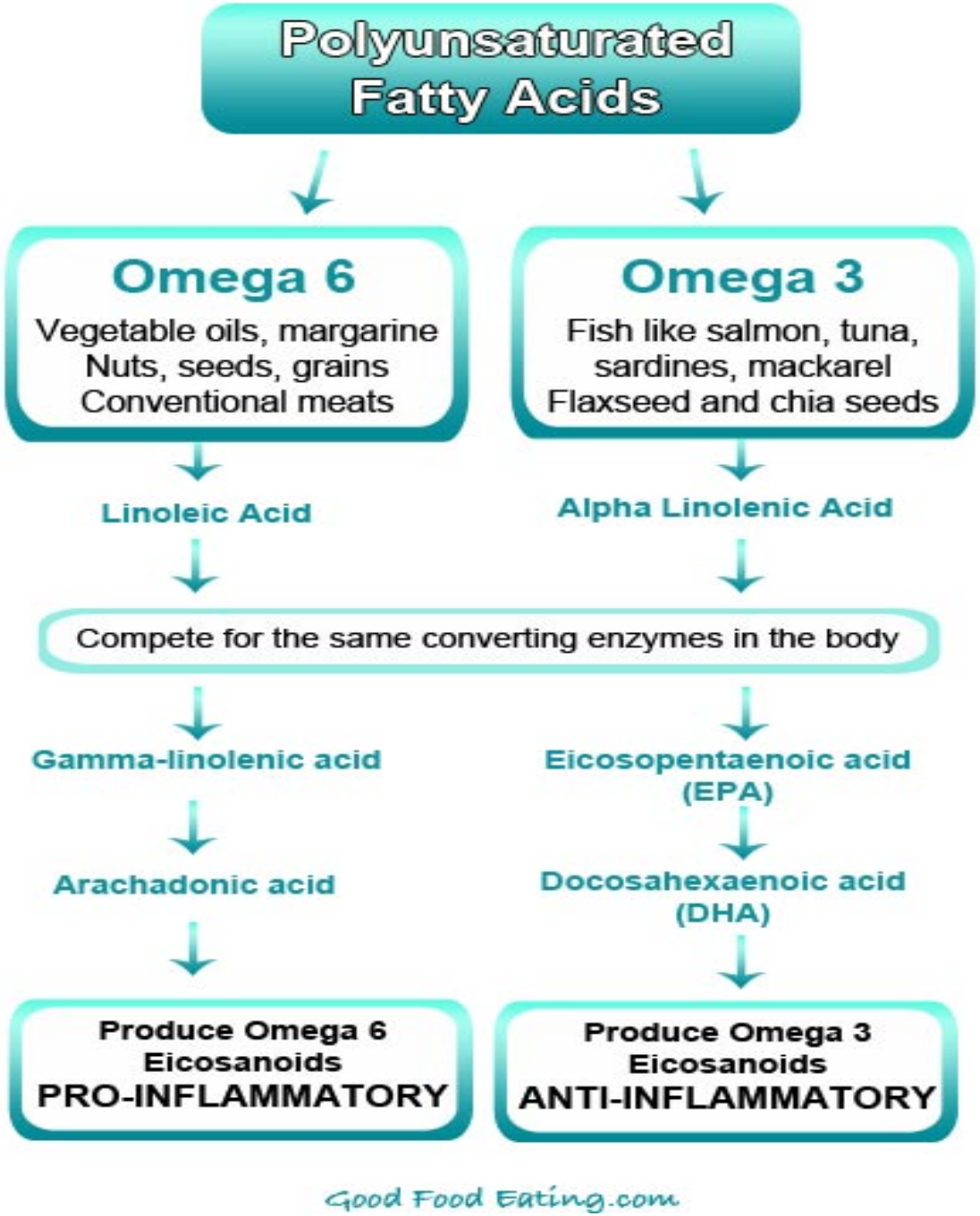
- **Stimulate production of WBCs**
- **Increase phagocytosis**
- **Shift Th2 dominance to Th1**

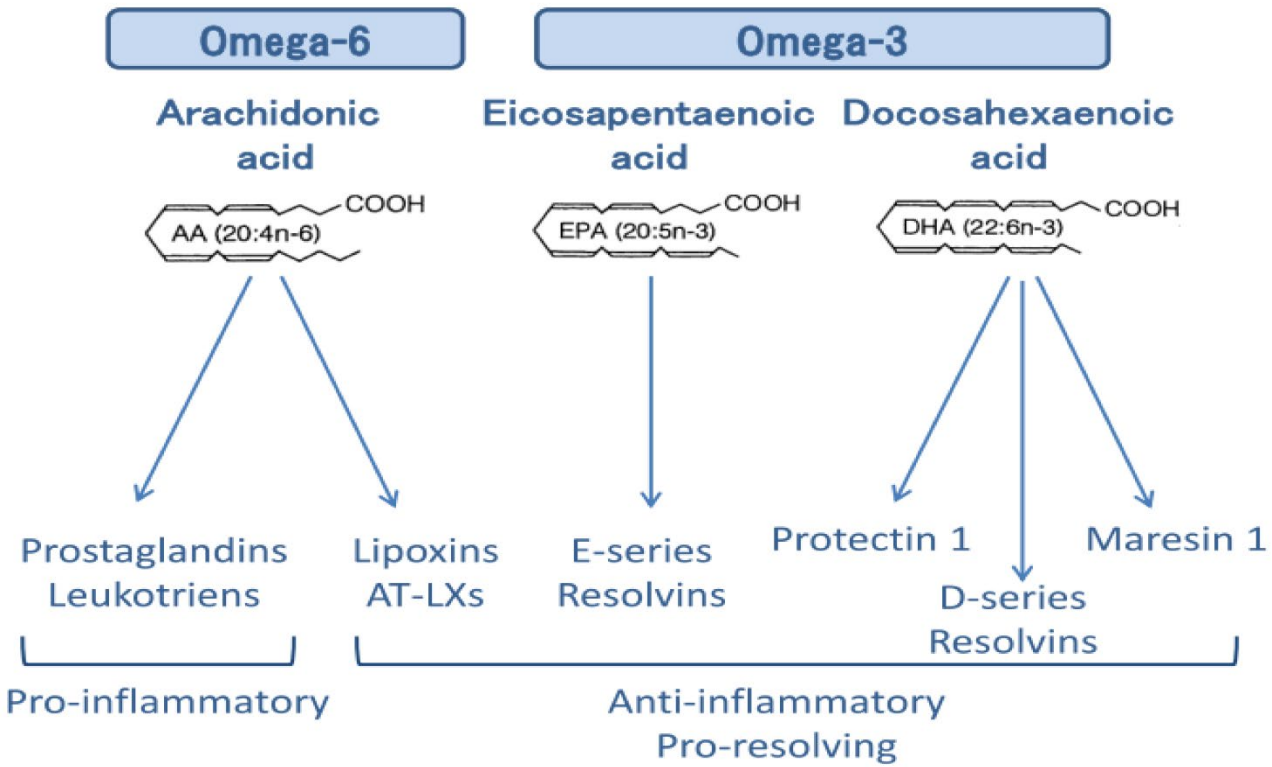
Strategy:

- Beta glucans 1/3,1/6 – Probiotic c
- Echinacea, Silymarin
- Andrographolide, Quercetin

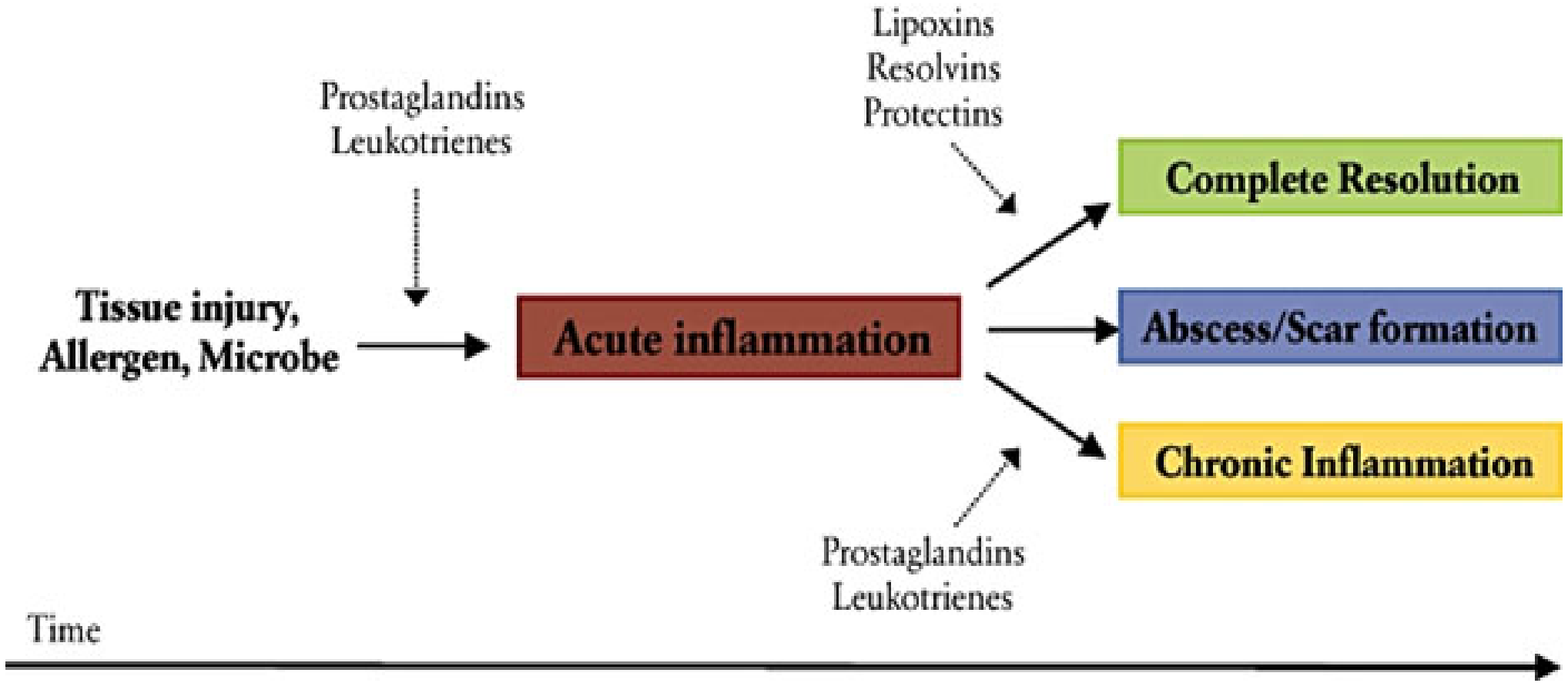


Inflammation Cellular Omega 3 Fatty Acids

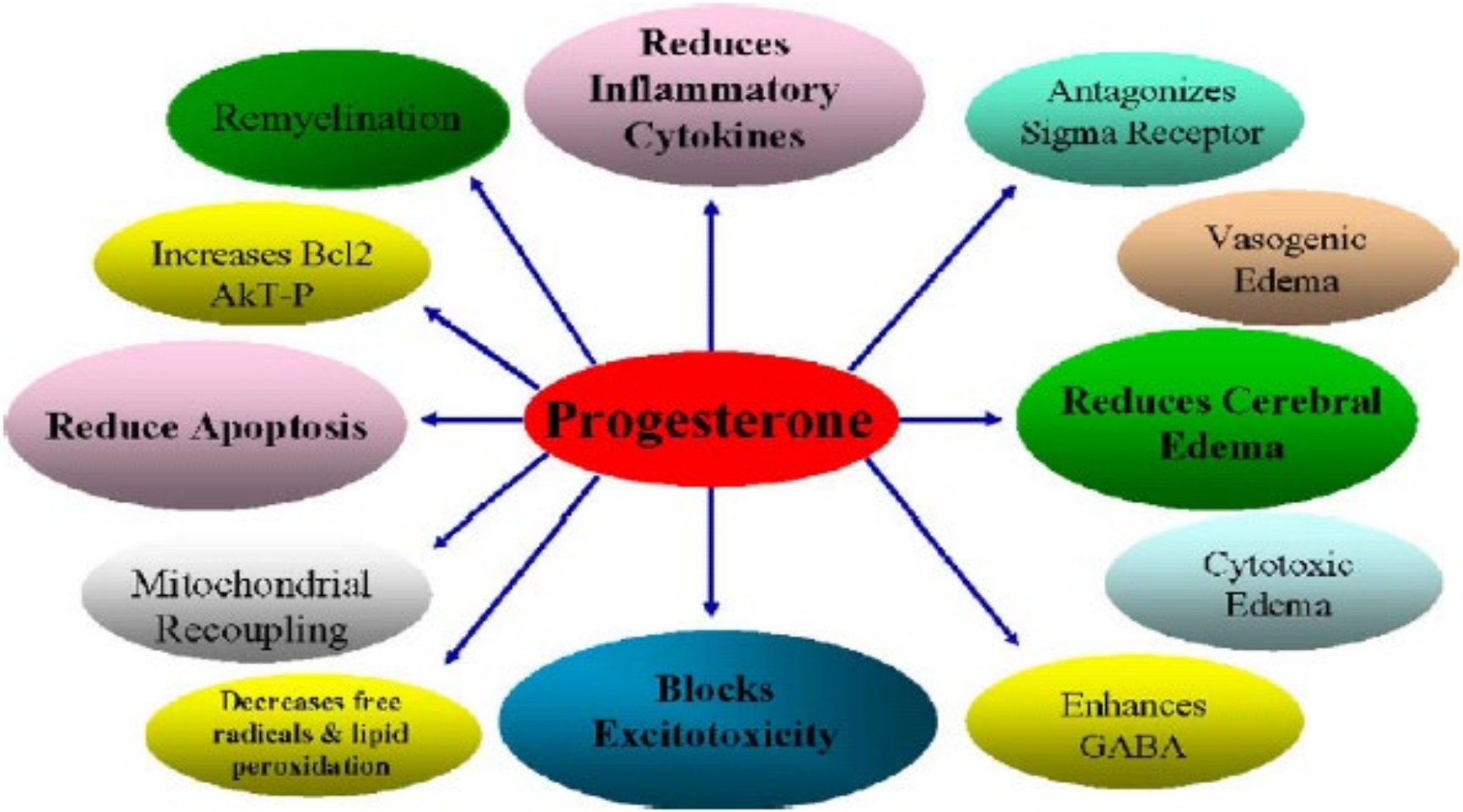




Omega 3 Fatty Acids
Resolvins, Lipoxins and Protectins



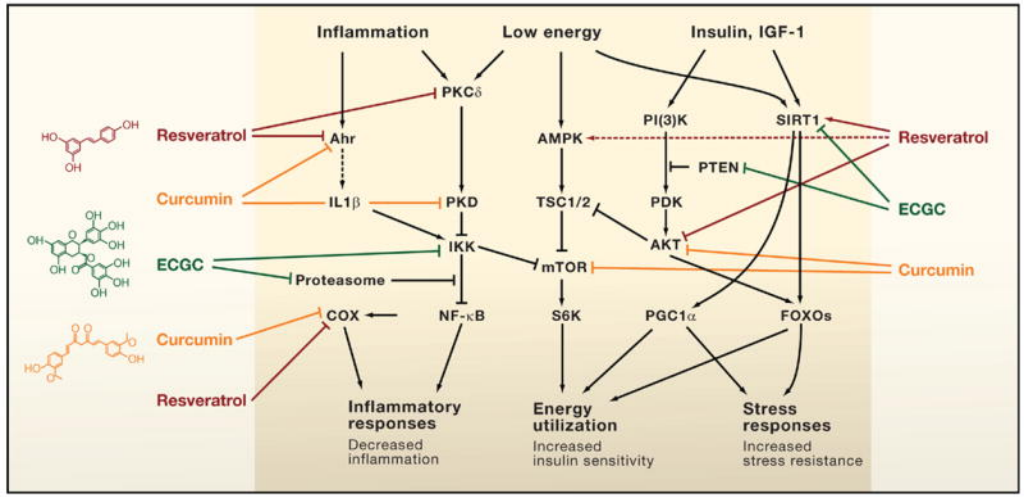
Progesterone and Inflammation Control



Inflammation Control
Curcuminoids and Resveratrol

Inflammation Control

Autophagy



Biochemistry Review

Inflammation External Gastrointestinal

Immune Inflammatory Gastrointestinal SNPs

- ***AOC1 (Amine Oxidase Copper Containing 1) Diamine Oxidase***
  - Homo or Hetero in combination
  - Involved in breakdown of histamine from external sources
  - Highly concentrated in the intestinal tract

- ***HNMT (Histamine N-methyltransferase) -***
  - Homo or Hetero in combination
  - Involved in the breakdown of histamine from external sources
  - Requires SAMe as a co-factor
  - Highly concentrated in the intestinal tract

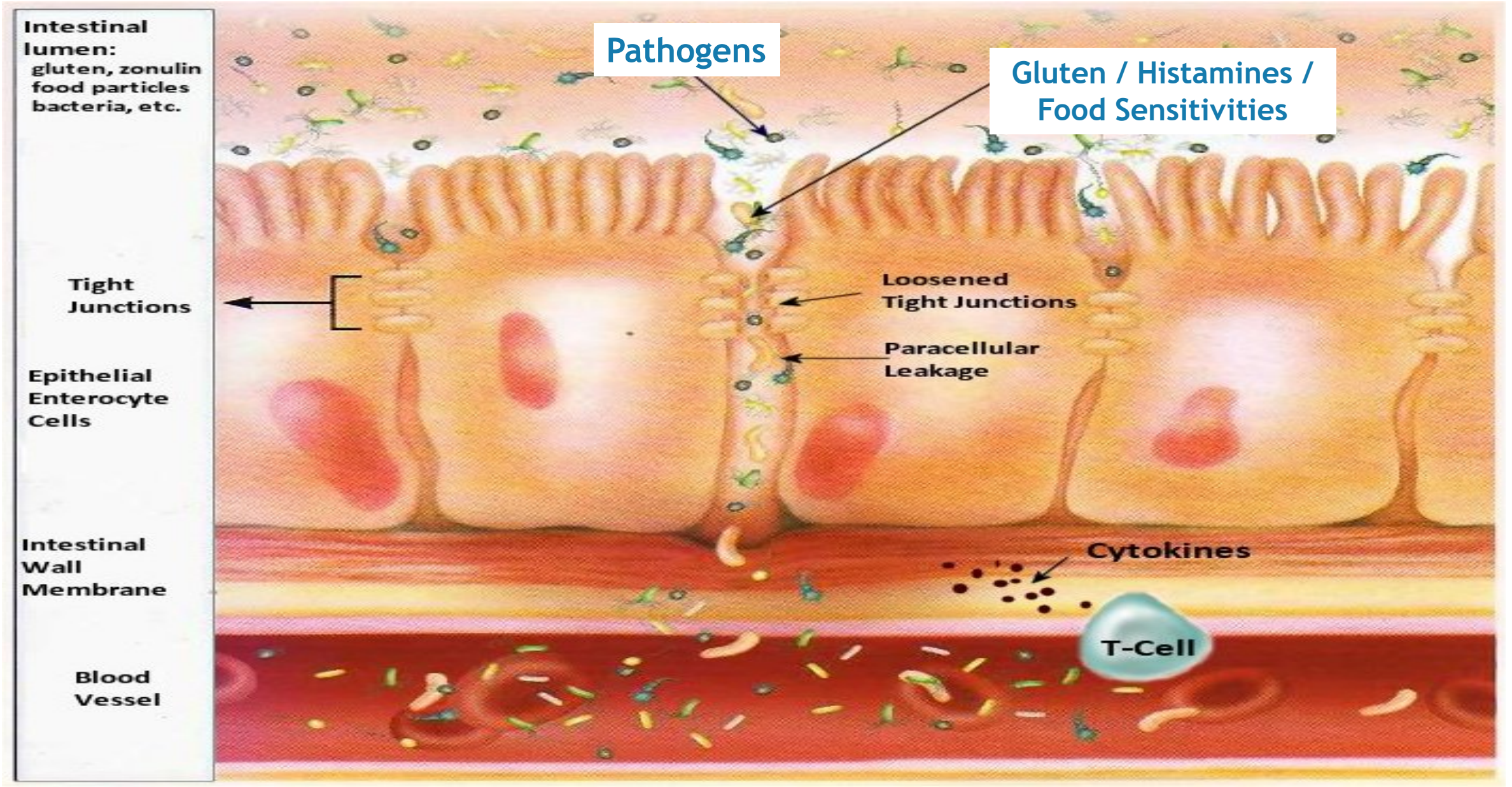
- ***FUT2 (Fucosyl Transferase 2) - Hetero / Homo significance***
  - Functions to provide fucosyl sugars to intestinal lining for promotion of probiotic growth
  - Secretor vs. Non-secretor
  - Homo = Non-secretor Hetero = Partial Secretor

Immune Inflammatory Gastrointestinal SNPs

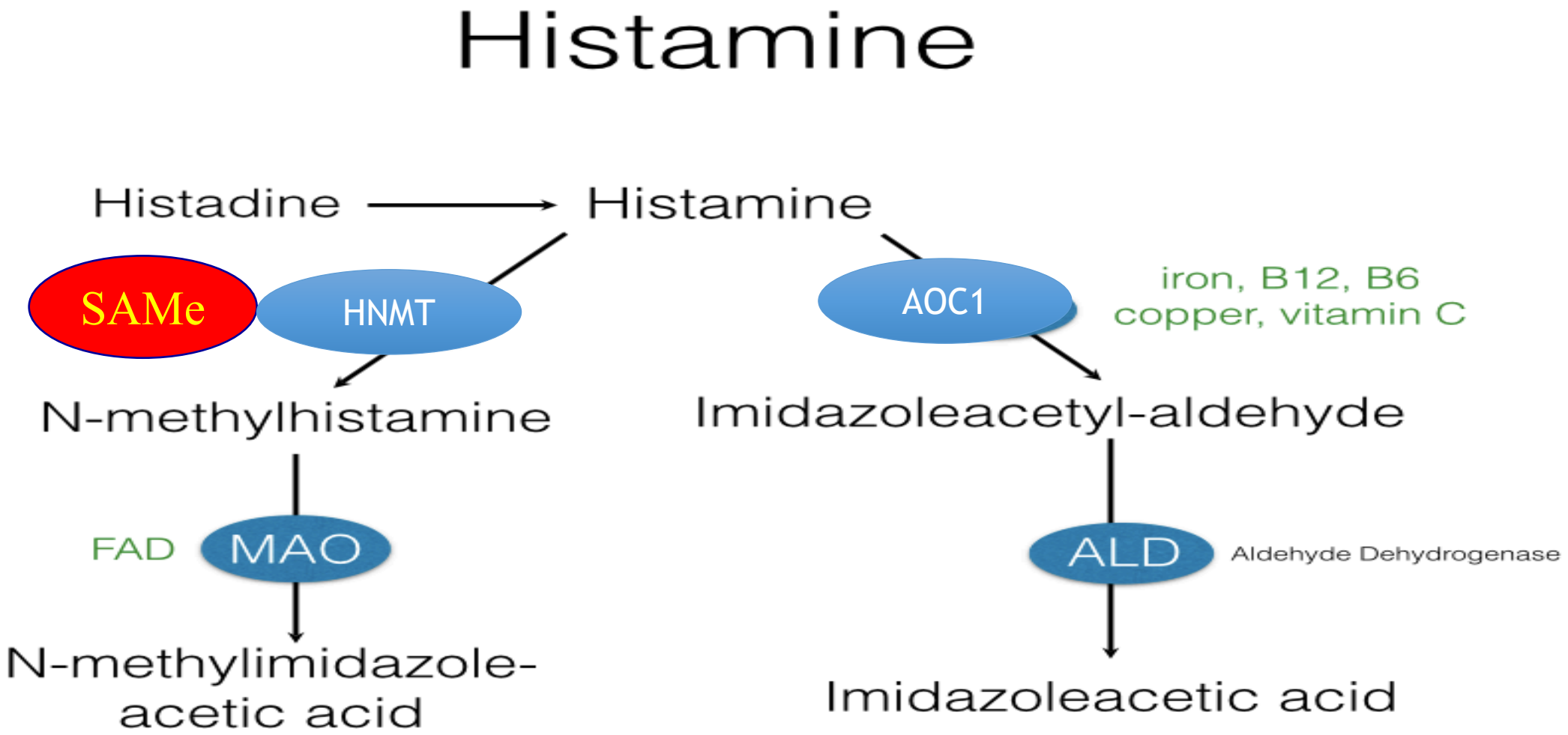
- ***HLA DQA1 / DQA2***
  - Homo or Both Hetero
  - Polymorphism creates higher risk of severe antigenicity to gluten
  - Also associated with higher risk of gluten and casein sensitivity

- ***HLA DRB1 / DRB2***
  - Homo significance
  - Polymorphism creates higher risk of mold sensitivity and explosive IgE response
  - More severe inflammation from yeast overgrowth
  - Essential to improve microbiome

The "Leaky Gut"



AOC1 and HNMT Polymorphisms



Inflammation External
AOC1 and HMNT

Genes and Treatment Indication:

- **AOC1 polymorphism (formerly DAO Gene)**
- **HMNT polymorphism**
- **Histamine food response**

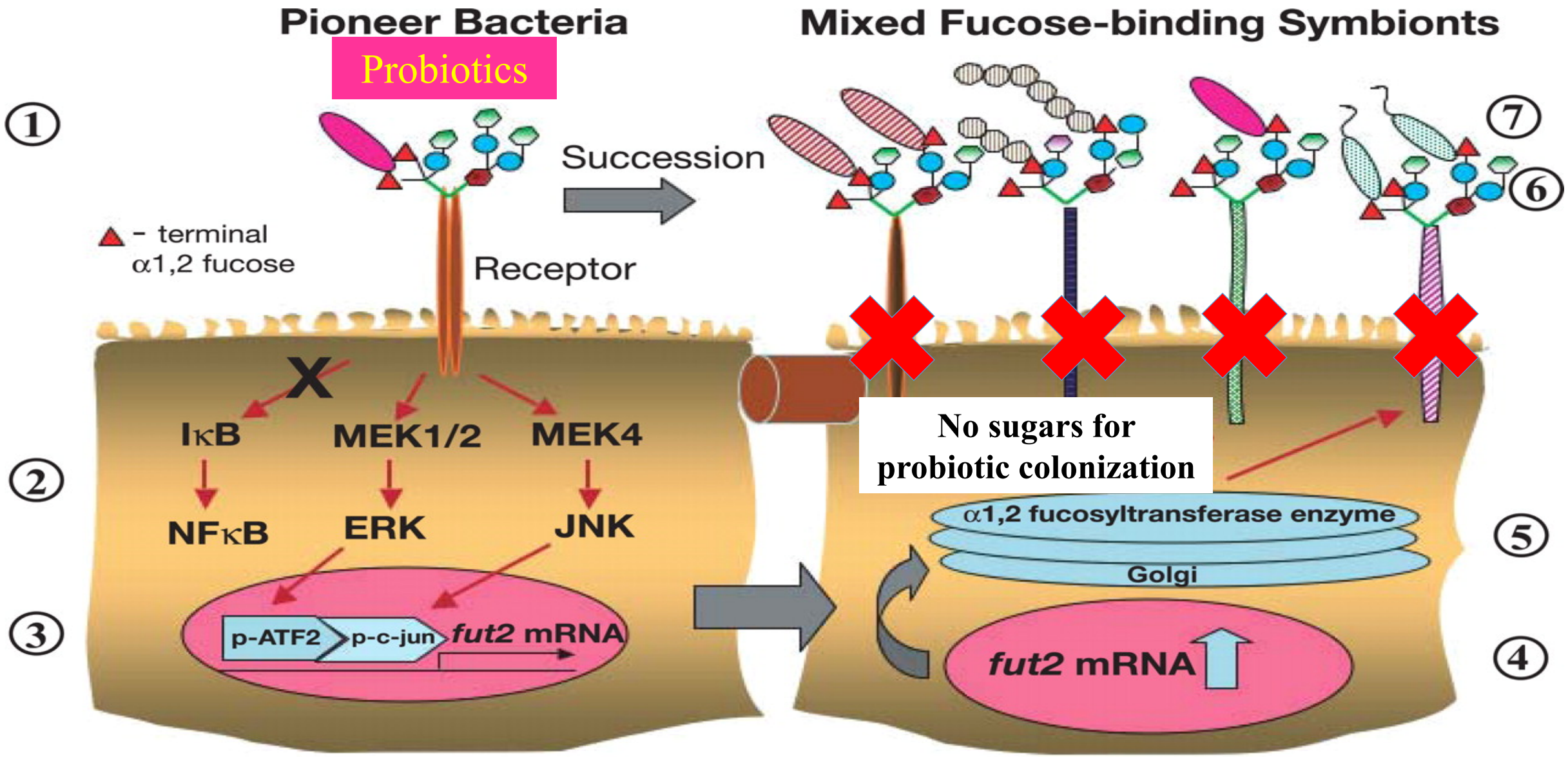
Objective:

Provide histamine enzymes to assist with histamine breakdown

Strategy:

- **Diamine Oxidase (Porcine kidney)**
- **NAC**
- **Vitamin C**
- **ALA**
- **Stinging Nettle**
- **Bromelain**
- **Avoid Histamine Foods if Homozygous on Either SNP**

FUT2 (Fucosyltransferase 2) Polymorphism



Inflammation External
FUT2

Gene and Treatment Indication:

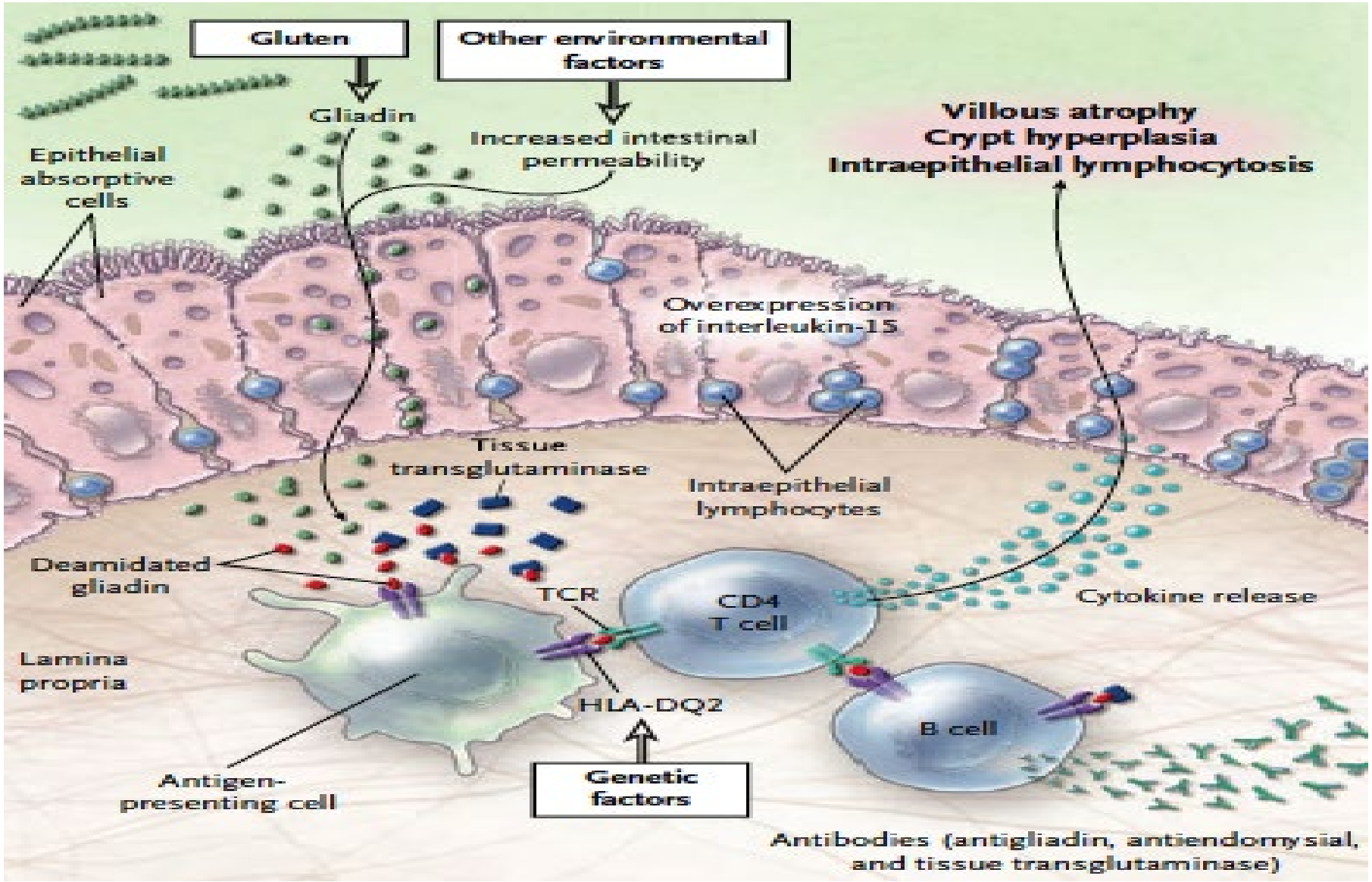
- ***FUT2* polymorphism**
- **Immune Weakness**
- **Post Antibiotics**
- **+/+ is “non-secretor”**
- **+/- is “partial secretor”**

Objective: Provide broad spectrum probiotics for beta glucan production and dysbiosis control

Strategy:

- **Prebiotics and Broad Spectrum Probiotics**

HLA DQA1 and DQA2
Celiac Potential



Inflammation External
HLA-DQA

Gene and Treatment Indication:

- ***Homo HLA DQA1 / DQA2***
- **Gluten Sensitivity**
- **IBS**
- **Food Sensitivities**

Objective: Assist in digestions of complex proteins that can cause inflammation

Strategy:

- **Broad based digestive enzymes**
- **Chews or capsules**
- **Gluten Avoidance if Homozygous**

Inflammation External
HLA-DRB

Gene:

- *Homo HLA DRB mutation*

Associated Syndromes:

- "Sick House Syndrome"
- "CPAP Syndrome"
- Explosive Mold Sensitivity

Strategy:

- **Mold Avoidance**
- **Down Regulation of Immune Cells (CBD, LDN, PEA)**

Biochemistry Review

Autophagy Consideration

Specific Autophagy Deficient Syndromes

- Alzheimer's
- Dementia
- Parkinson's
- Multiple Sclerosis
- Amyotrophic Lateral Sclerosis
- Huntington's Chorea
- Benign Essential Tremor
- Inflammatory Bowel Disease
- Diabetes Type 2
- Macular Degeneration
- Hearing Loss
- Auto-Immune Disease
  - Lupus
  - Sjogren's
  - Rheumatoid
- Most Cancers
- Autism / Developmental Delay

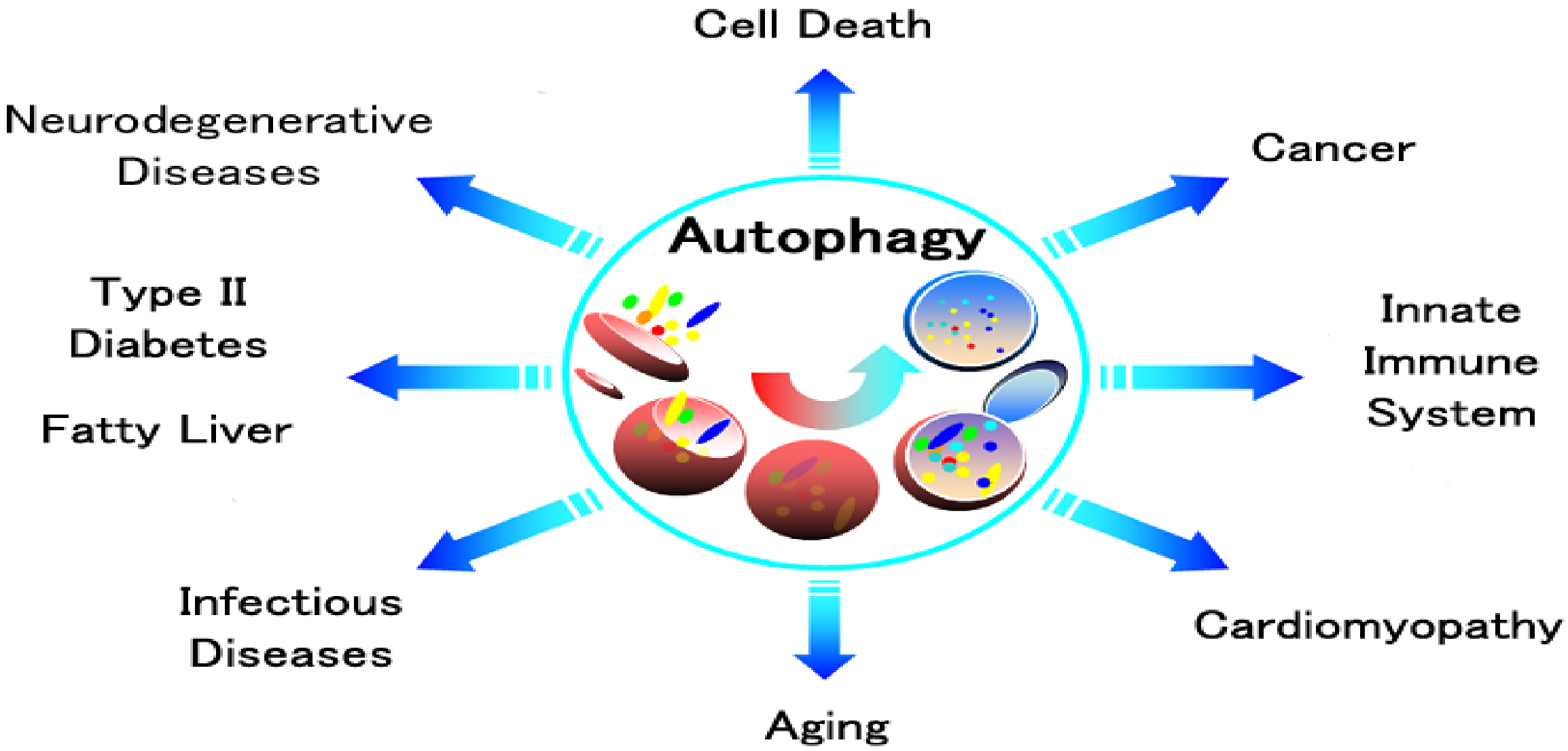
What is Autophagy?

Autophagy is the natural, intracellular degradation mechanism that disassembles unnecessary or dysfunctional components (garbage) from the cell cytoplasm. Autophagy performs the orderly clearance and recycling of cellular components.

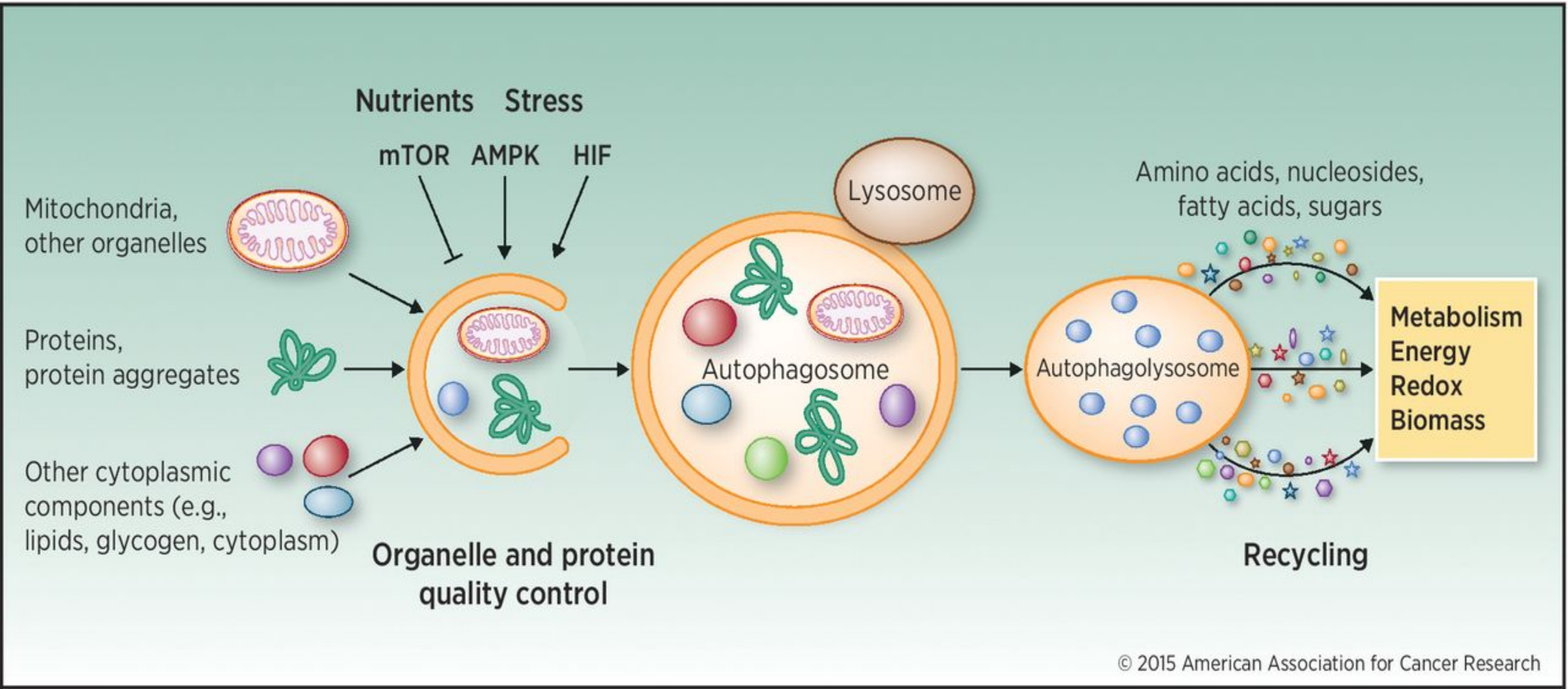
Mechanisms of Autophagy led to the award of the 2016 Nobel Prize in Physiology and Medicine to Japanese autophagy researcher Yoshinori Ohsumi.

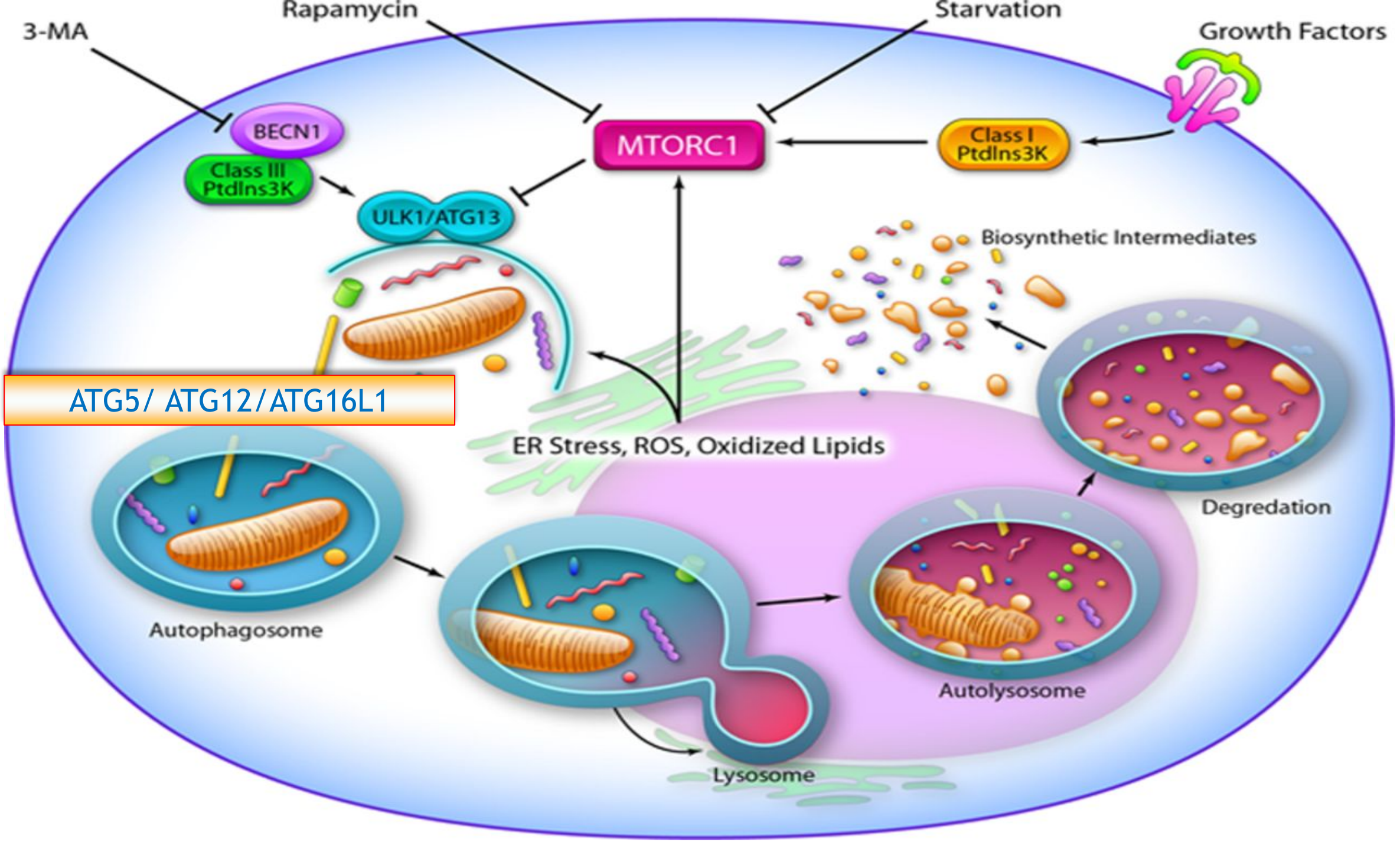
Autophagy has it's most profound effects on high energy cells (ie nervous system, immune system and endocrine system).

Pathological and Physiological Functions of Autophagy

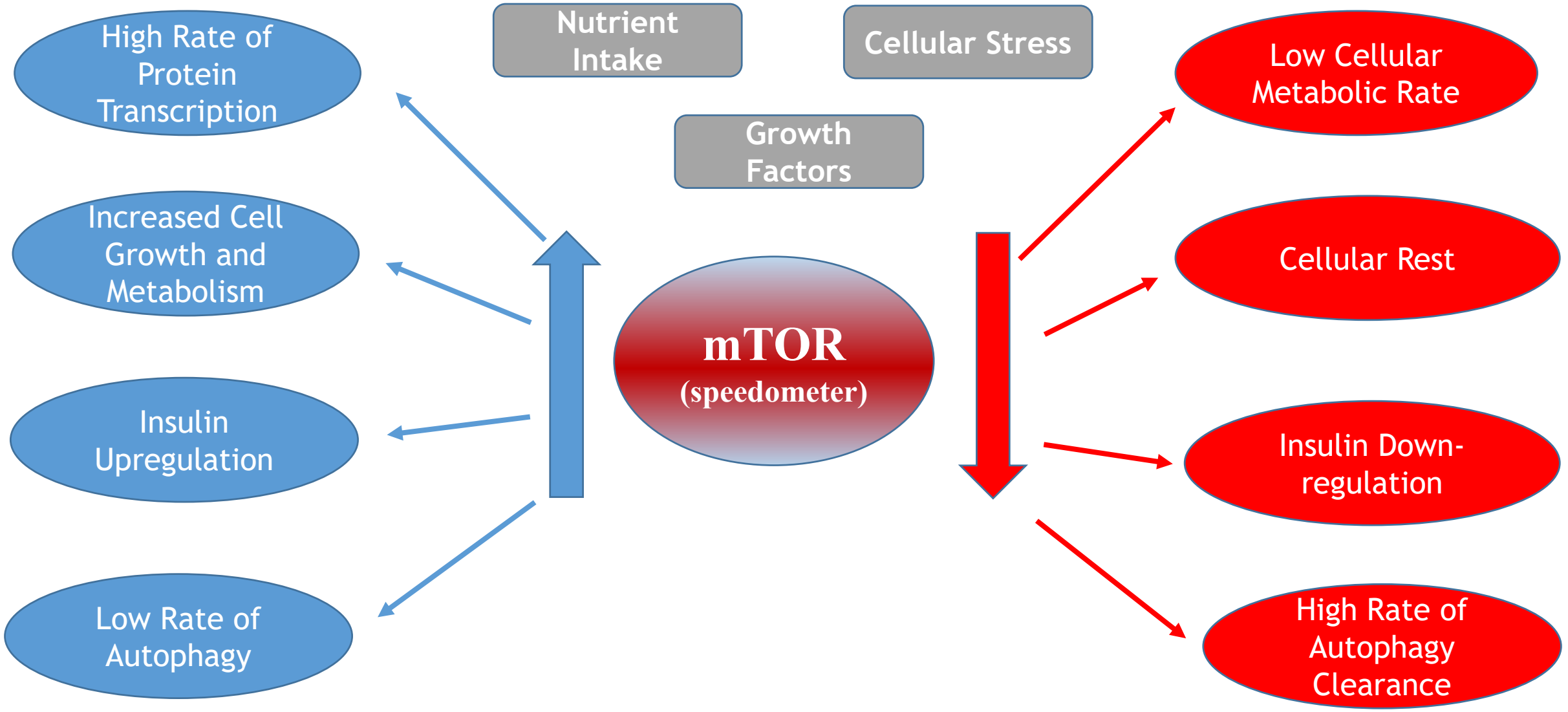


Autophagy Recycles Intracellular Garbage

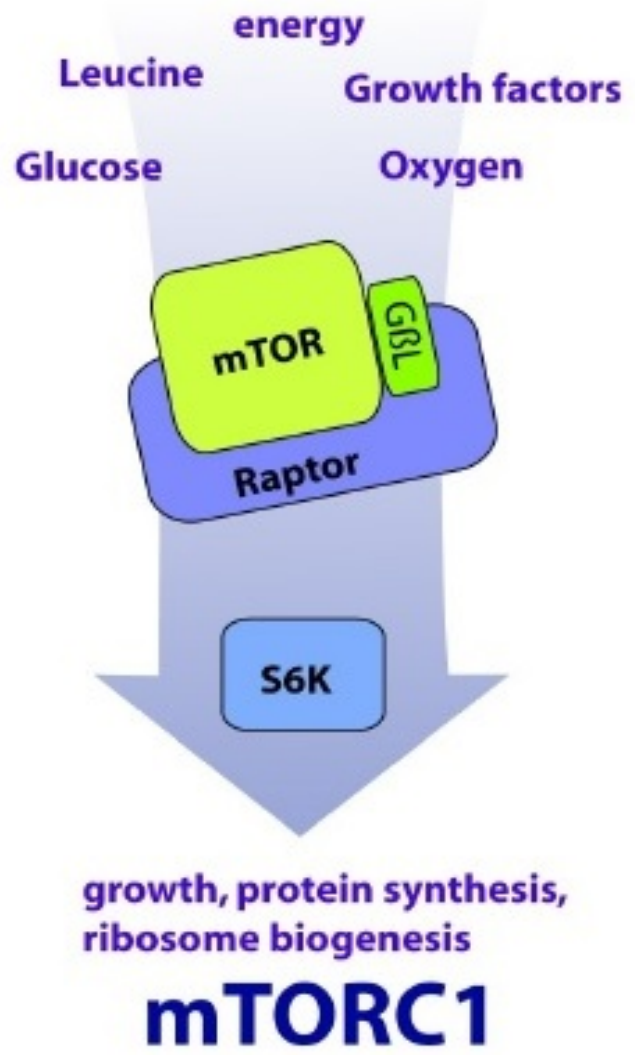


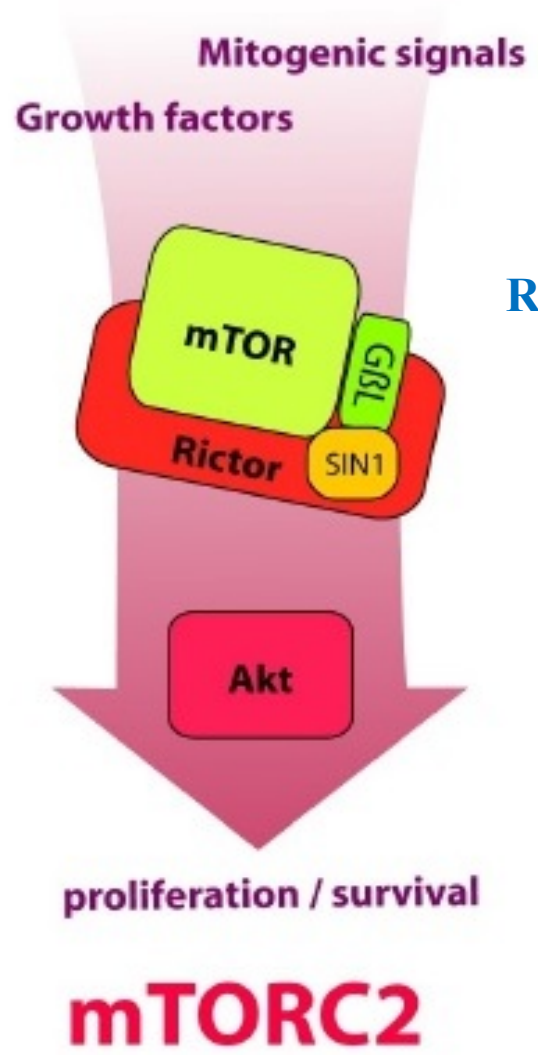

3-MA
Rapamycin
Starvation
Growth Factors
BECN1
Class III PtdIns3K
MTORC1
Class I PtdIns3K
ULK1/ATG13
Biosynthetic Intermediates
ATG5/ ATG12/ATG16L1
ER Stress, ROS, Oxidized Lipids
Degredation
Autophagosome
Autolysosome
Lysosome

mTOR (Mechanistic Target of Rapamycin)



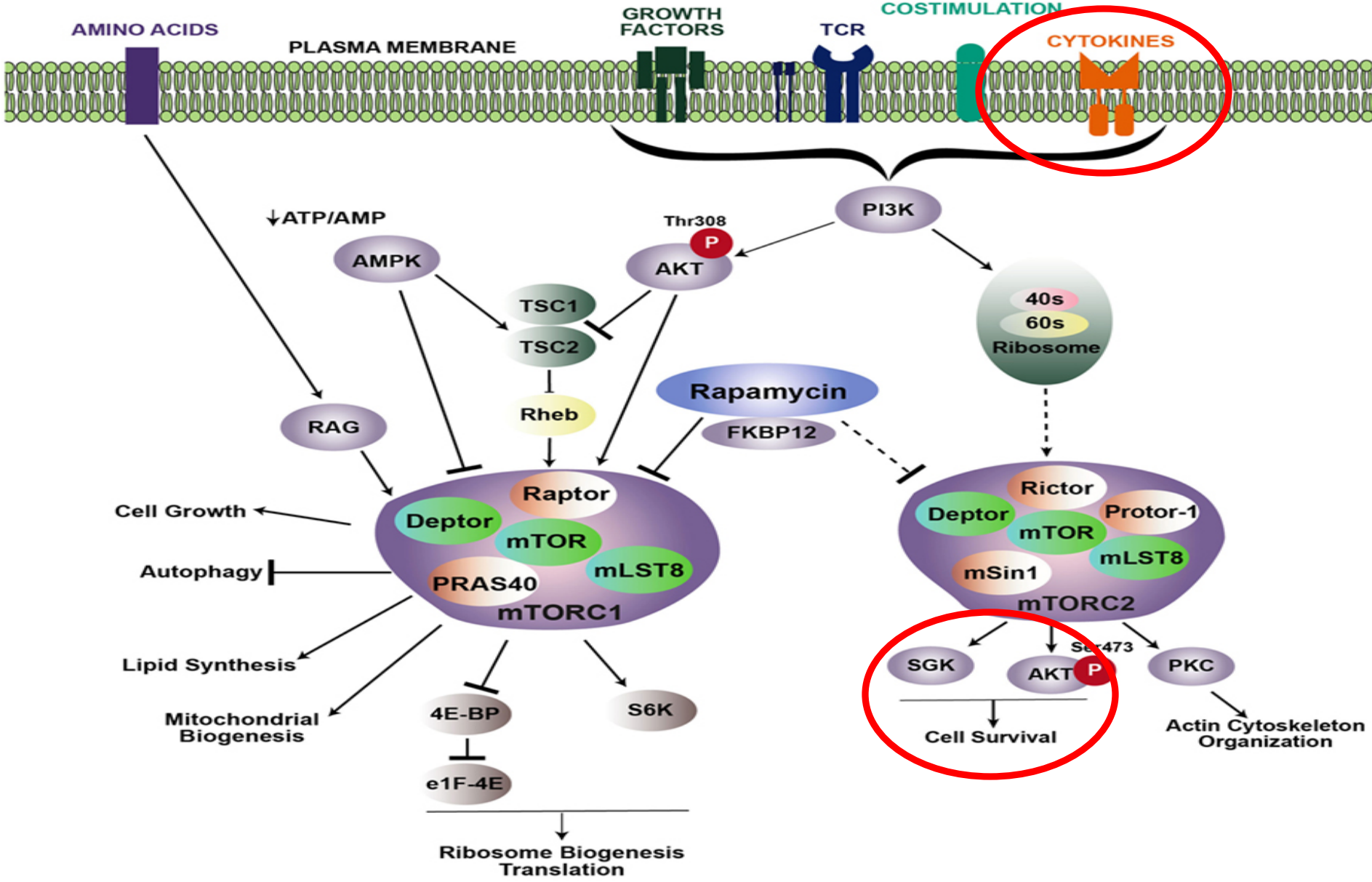
mTOR functions in two distinct complexes and pathways





Rictor Pathway Overactivation is common in Pathogenesis

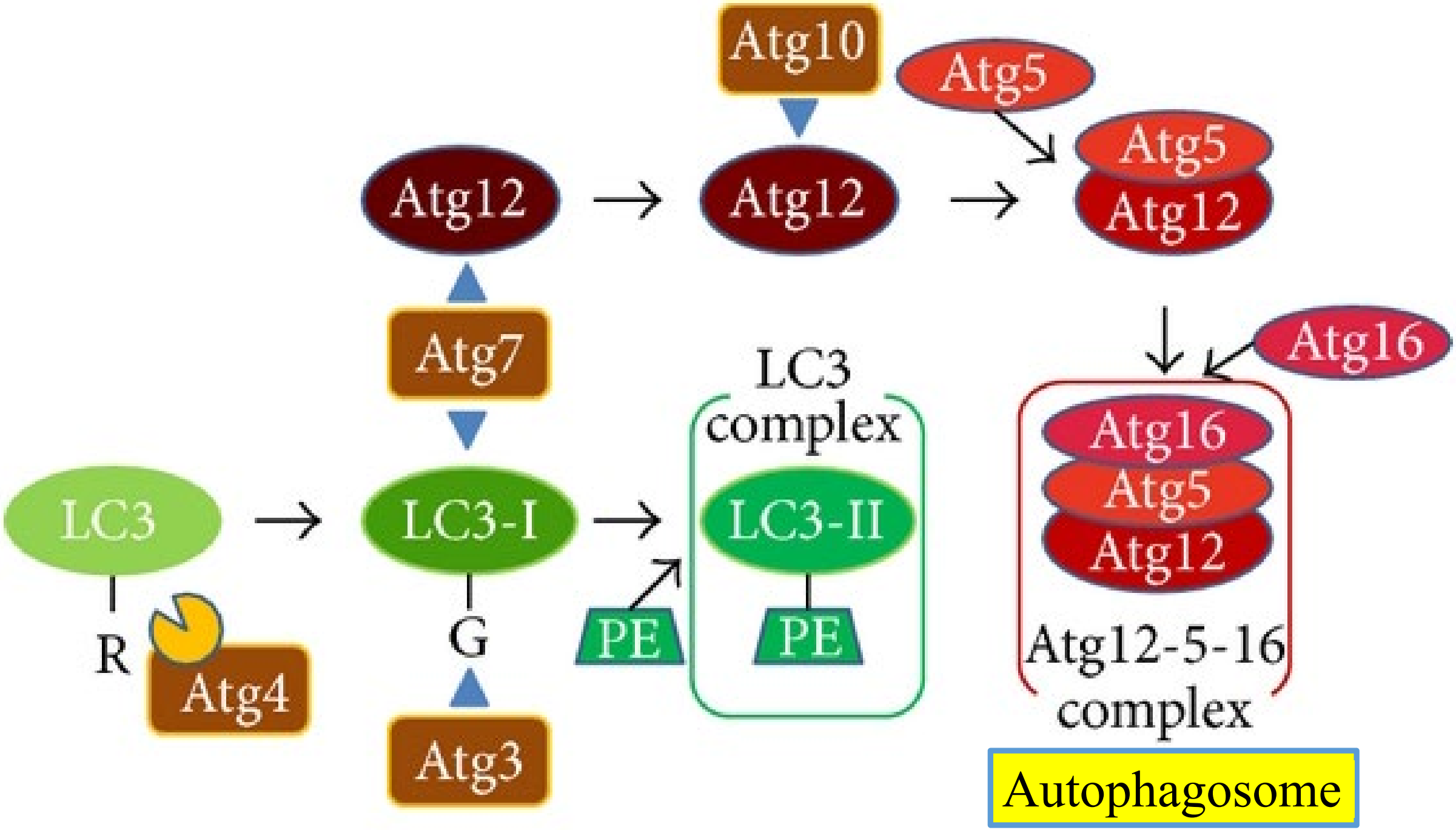
mTOR Rictor is Activated in Cell Survival



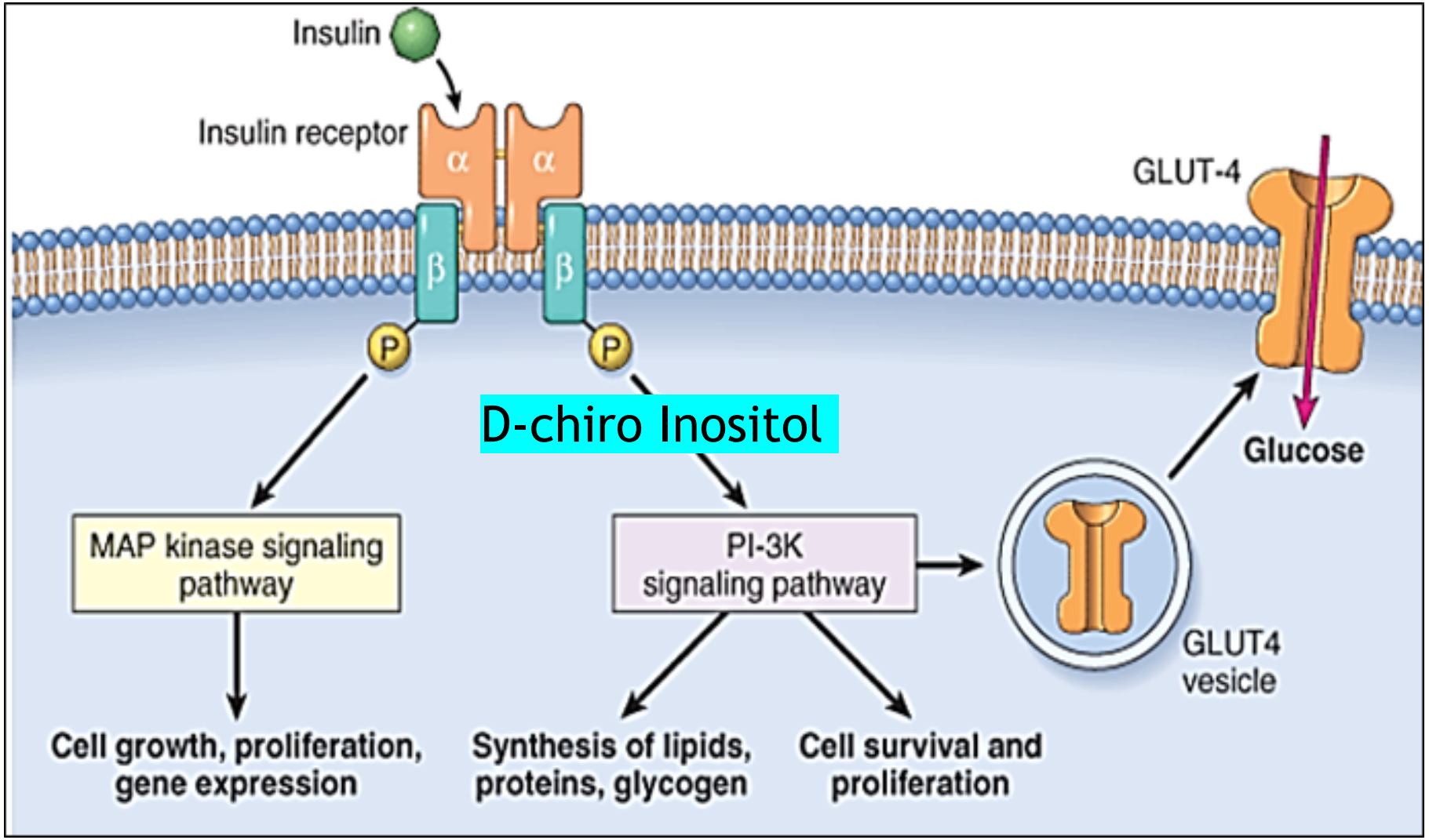
Autophagy Related Polymorphisms

- ***ATG5 / ATG12 / ATG16L1 (MAF: .39)***
  - Hetero / Homo significance
  - These three genes code for protein complex that forms wall of autophagosome
  - Highly correlated with:
    - Type 2 Diabetes
    - Insulin Resistance
    - PCOS
    - Fatty Liver Disease
    - Neurological Disease
    - Autoimmune Disease
    - Hearing Loss
    - Ophthalmic Disorders

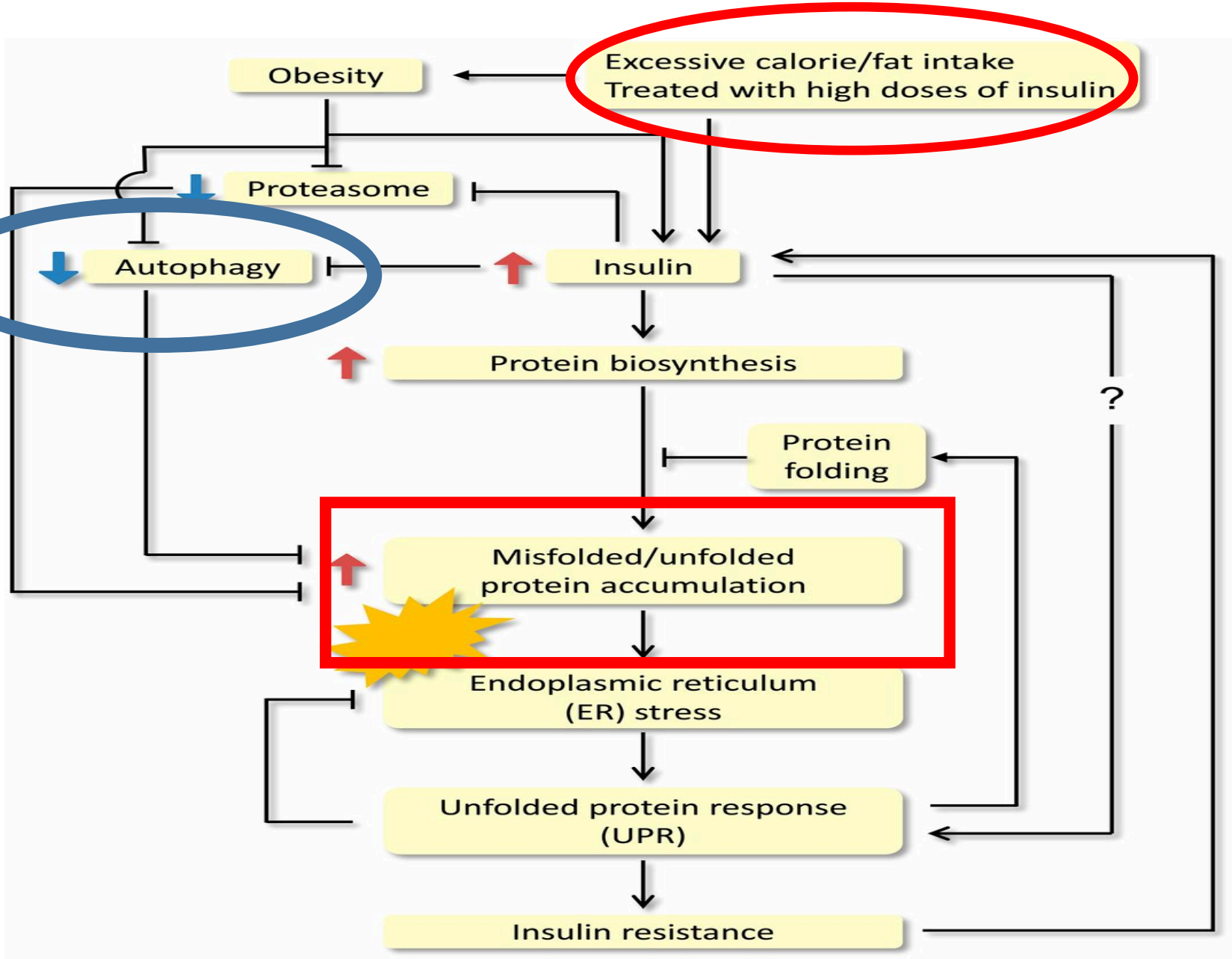
- ***NOD2 / CARD15 (Nucleotide Oligomerization Domain Protein 2) (MAF: .09)***
  - Hetero / Homo significance
  - Associated with lower ability to clear bacterial antigens


Atg10
Atg5
Atg12
Atg12
Atg5
Atg12
Atg7
Atg16
LC3
complex
LC3
LC3-I
LC3-II
Atg16
Atg5
Atg12
R
G
PE
PE
Atg4
Atg3
Atg12-5-16
complex
Autophagosome

Autophagy Weakness Interrupts Cellular Glucose Delivery
D-chiro Inositol and Insulin



Autophagy and Insulin Resistance Vicious Cycle



Treatment of Autophagy Deficiencies

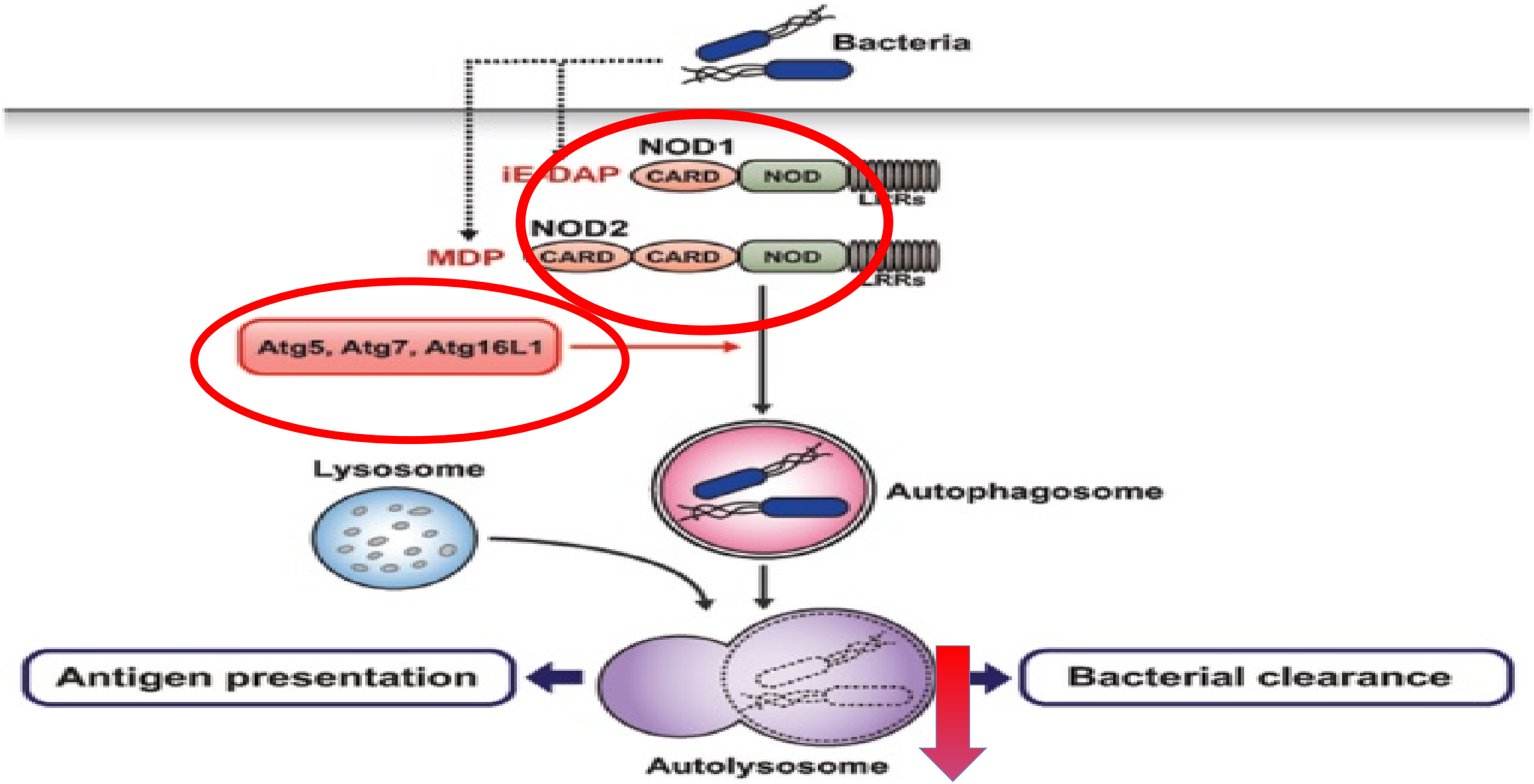
- Caloric Restriction (12-15 hour fast), Limit Protein intake to 70 gm/day
- Energy Depletion (Exercise)
- High Dose Antioxidants (IV Vitamin C) and High Dose Glutathione
- Medications:
  - Rapamycin (mTOR Inhibitor)
  - Growth Hormones
- Supplements:
  - D-Chiro Inositol (600mg bid)
  - Resveratrol
  - Curcumin
  - Catechins
  - Piper Nigrum
  - Lithium Orotate

Autophagy Related Polymorphisms

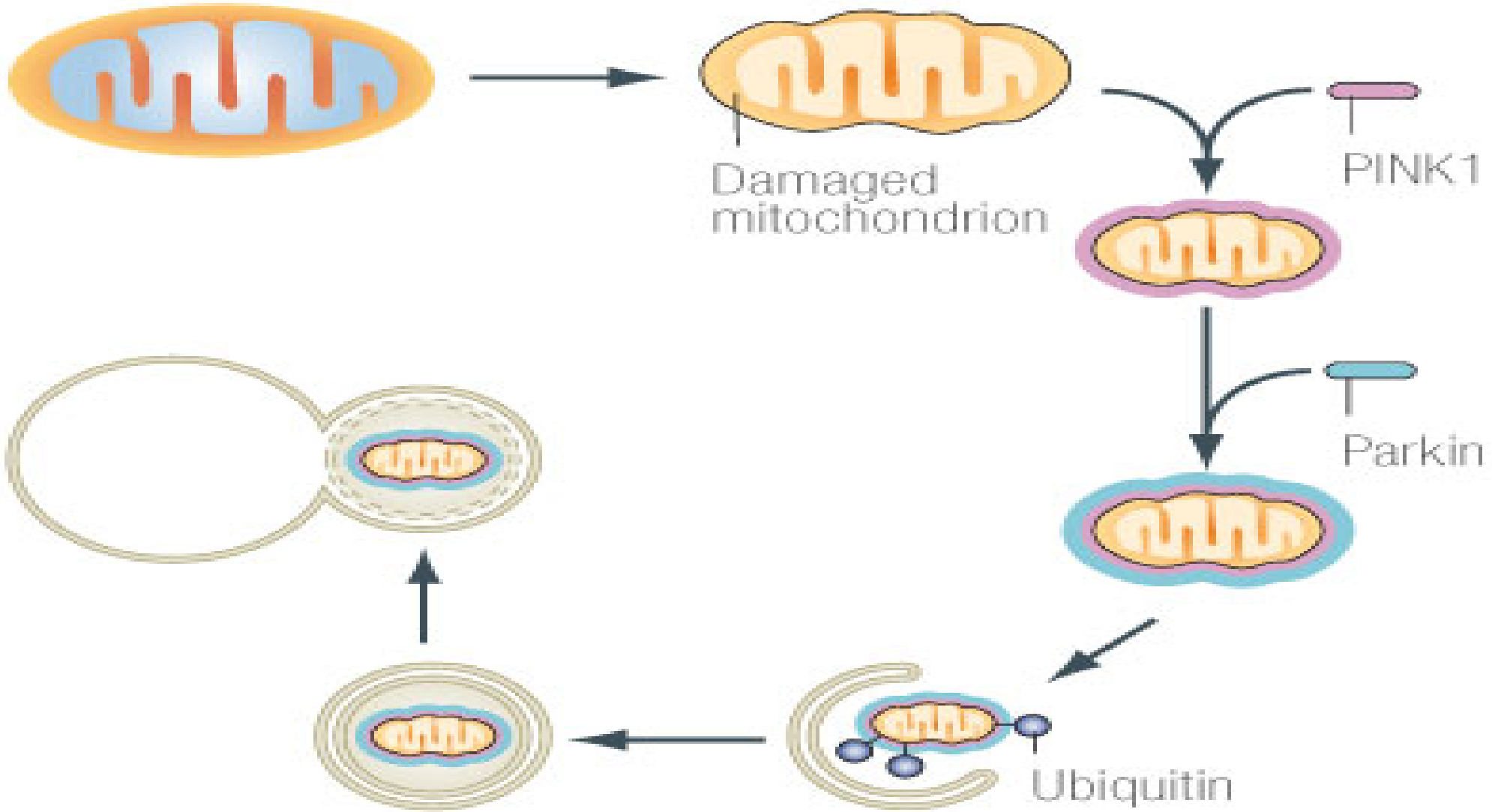
- ***PARK2 (parkin)***
  - Homo significance
  - PARK2 – Autosomal Recessive Ubiquitin Ligase - Early onset of Parkinsonism - Slow Progression

- ***APOE (Apo-lipoprotein E) – Hetero / Homo significance***
  - Intermediate Density Lipoprotein - Principle cholesterol carrier for the Brain
  - 3 Polymorphisms E2 / E3 / E4
  - E4 being the polymorphism correlated with Alzheimer's, Atherosclerosis, Post Concussion Syndrome and Macular Degeneration

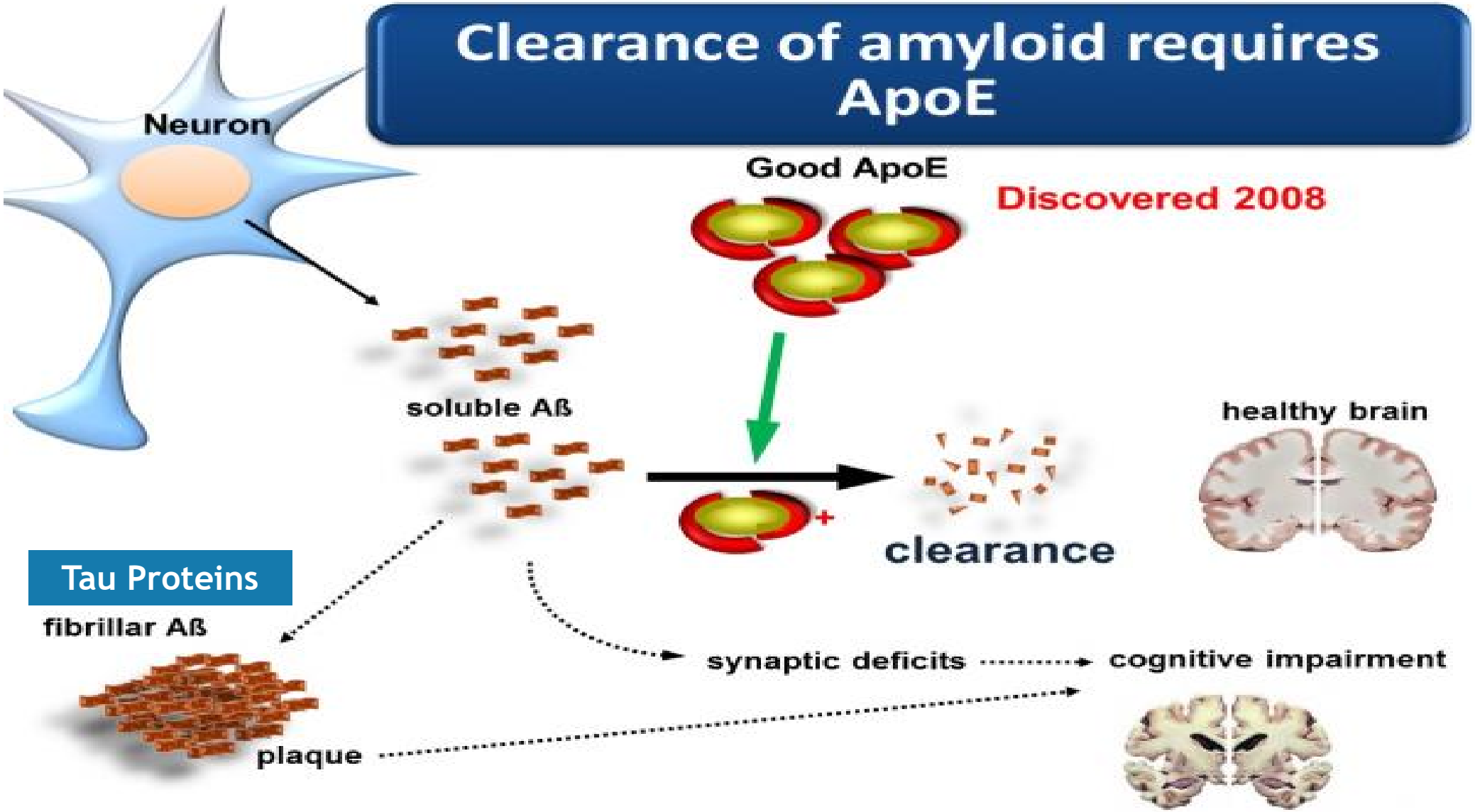
NOD/CARD /ATG5 / ATG16L1 and the Microbiome



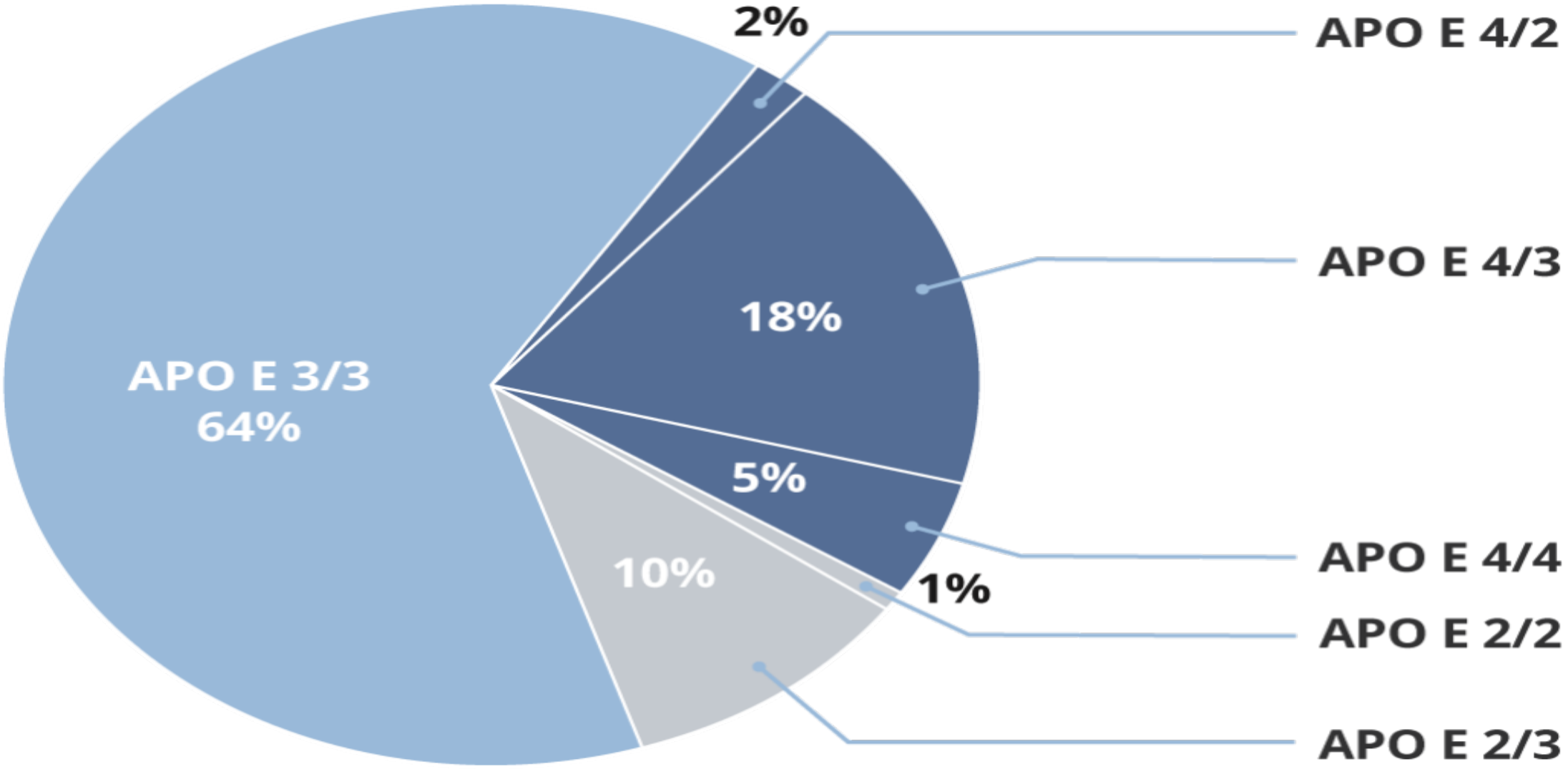
PARK2 (Parkin) / PARK6 (PINK1)



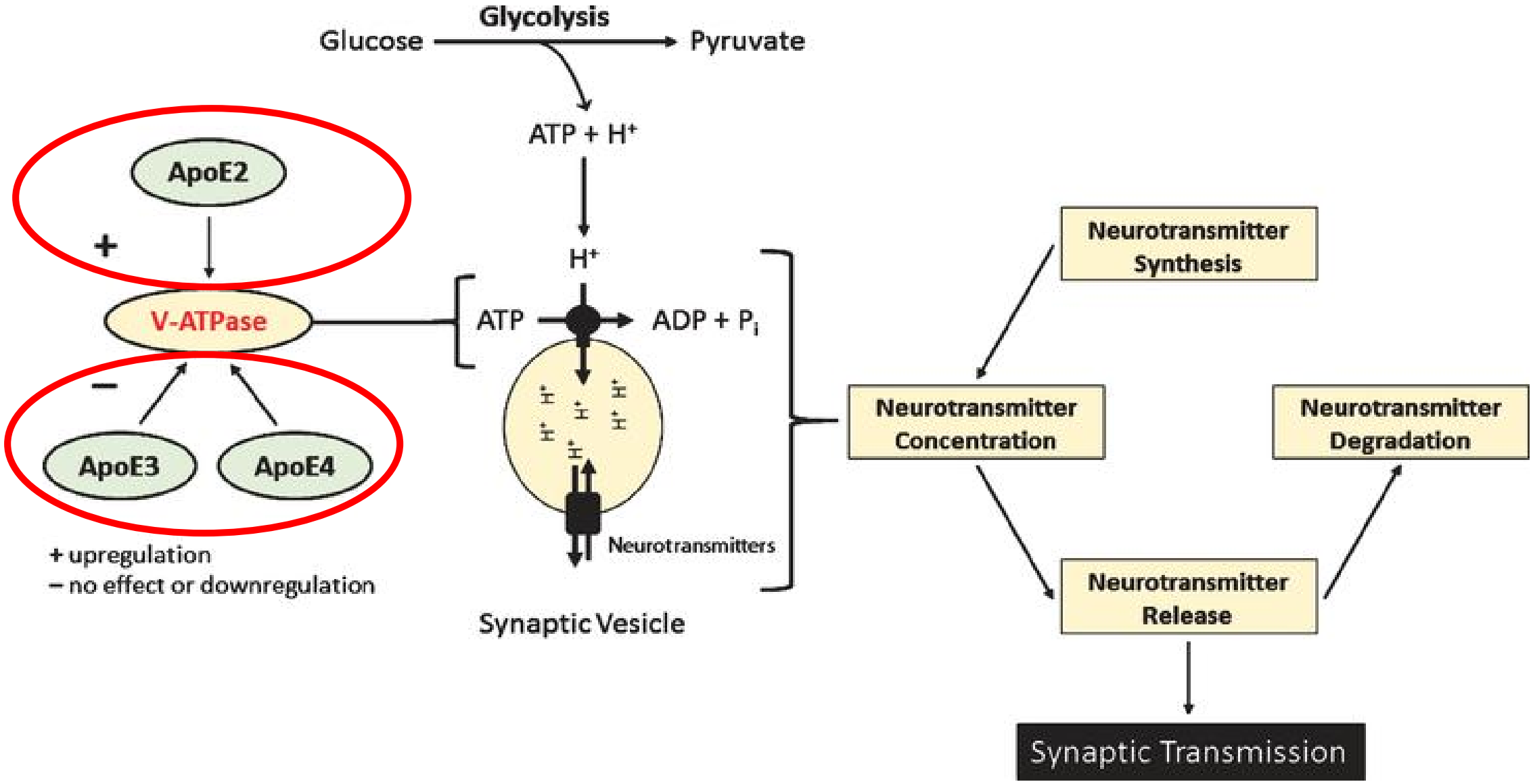
APOE (Apolipoprotein E)



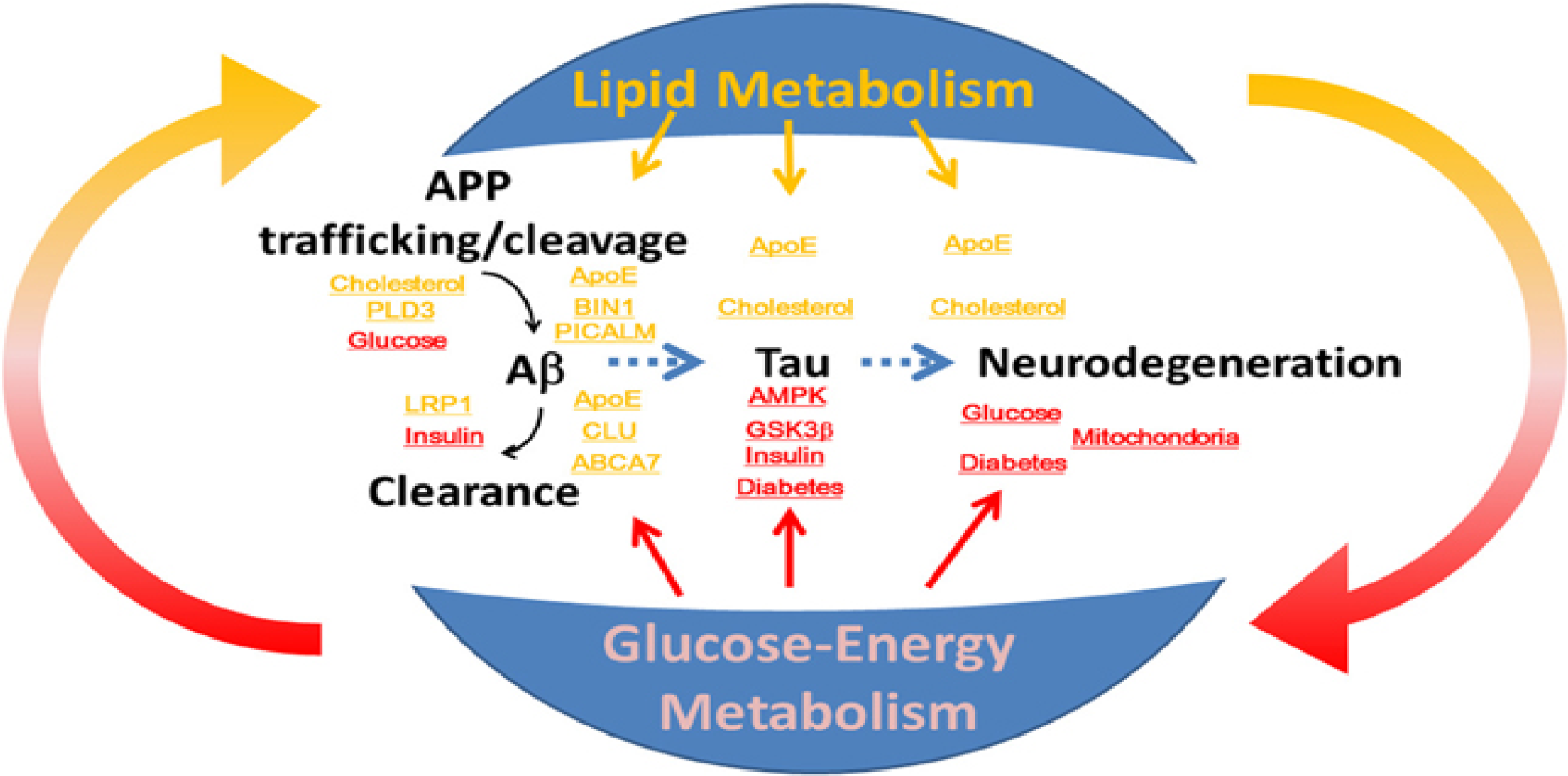
APOE Distribution



APOE Variant and Neurotransmission



Autophagy and APOE



APOE Genetic Interpretation

SNP, rs#	rs429358
"-" variant	T (85%)
"+" variant	C (15%)

SNP, rs#	rs7412
"-" variant	C (92%)
"+" variant	T (8%)

ApoE Sub-Type				
Apo-ε1/ε1	+/+	(C;C)	+/+	(T;T)
Apo-ε1/ε2	+/-	(C;T)	+/+	(T;T)
Apo-ε1/ε3	+/-	(C;T)	+/-	(C;T)
Apo-ε2/ε4	+/-	(C;T)	+/-	(C;T)
Apo-ε1/ε4	+/+	(C;C)	+/-	(C;T)
Apo-ε2/ε2	-/-	(T;T)	+/+	(T;T)
Apo-ε2/ε3	-/-	(T;T)	+/-	(C;T)
Apo-ε3/ε3	-/-	(T;T)	-/-	(C;C)
Apo-ε3/ε4	+/-	(C;T)	-/-	(C;C)
Apo-ε4/ε4	+/+	(C;C)	-/-	(C;C)

Food for Thought

"He is the best physician who is the most ingenious inspirer of hope."

Samuel Taylor Coolridge

Nutrigenomic Guided Precision Supplementation for Maximizing Health and Recovery

Part 2

Kendal Stewart, MD

Neurotology / Skull Base Surgery
Neuro-Immune Specialist
Chairman and CMO
Neuro-Sensory Center of Austin
GX Sciences

Biochemistry Review

Methylation

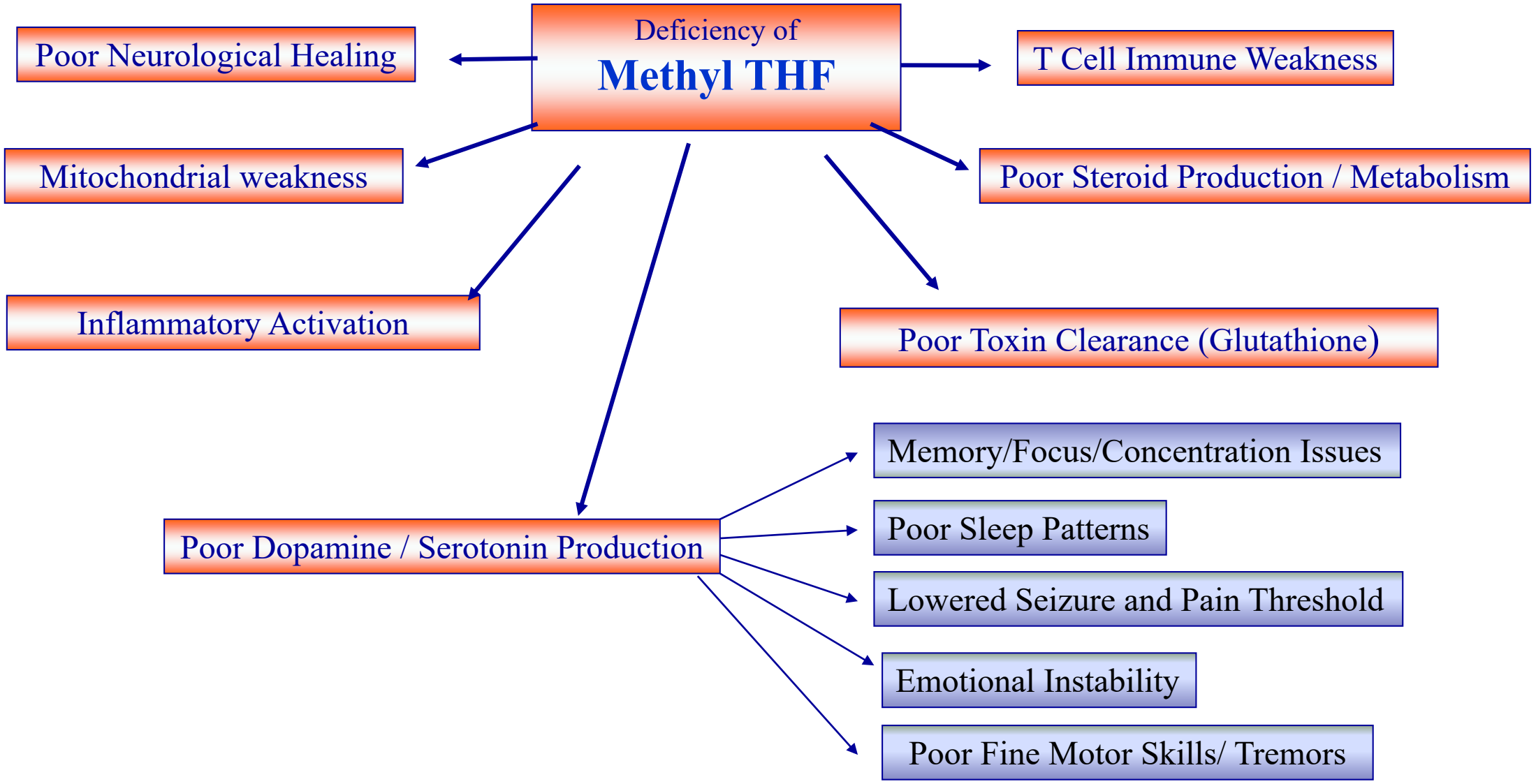
Why should we care about Methylation?

- *Methylation* involves the addition of a “methyl” chemical group to a substrate
- Used in over 250 biochemical processes in the body
- Methylation utilized in major functions of:

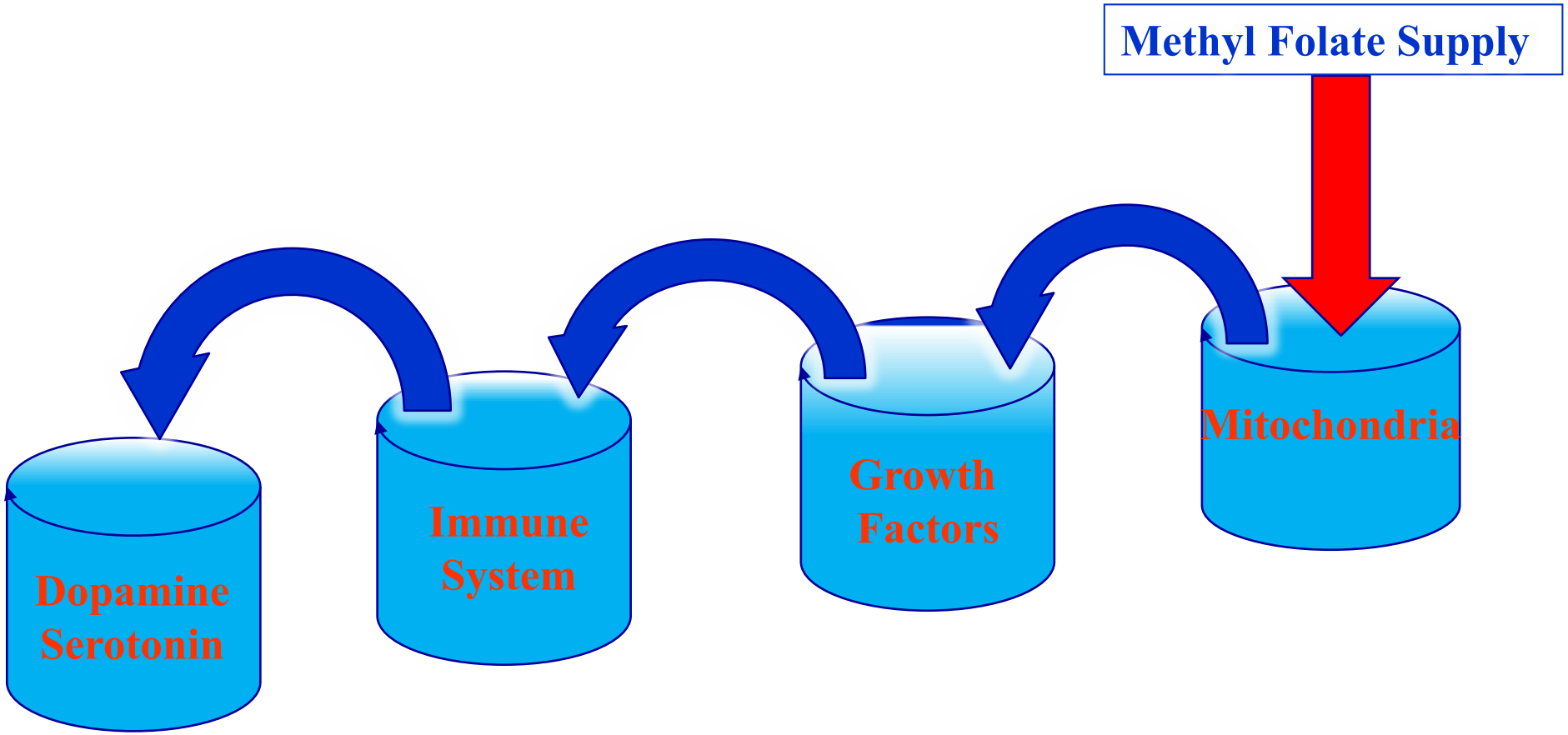
  - **Neurotransmitter production**
  - **Cell turnover and repair**
  - **Membrane function**
  - **Energy (mitochondrial) function**
  - **Immune Function**

- Therefore, problems with methylation will affect the cellular delivery, epigenetics and intra-cellular functionality of almost all cells

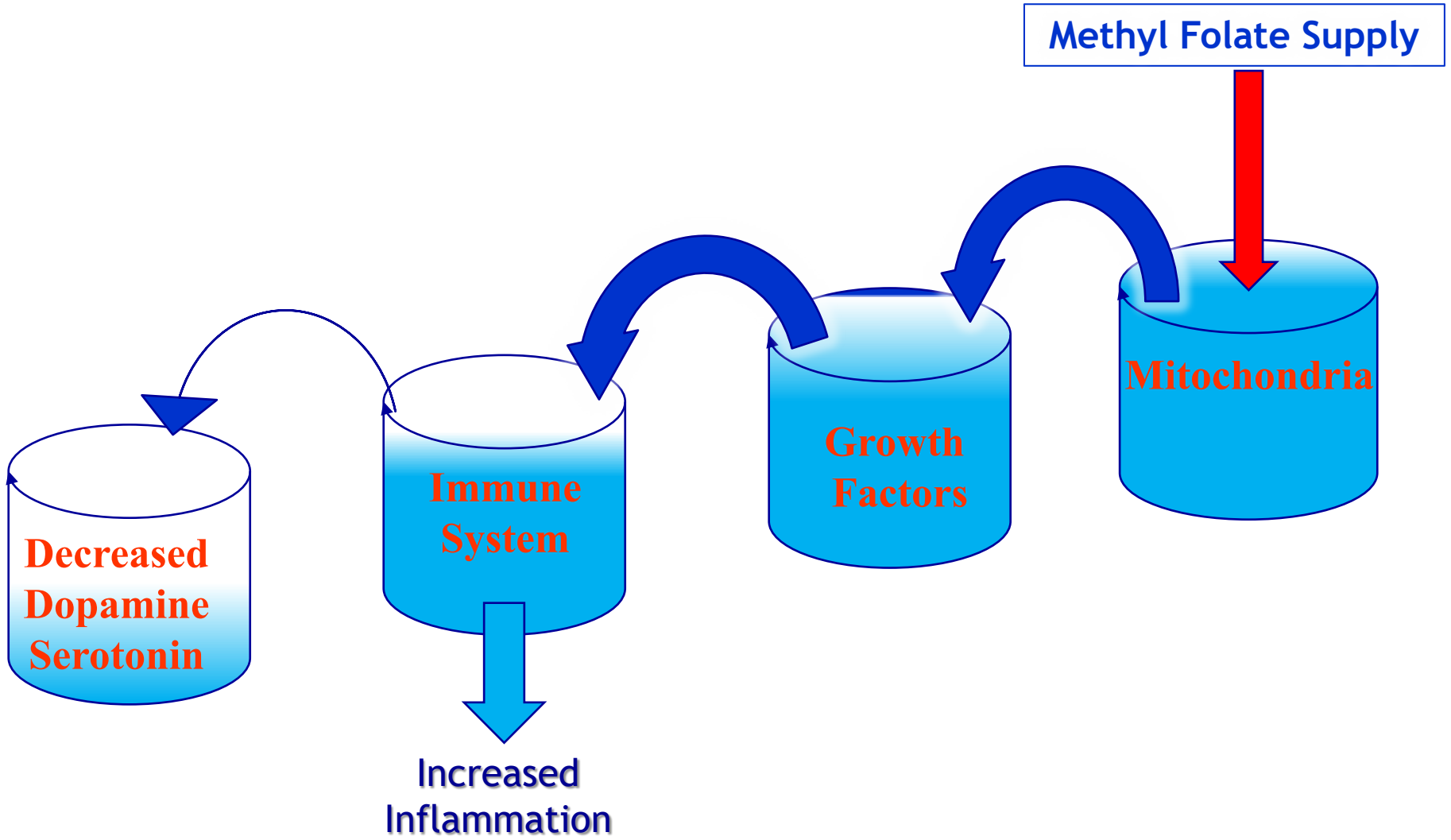
Biochemical Overview Methyl Folate Deficiency



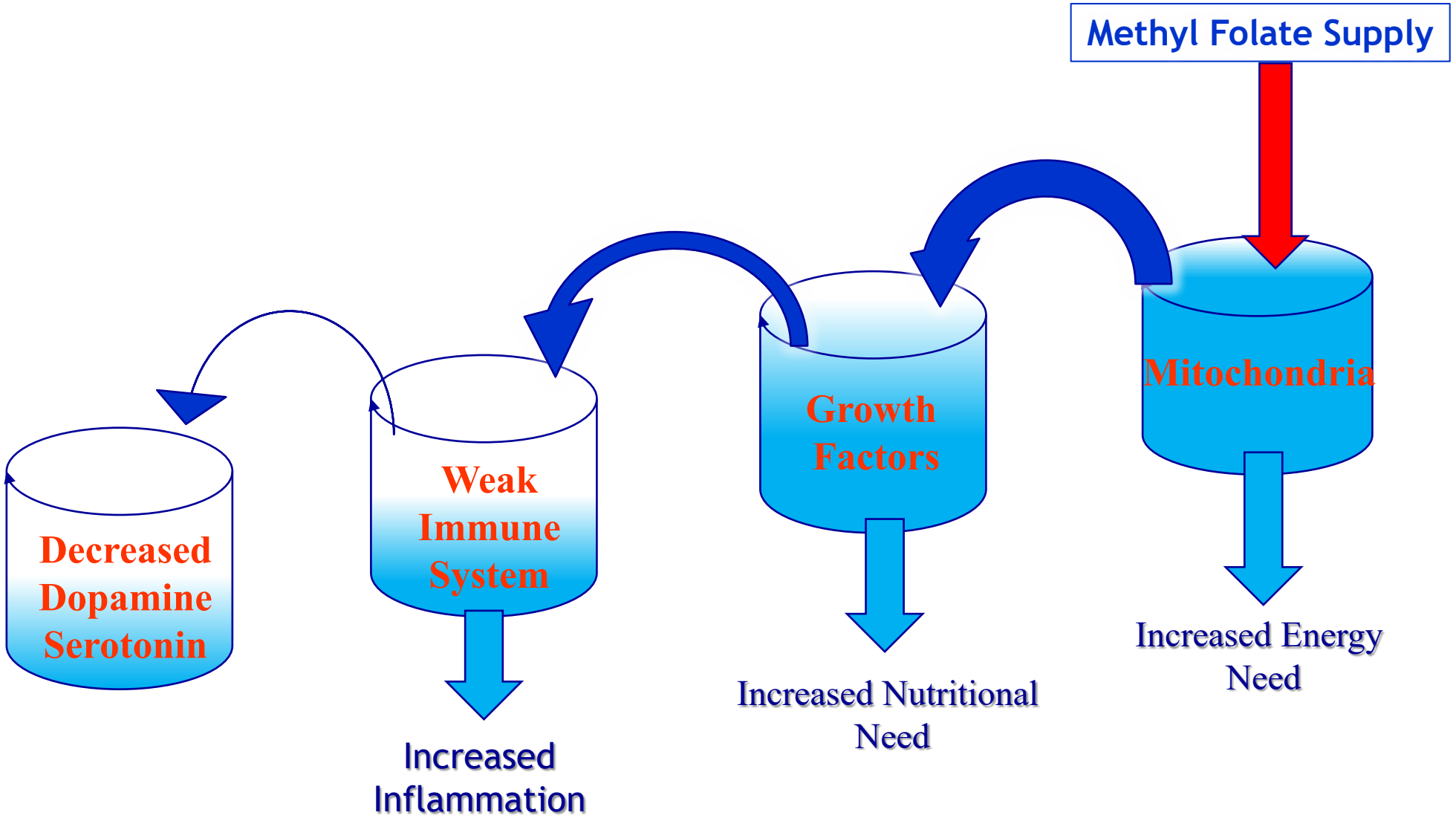
Simplified “Bucket” Theory
Proper Methylation



Immune Challenge Bucket Theory
Methylation Deficiency and Oxidative Challenge

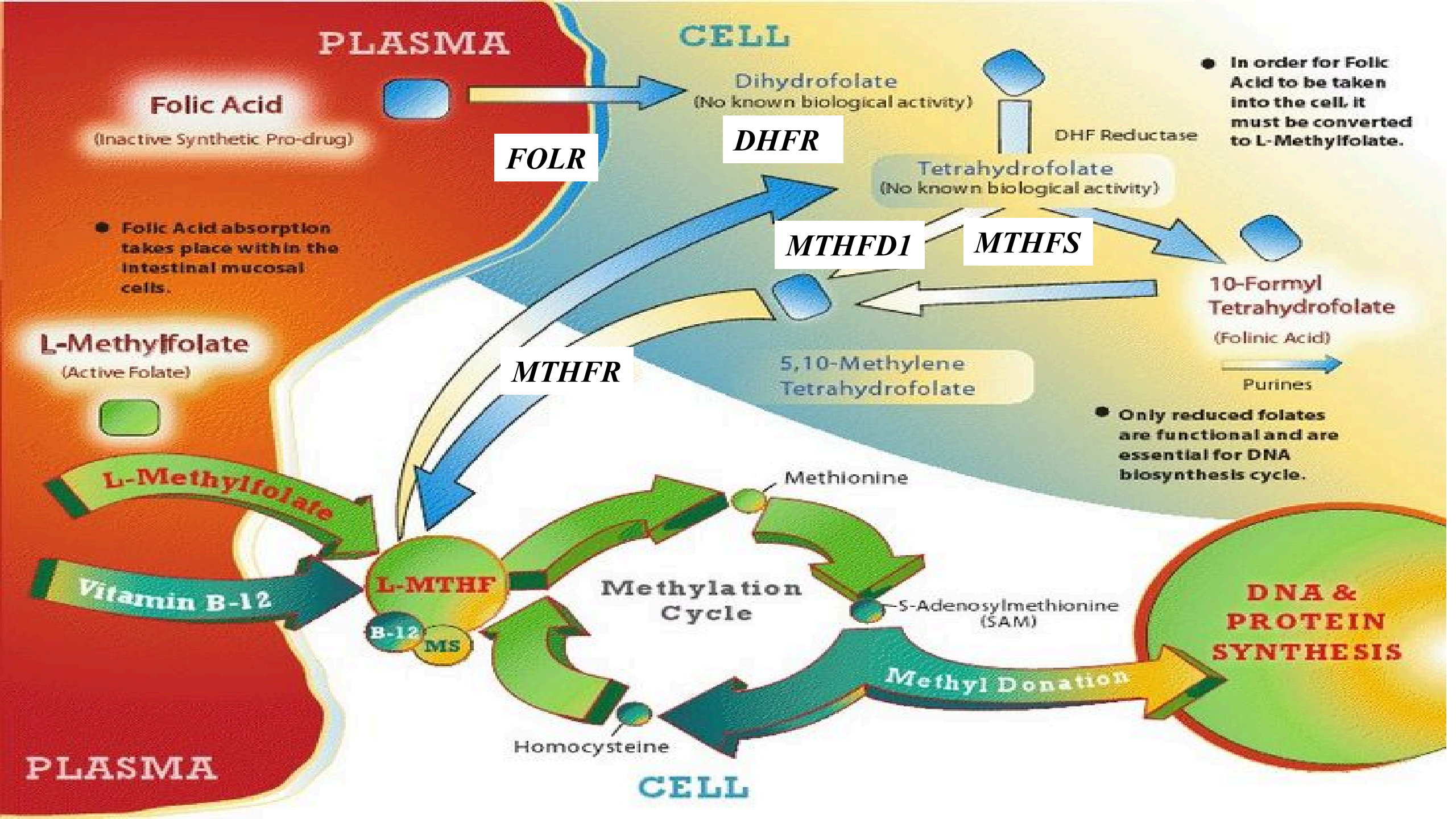


Healing Crisis / Chronic Inflammation Bucket Theory
Healing and Methylation Deficiency

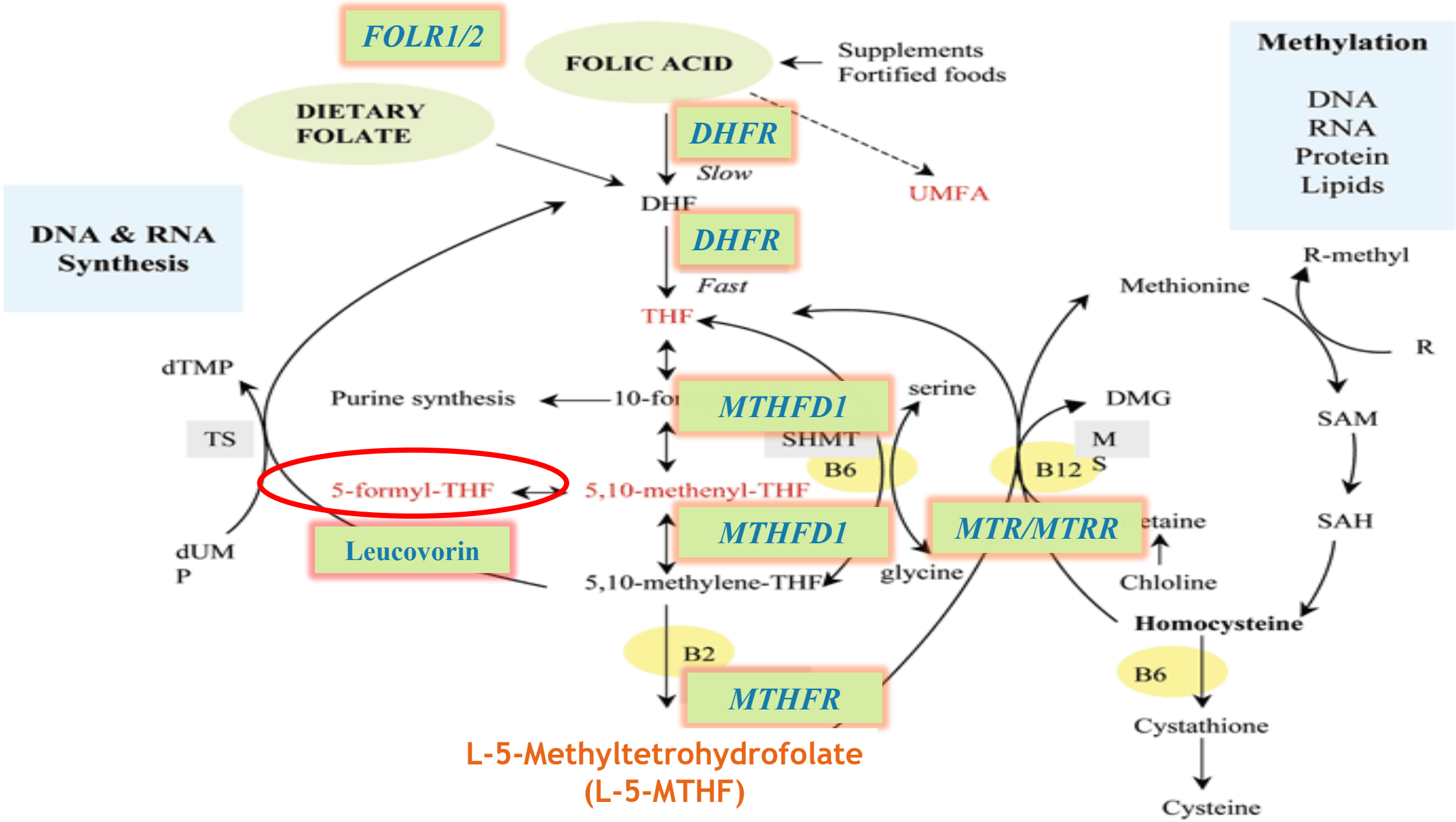


Important Folate Methylation Enzymes

- ***FOLR 1,2 (Folate Receptor)***
  - Actively transports folate into cells
-
- ***DHFR (Di-Hydrofolate Reductase)***
  - Converts DHF to THF
- ***MTHFD (Methylenetetrahydrofolate Dehydrogenase)***
  - Converts Formyl THF and Methenyl THF to Methylene THF
- ***MTHFS (5,10-methenyltetrahydrofolate Synthetase)***
  - Converts 5-formyl THF to 5,10 Methenyl THF
- ***MTHFR (Methylenetetrahydrofolate Reductase)***
  - Converts 5,10 Methylene THF to MTHF


PLASMA
CELL
Folic Acid
(Inactive Synthetic Pro-drug)
FOLR
Dihydrofolate
(No known biological activity)
DHFR
DHF Reductase
Tetrahydrofolate
(No known biological activity)
In order for Folic Acid to be taken into the cell, it must be converted to L-Methylfolate.
Folic Acid absorption takes place within the intestinal mucosal cells.
MTHFD1
MTHFS
10-Formyl Tetrahydrofolate
(Folinic Acid)
Purines
L-Methylfolate
(Active Folate)
MTHFR
5,10-Methylene Tetrahydrofolate
Only reduced folates are functional and are essential for DNA biosynthesis cycle.
L-Methylfolate
Vitamin B-12
L-MTHF
B-12
MS
Methionine
Methylation Cycle
S-Adenosylmethionine (SAM)
DNA & PROTEIN SYNTHESIS
Methyl Donation
Homocysteine
PLASMA
CELL

Folate Metabolism

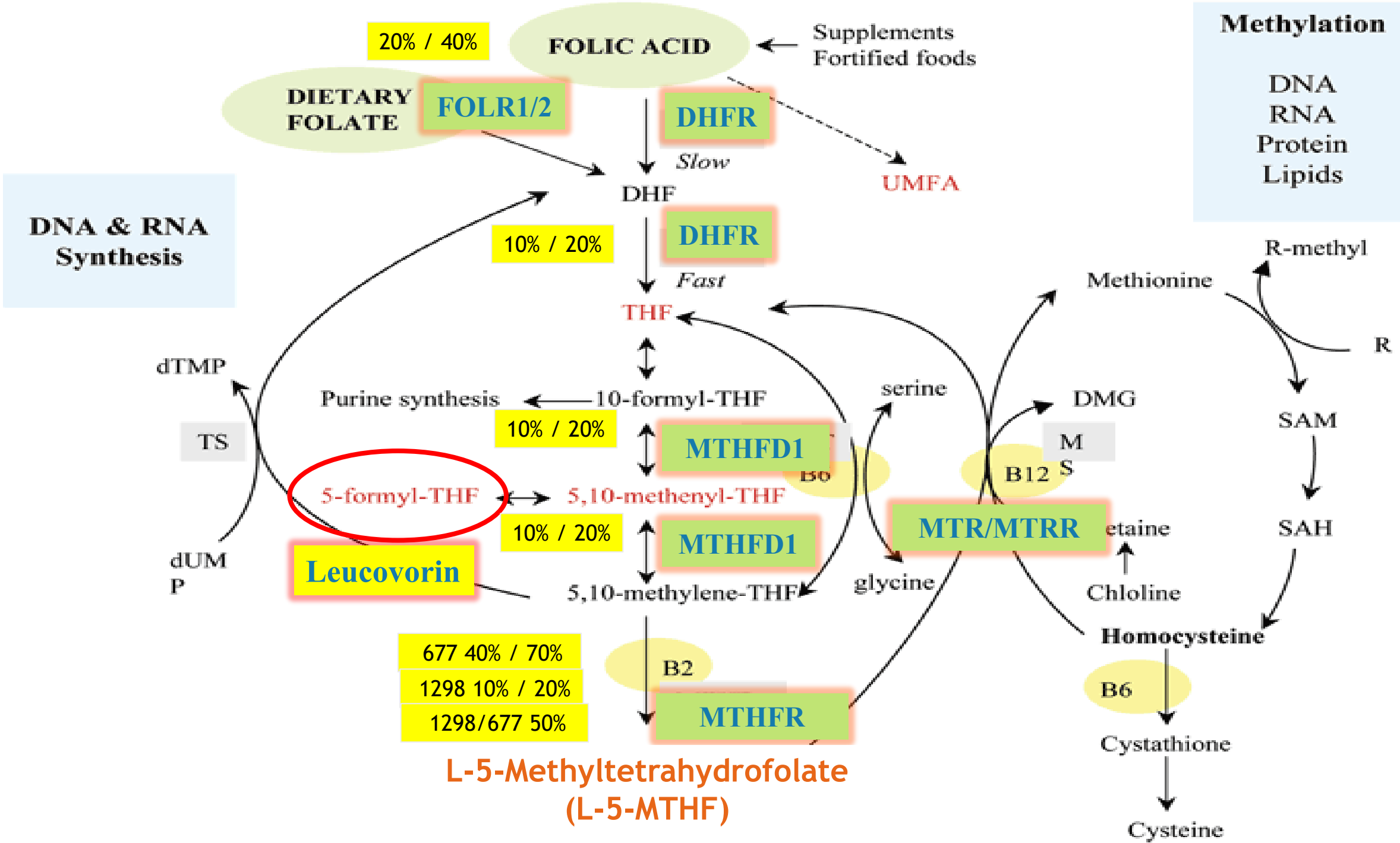


L-5-Methyltetrohydrofolate
(L-5-MTHF)

Approximating Methylfolate Deficiency

- **Significant SNPs:**
  - ***FOLR* (20% / 40%)**
  - ***MTHFD1* (10% / 20%) (two steps in process)**
  - ***MTHFS* (30% / 60%) (cannot use leucovorin)**
  - ***MTHFR 677* (40% / 70%)**

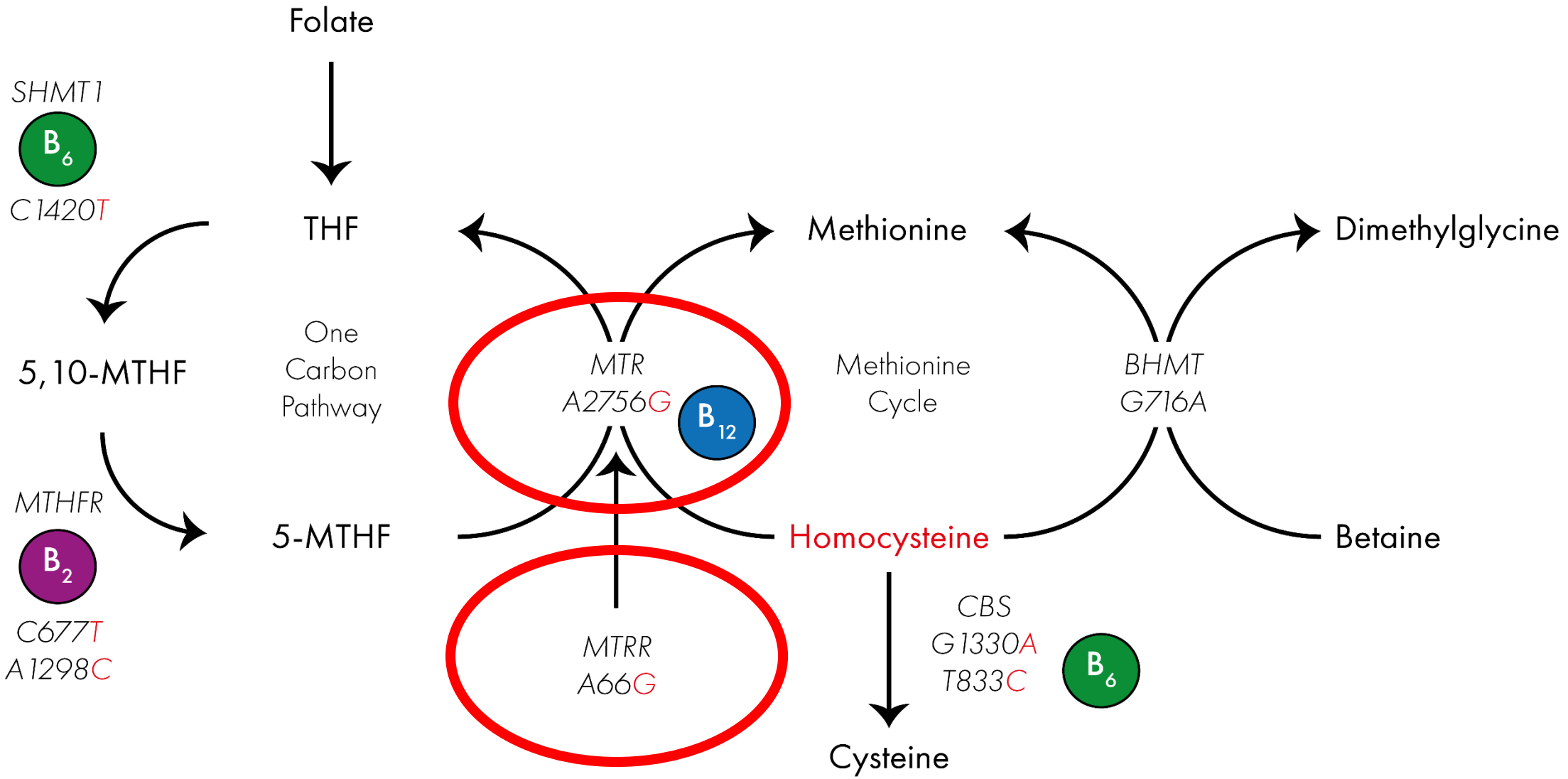
- **Lesser SNPs:**
  - ***DHFR* (10% / 20%)**
  - ***MTHFR 1298* (10% / 20%)**

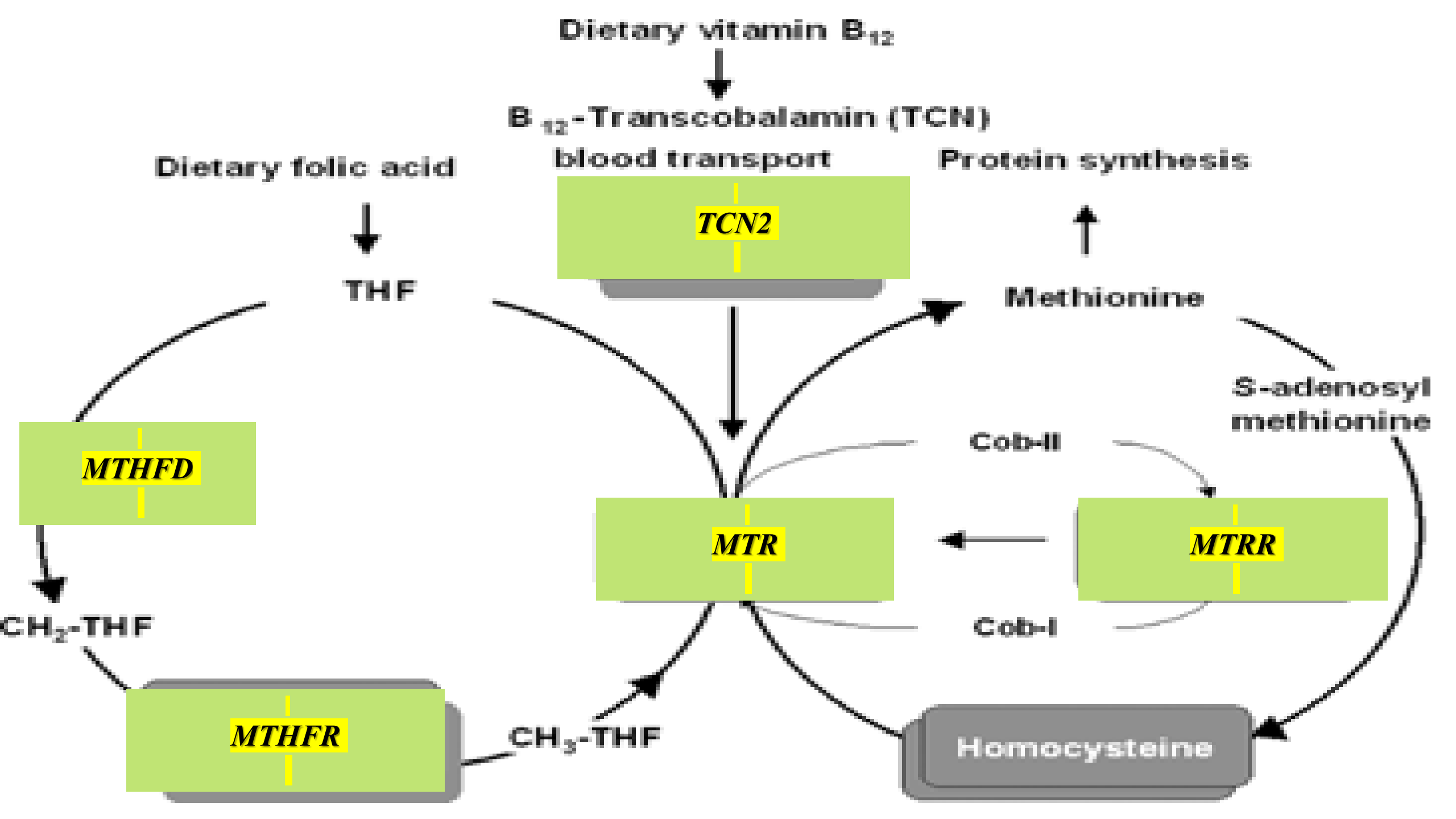

20% / 40%
FOLIC ACID
Supplements
Fortified foods
DIETARY FOLATE
FOLR1/2
DHFR
Slow
UMFA
DHF
10% / 20%
DHFR
Fast
THF
DNA & RNA Synthesis
Methylation
DNA
RNA
Protein
Lipids
dTMP
TS
Purine synthesis
10-formyl-THF
10% / 20%
MTHFD1
5-formyl-THF
5,10-methenyl-THF
10% / 20%
MTHFD1
Leucovorin
dUMP
5,10-methylene-THF
677 40% / 70%
1298 10% / 20%
1298/677 50%
B2
MTHFR
serine
glycine
DMG
B12
MTR/MTRR
Methionine
R-methyl
R
SAM
SAH
Chloline
Homocysteine
B6
Cystathione
Cysteine
L-5-Methyltetrahydrofolate
(L-5-MTHF)

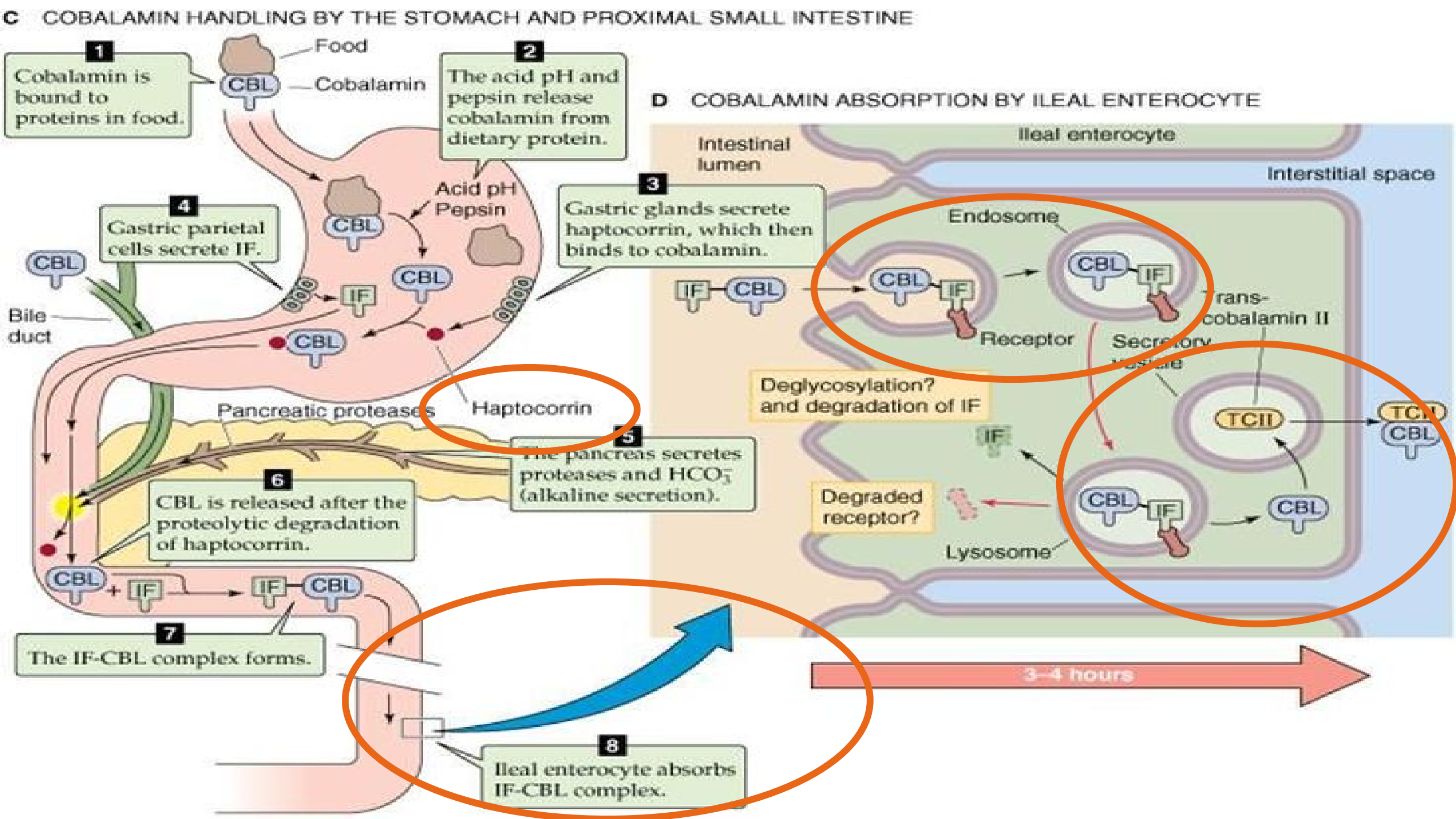
Important B12 Methylation Enzymes

- ***MTRR (Methionine Synthase Reductase)***
  - Responsible for the regeneration of methyl-cobalamin in the methionine reaction
- ***MTR (Methionine Synthase)***
  - Responsible for Conversion of Homocysteine to Methioinine
  - MTHF, MB12 are co-factors
- ***GIF (Gastric Intrinsic Factor)***
  - Binds to B12 in the stomach and is necessary for B12 absorption by the ileum
- ***TCN1 (Transcobalamin 1 or Haptocorrin)***
  - Binds to B12 to protect it from acid degradation
- ***TCN2 (Transcobalamin 2)***
  - Binds Cobalamin in the enterocytes and transports it through the body

MTR and MTRR


Folate
SHMT1
B6
C1420T
THF
5,10-MTHF
MTHFR
B2
C677T
A1298C
5-MTHF
One Carbon Pathway
MTR
A2756G
B12
MTRR
A66G
Methionine
Methionine Cycle
Homocysteine
BHMT
G716A
Dimethylglycine
Betaine
CBS
G1330A
T833C
B6
Cysteine


Dietary vitamin B_{12}
B_{12}-Transcobalamin (TCN)
blood transport
Dietary folic acid
Protein synthesis
TCN2
THF
Methionine
S-adenosyl methionine
MTHFD
Cob-II
MTR
MTRR
Cob-I
CH_2-THF
MTHFR
CH_3-THF
Homocysteine

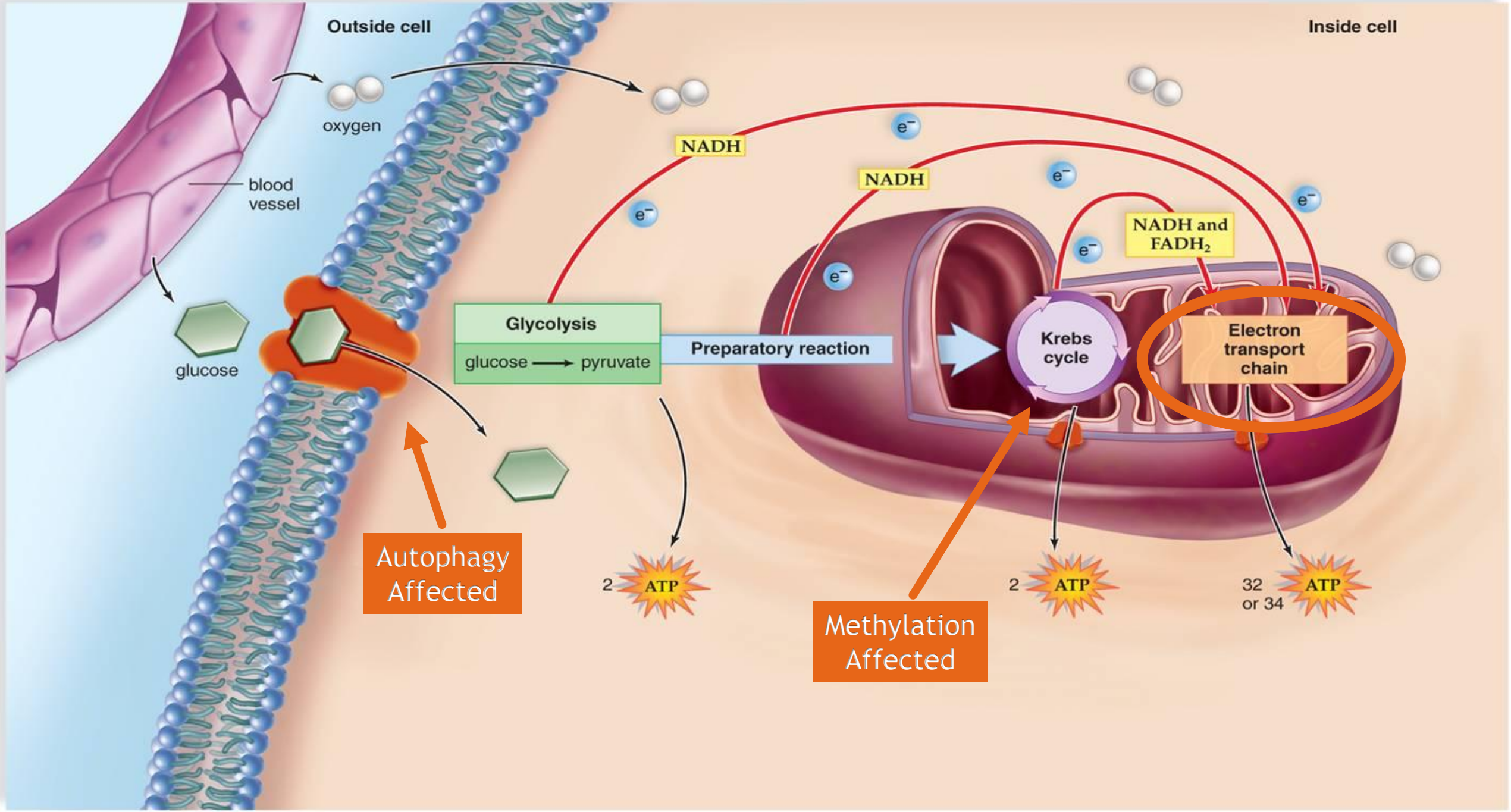

C COBALAMIN HANDLING BY THE STOMACH AND PROXIMAL SMALL INTESTINE
1
Cobalamin is bound to proteins in food.
Food
Cobalamin
CBL
2
The acid pH and pepsin release cobalamin from dietary protein.
Acid pH
Pepsin
3
Gastric glands secrete haptocorrin, which then binds to cobalamin.
4
Gastric parietal cells secrete IF.
IF
Bile duct
Haptocorrin
Pancreatic proteases
5
The pancreas secretes proteases and HCO_3^- (alkaline secretion).
6
CBL is released after the proteolytic degradation of haptocorrin.
7
The IF-CBL complex forms.
8
Ileal enterocyte absorbs IF-CBL complex.
D COBALAMIN ABSORPTION BY ILEAL ENTEROCYTE
Intestinal lumen
Ileal enterocyte
Interstitial space
Endosome
Receptor
Secretory vesicle
Deglycosylation? and degradation of IF
Degraded receptor?
Lysosome
Trans-cobalamin II
TCII
TCII
3–4 hours

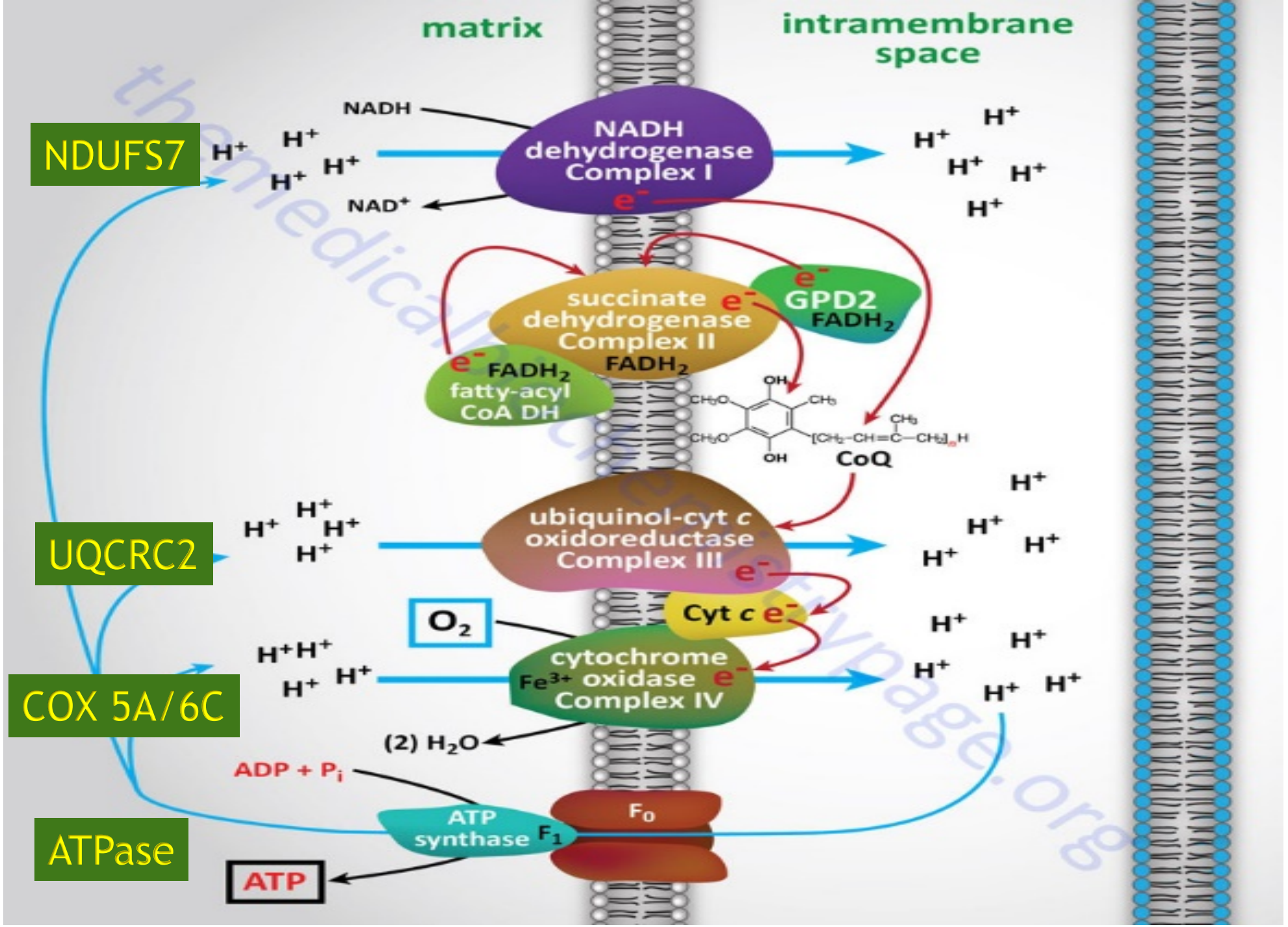
Biochemistry Review

Mitochondria

Mitochondrial Concepts

- **Every cell requires energy**
- **Highest energy organs are nervous system and immune system**
- **Mitochondrial weakness is more common than previously thought**
  - Chronic Fatigue
  - Exercise Intolerance
  - Low Muscle Tone
  - Mental Fatigue
  - Cognitive Decline




matrix
intramembrane space
NDUFS7
NADH
NAD+
NADH dehydrogenase Complex I
succinate dehydrogenase Complex II
FADH2
GPD2
FADH2
FADH2 fatty-acyl CoA DH
CoQ
UQCRC2
ubiquinol-cyt c oxidoreductase Complex III
Cyt c
O2
COX 5A/6C
cytochrome Fe3+ oxidase Complex IV
(2) H2O
ADP + Pi
ATP synthase
F1
F0
ATP
ATPase

Mitochondrial Polymorphisms
CoQ-10 Related

- ***NDUFS3 / NDUFS7 / NDUFS8 (NADH Dehydrogenase Complex)***
  - Complex 1 protein in Respiratory Chain

- ***UQCRC2 (Ubiquinol-cyt c Oxidoreductase)***
  - Complex 3 protein in Respiratory Chain

- ***COQ2 (Ubiquinone Polyprenyltransferase)***
  - The final enzyme in the production of CoQ-10

- **Treatment: Ubiquinone / PQQ / NADH**

Important Mitochondrial Supplement
What is PQQ?

- **PQQ (Pyrolloquinoline Quinone):**

  - Stimulates production of nerve growth factors
  - Protects cells from oxidative stress
  - Shown to protect memory and cognition of ageing humans
  - Shown to stimulate **new mitochondria biogenesis**
  - Prevents the aggregation of alpha-synuclein (Parkinson's)

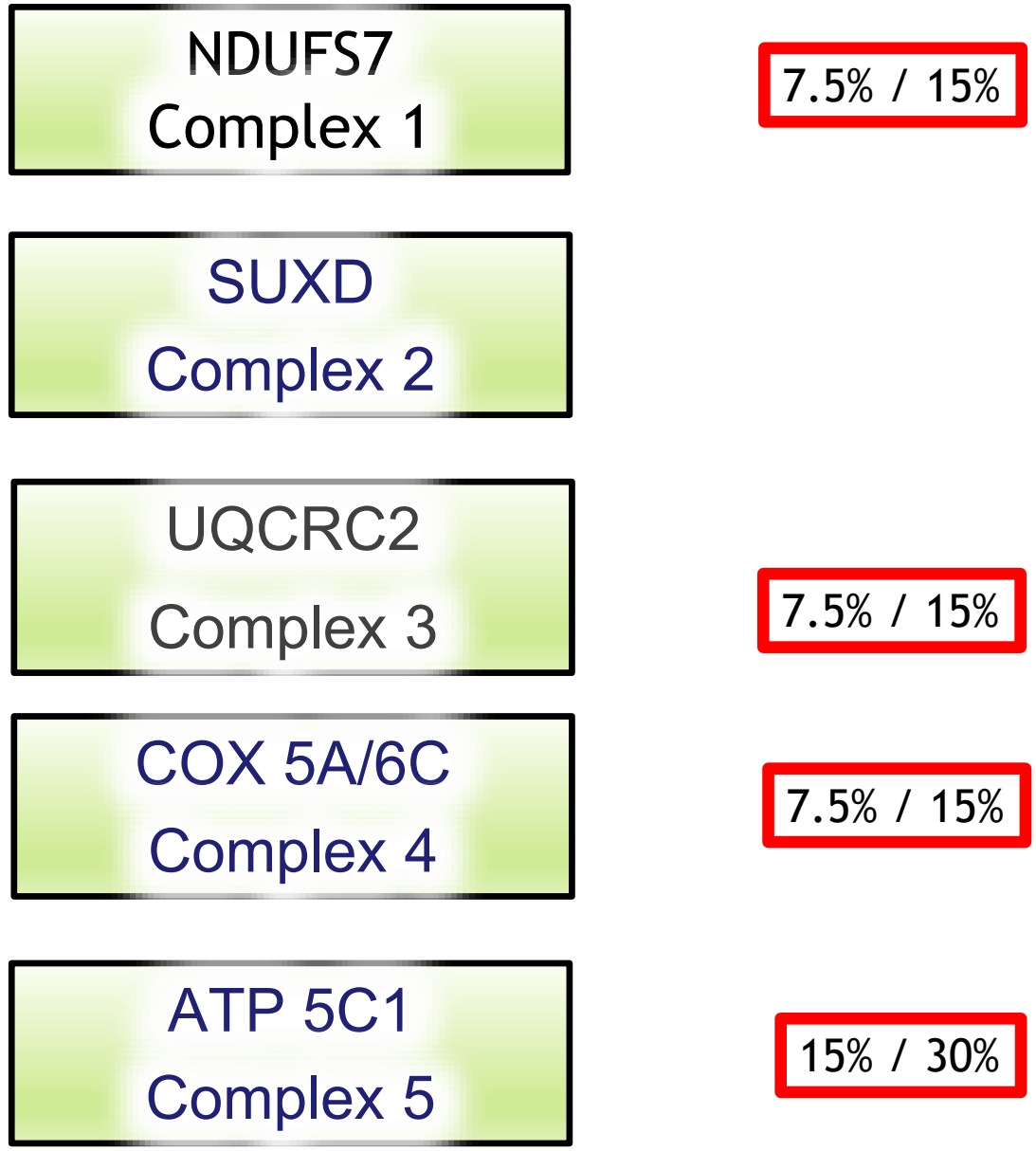
Mitochondrial Polymorphisms
Not CoQ-10 Related

- ***COX5A / COX6C (Cytochrome Oxidase)***
  - Complex 4 protein in Respiratory Chain

- ***ATP5C1 (ATP Synthase)***
  - Complex 5 protein in Respiratory Chain
  - Responsible for production of ATP

- **Treatment:**
  - **Acetyl-L-Carnitine**
  - **L-Ornithine**
  - **NADH**
  - **Resveratrol**
  - **Quercitin**

Approximating Mitochondrial Respiration Weakness



Overcome Mitochondrial Weakness

- **Indication**:
  - **Multiple Polymorphism of Respiratory Chain**
  - **NDUFS / UQCRC2 / ATP5C1**
  - **≤ 80% Mito Strength**

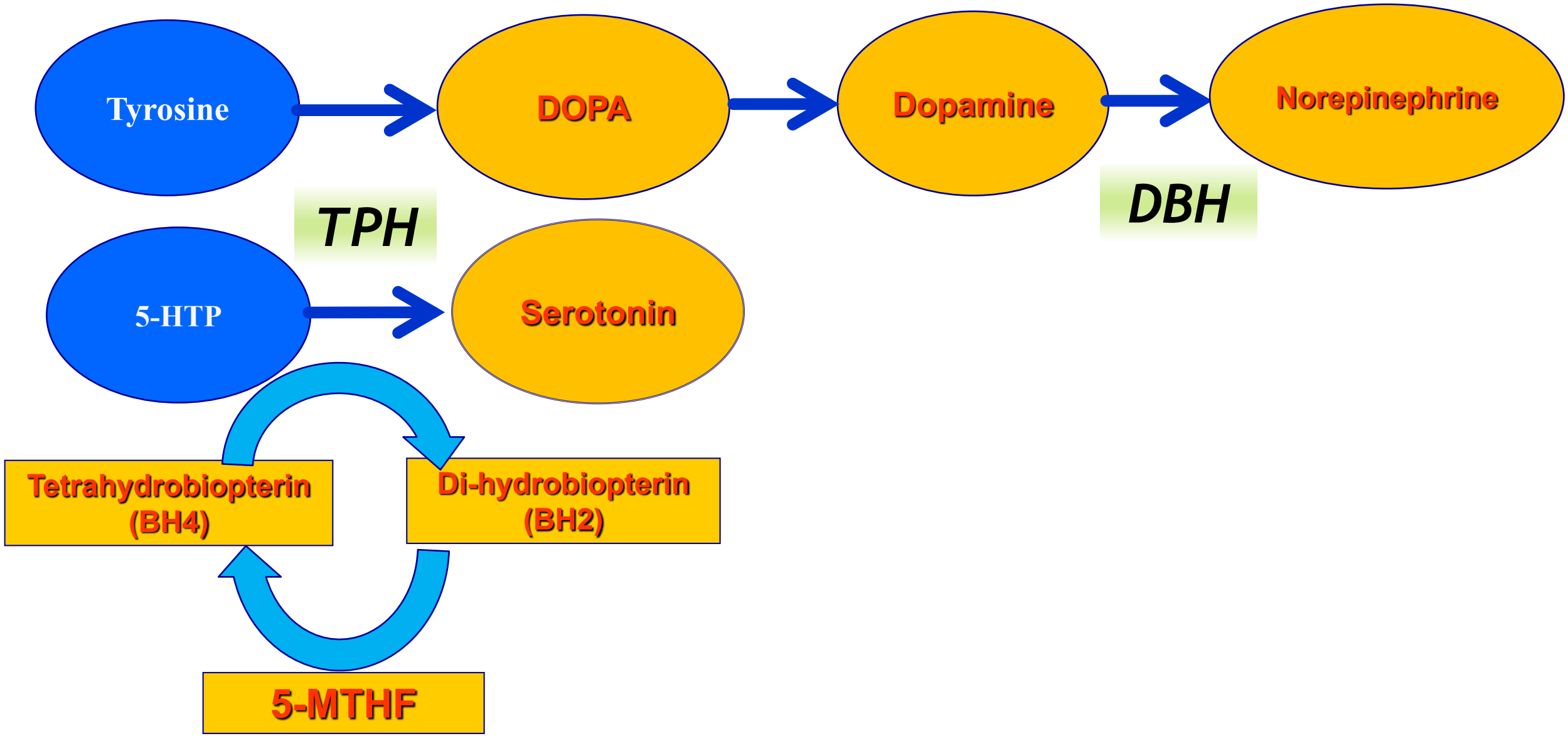
- **Objective**: Improve energy and Mitochondrial biogenesis

- **Strategy:**
- **NADH (cofactor)**
- **Ubiquinone (cofactor)**
- **PQQ (biomodulator)**
- **Acetyl-L-Carnitine (substrate)**
- **Resveratrol (antioxidant)**
- **Quercetin (antioxidant)**
- **L-Ornithine (substrate)**

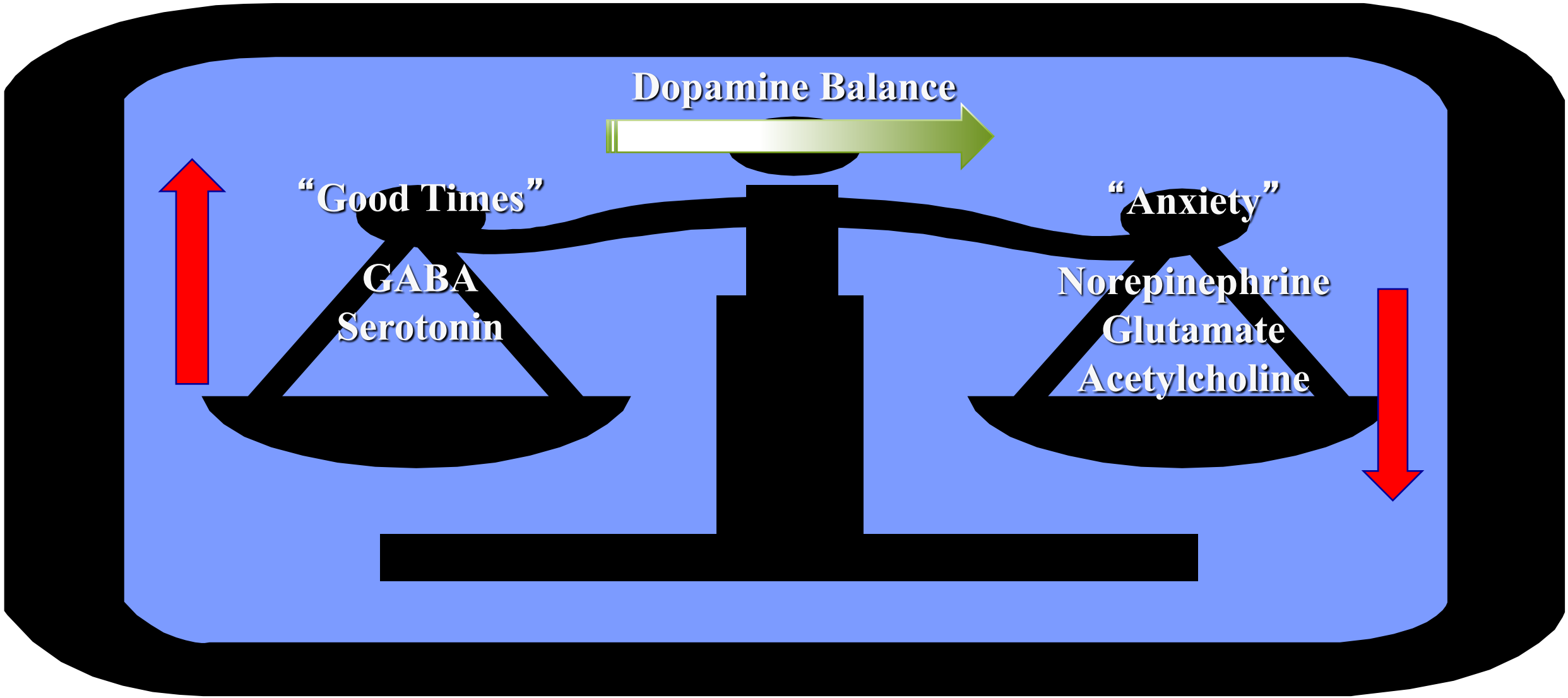
Biochemistry Review

Neurotransmitter Production and Bioavailability

Dopamine, Serotonin and Norepienphrine Neurotransmitter Production



What Do We Desire For Our Patients



"Relaxed State-of-Mind"

Important Neurotransmitter Enzymes

- ***COMT (Catecholamine-O-methyl Transferase) - Hetero / Homo***
  - Degrades catecholamines (dopamine, epi, norepi)
  - Normal function leads to low anxiety

- ***MAOA and MAOB (Monoamine Oxidase) - Homo significance***
  - Degrades monoamines (dopamine, serotonin)
  - Normal function leads to low risk of depression

- ***GAD1(Glutamic Acid Decarboxylase) - Hetero / Homo***
  - Converts Glutamic Acid to GABA
  - Normal function leads to calmness (relaxation, normal sleep, low pain and seizure risk)

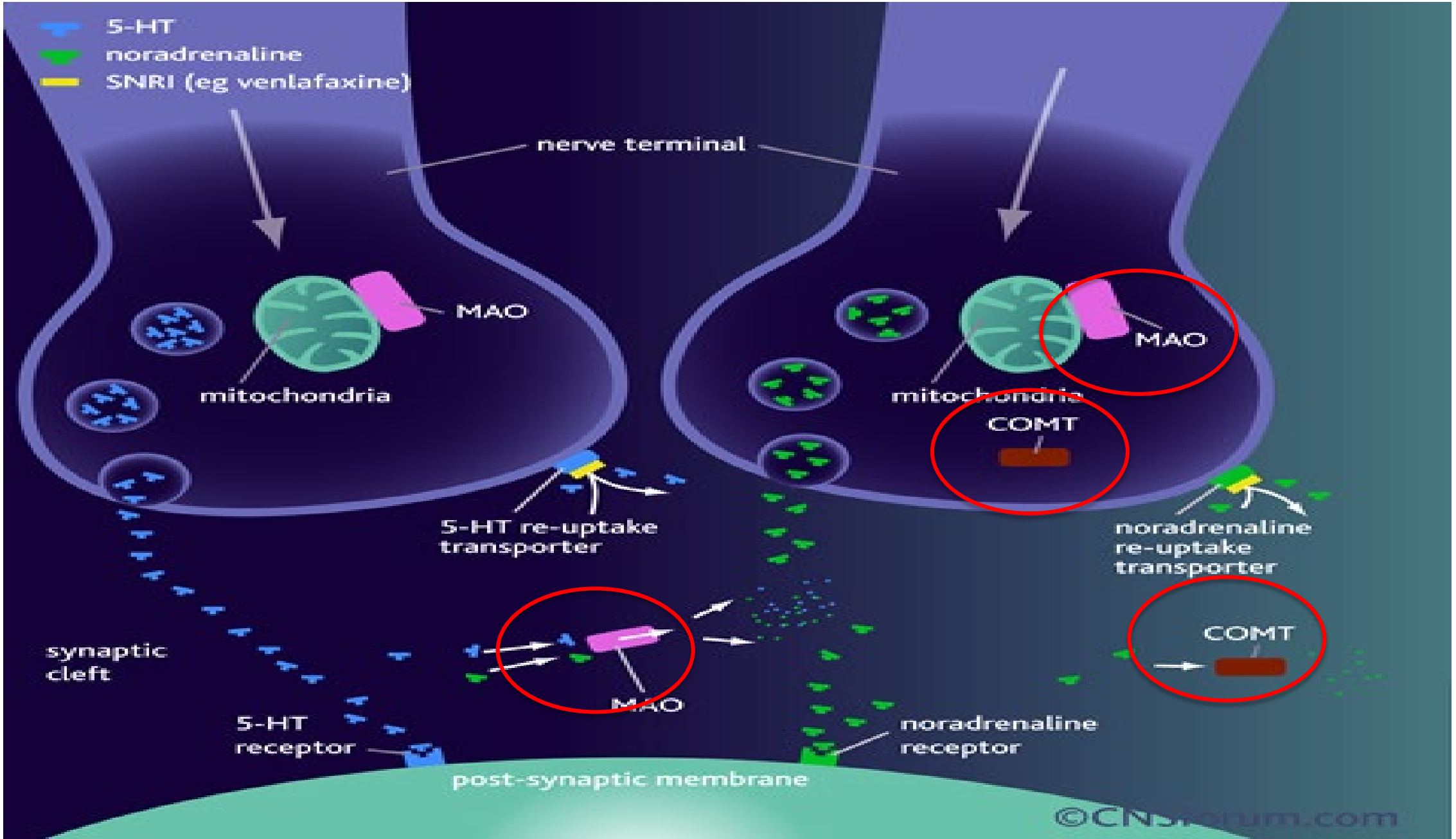
Neurotransmitter SNP
COMT Val158Met

- ***Catechol-O-methyltransferase (COMT)***
  - Hetero / Homo significance = **Decreased activity**
  - Responsible for degradation of catecholamines (dopamine, epi, norepi)
  - **Val/Val (wild type) - "Happy go lucky" people**
  - **Val/Met (hetero) - "Stoners"**
  - **Met/Met (homo) – "Mood disorder stays all day"**
  - Met/Met have higher rate of anxiety disorders, processing disorders and depression
  - **Treatment: Methyl donors (Taurine, Choline, Methionine, Inositol, DMG, TMG)**

Neurotransmitter SNP
MAOA and MAOB

- ***Monoamine Oxidase B (MAOB)***
  - Homo significance = **Decreased activity**
  - Responsible for degradation of catecholamines (dopamine, serotonin, norepiphrine)
  - **X linked inheritance**
  - Known as “warrior gene” and “depression gene” respectively.
  - Patients are more refractory to recovery from anxiety and depression
  - **Treatment: Methyl donors (Taurine, Choline, Methionine, Inositol, DMG, TMG), 5-HTP**

COMT / MAO-A and MAO-B



Neurotransmitter SNP
GAD 1

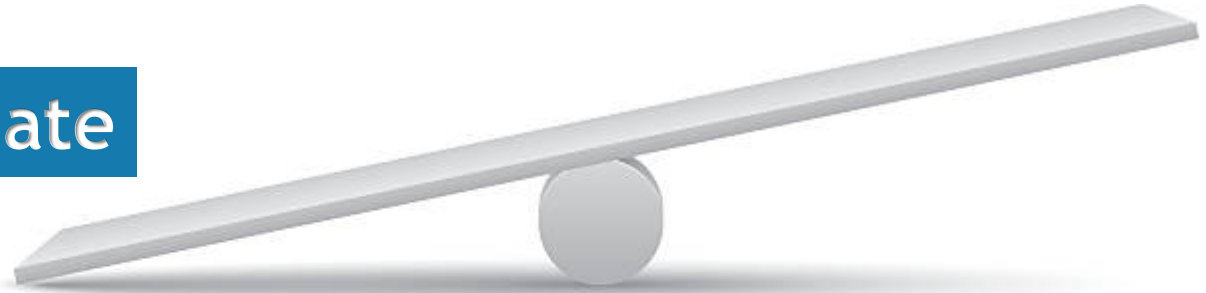
- ***Glutamic Acid Decarboxylase (GAD1)***
  - Hetero / Homo significance = **Decreased function**
  - Converts Glutamic Acid to GABA
    - Pyridoxal-5-phosphate (B6) cofactor
  - Decrease levels of GABA create:
    - Dysphoria
    - Anxiety
    - “Half Glass Empty” syndrome
    - Increased Pain Sensitivity
    - Sleep Disorders
    - Spasticity
    - Low Libido
  - **Treatment: Glycine, Zinc, Beta-Phenyl-GABA, Magnesium, B6**

Glutamate / GABA Balance

GAD1 +/- or +/+

GABA

Glutamate



Anxiety, Dysphoria, Inattentiveness, Muscle Spasms, Poor Sleep Initiation, Poor Peristalsis

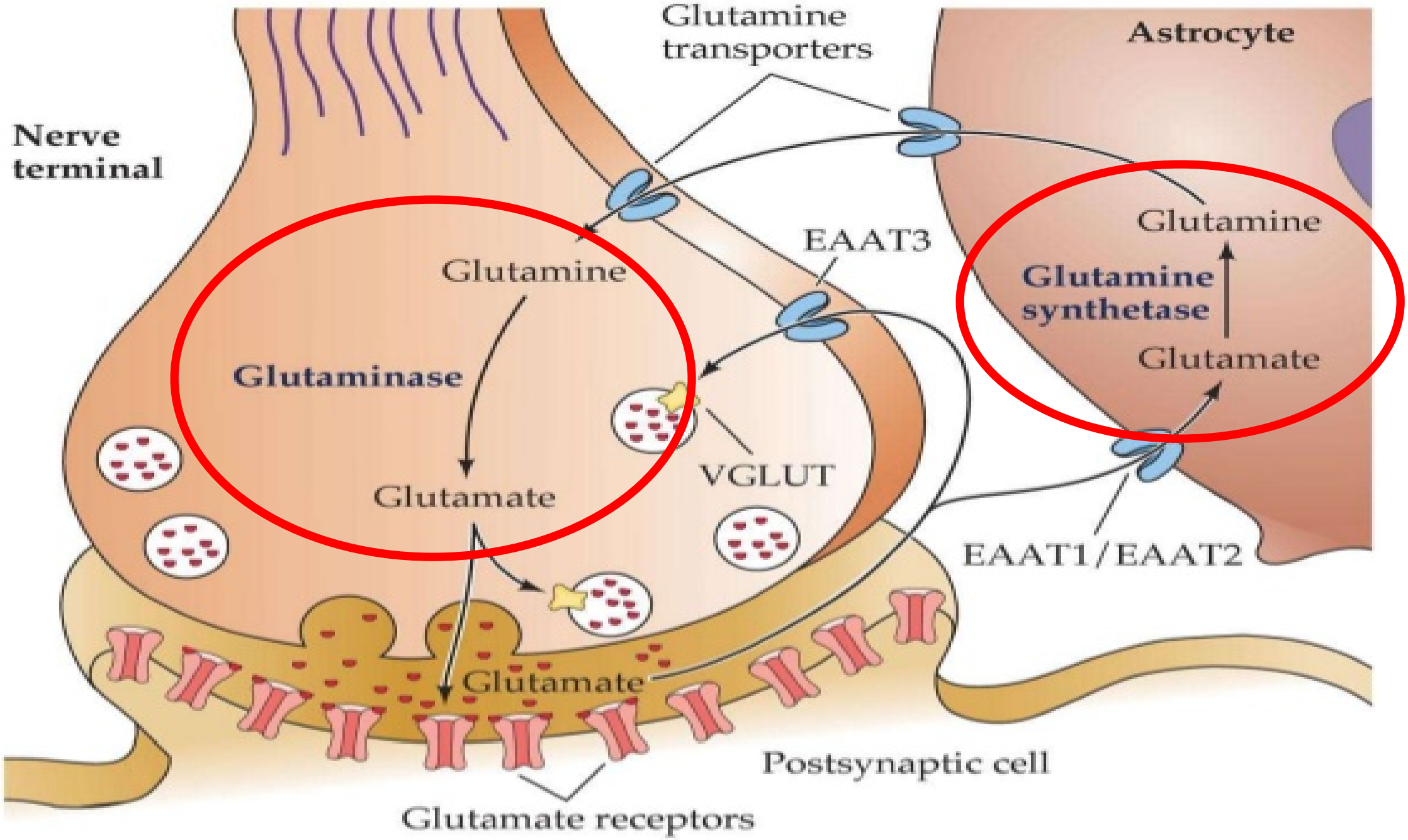
Amantadine, Namenda, Glycine, Mg, Zn

Beta Phenyl GABA

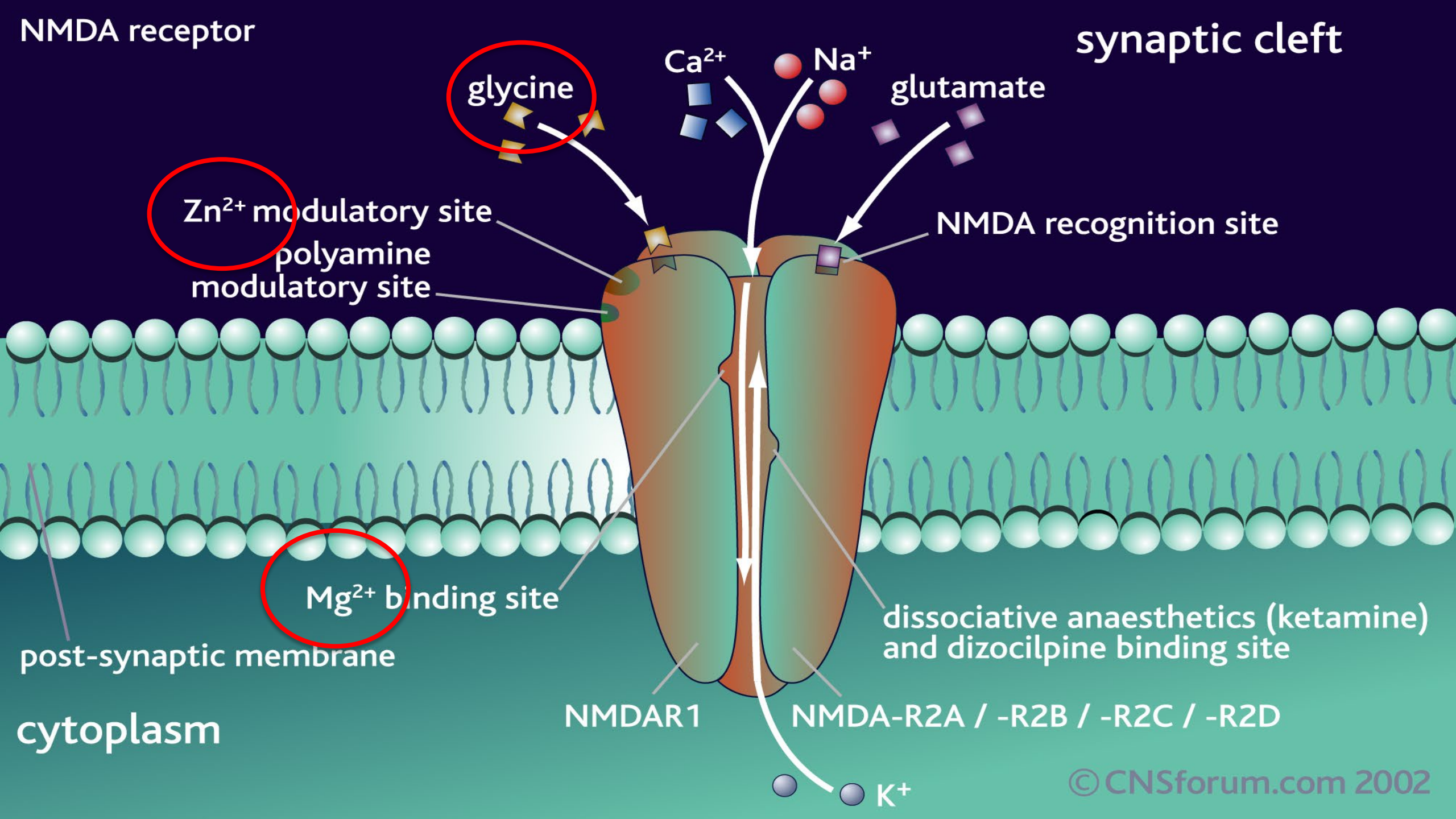
Glutamate

GABA

Calm, Relaxed, Focused, Good Sleep



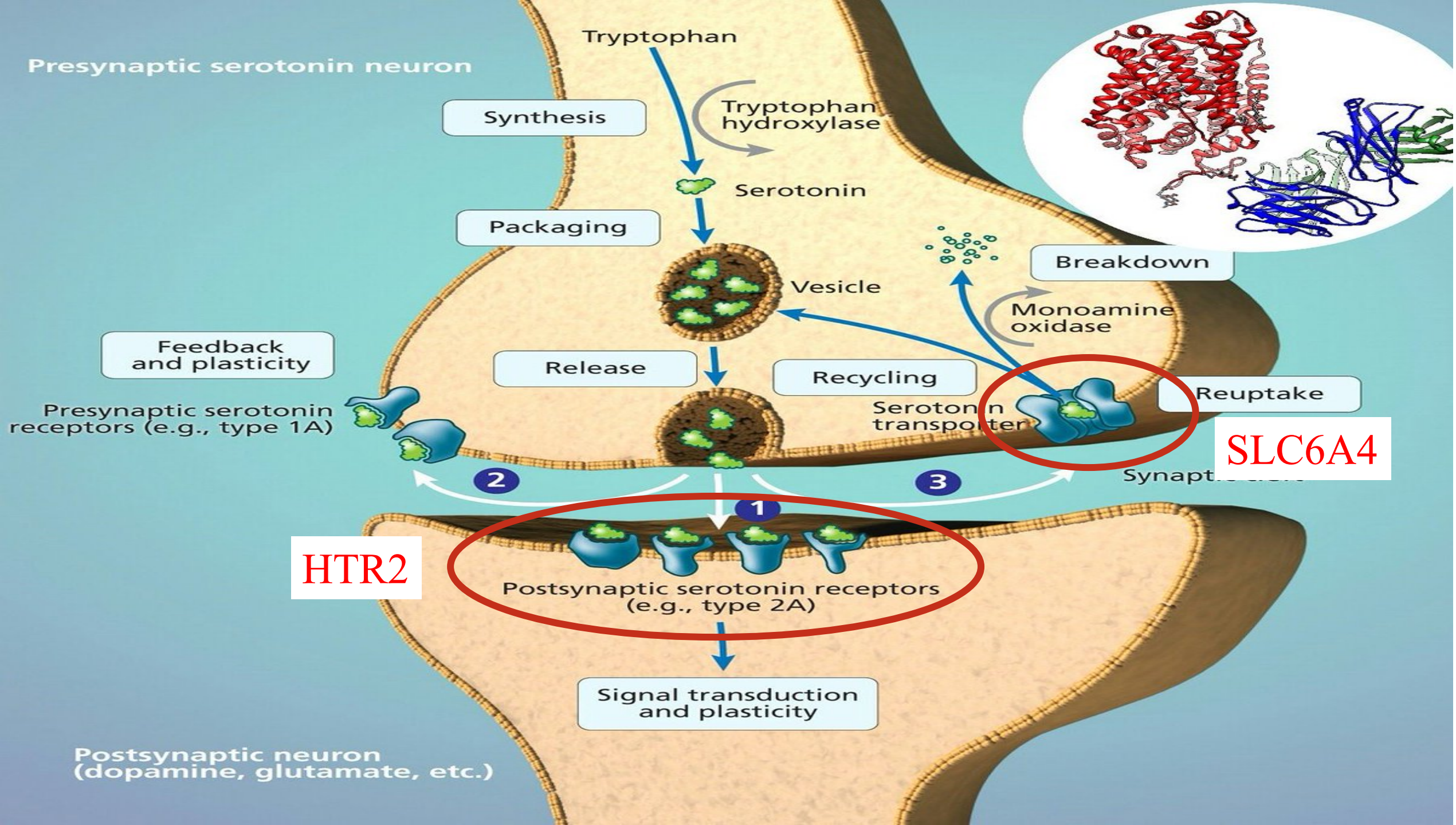
PSYCHOPHARMACOLOGY, Figure 7.3 © 2005 Sinauer Associates, Inc.


NMDA receptor
synaptic cleft
glycine
Ca^{2+}
Na^{+}
glutamate
Zn^{2+} modulatory site
polyamine modulatory site
NMDA recognition site
Mg^{2+} binding site
post-synaptic membrane
dissociative anaesthetics (ketamine) and dizocilpine binding site
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
cytoplasm
K^{+}
©CNSforum.com 2002

Important Neurotransmitter Enzymes

- ***HTR2 (5-Hydroxytrypamine Receptor 2) – Hetero / Homo significance***
  - Receptor for Serotonin
  - Mutation linked to higher rates of refractory depression
  - Mutation can be linked to lower levels of oxytocin, prolactin, ACTH and renin
  - Patients are more refractory to treatment with SSRIs
  - **Treatment: Higher doses of 5-HTP needed, oxytocin for women**

- ***SLC6A4 (Solute Carrier Family 6 Protein A4) - Hetero / Homo significance***
  - Transports serotonin from the synaptic space to the pre-synaptic neuron
  - Sodium dependent serotonin transporter
  - Mutation linked to higher rates of refractory depression and PTSD
  - Patients are more refractory to treatment with SSRIs due to mutation
  - **Treatment: Higher doses of 5-HTP needed, oxytocin for women**

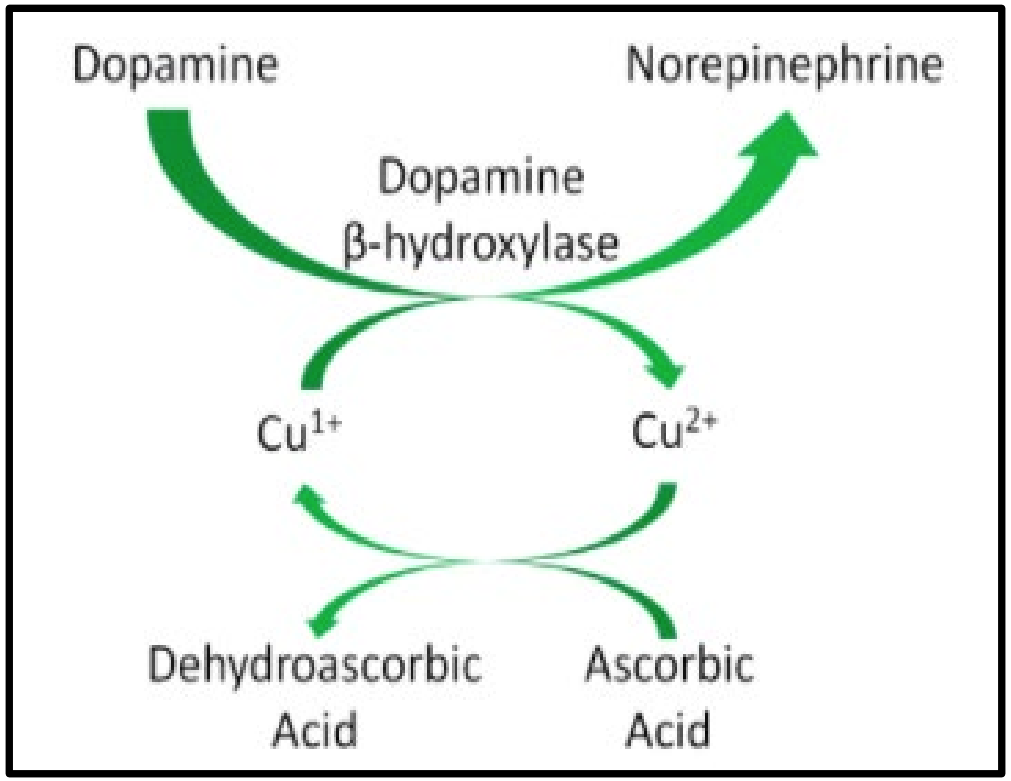

Presynaptic serotonin neuron
Tryptophan
Synthesis
Tryptophan hydroxylase
Serotonin
Packaging
Vesicle
Breakdown
Monoamine oxidase
Feedback and plasticity
Release
Recycling
Reuptake
Presynaptic serotonin receptors (e.g., type 1A)
Serotonin transporter
SLC6A4
2
3
1
HTR2
Postsynaptic serotonin receptors (e.g., type 2A)
Signal transduction and plasticity
Postsynaptic neuron (dopamine, glutamate, etc.)

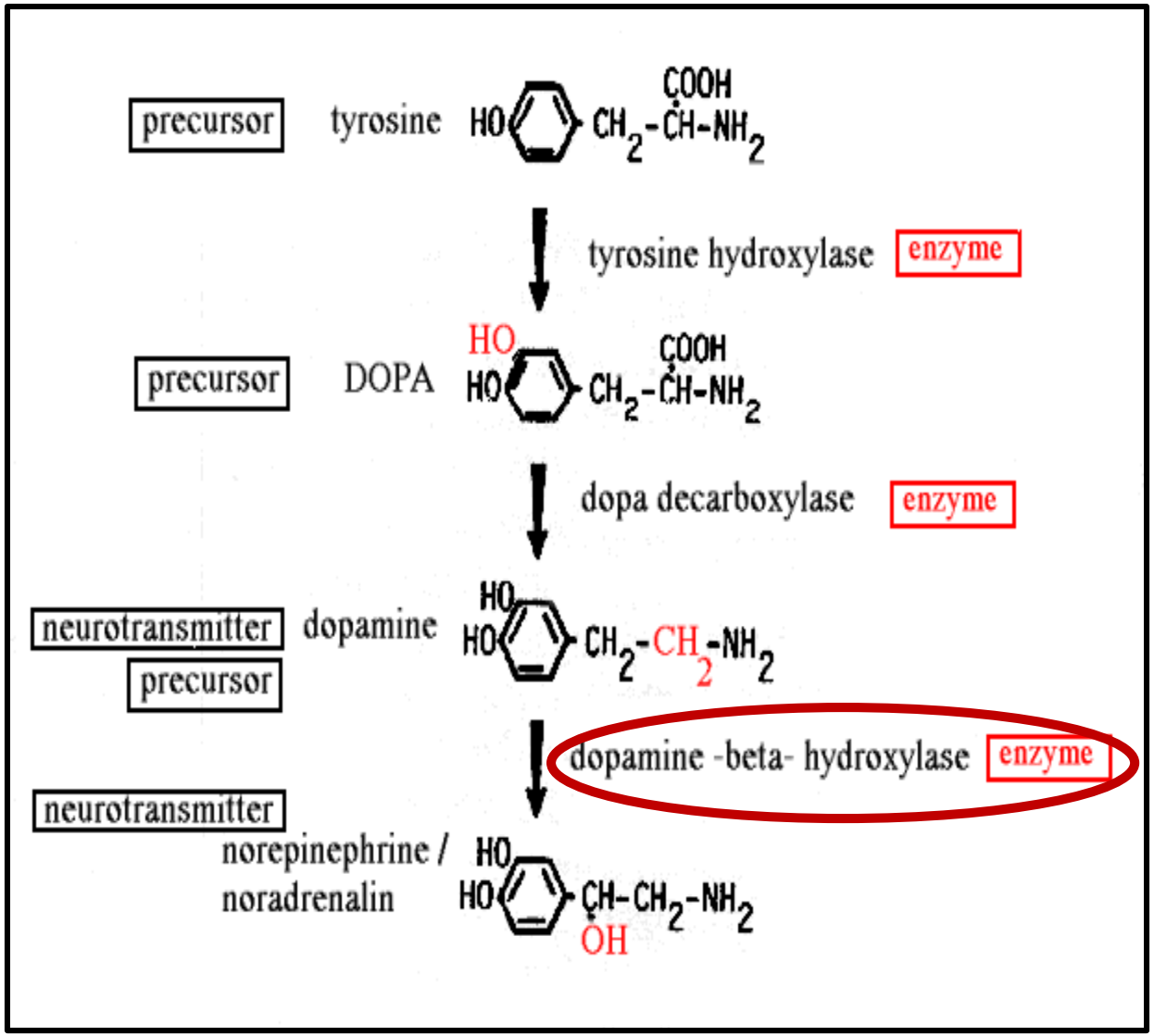
Important Neurotransmitter Enzymes

- ***DBH (Dopamine Beta Hydroxylase) (MAF: .43)***
  - Ascorbate (Vit C) and copper dependent
  - Catalyzed conversion of dopamine to Norepinephrine
  - Polymorphism leads to reduced production of Norepinephrine which lead to poor autonomic (dysautonomia) and cardiovascular function (hypotension)
  - Has also been **linked to ADD, Autism and POTS**
  - Treatment: Vitamin C, L-threo-dihydroxyphenylserine (Droxidopa) (Northera), Phenypropanolamine

- ***TPH (Tryptophan Hydroxylase) (MAF: .35)***
  - Catalyzes the rate limiting step in the production of serotonin
  - Biopterin, Niacin (B3) dependent hydroxylase
  - Correlated with anxiety, depression and bi-polar
  - Polymorphism leads to **increased efficacy of SSRIs**
  - Treatment: 5-HTP, 5-MTHF, Niacinamide, SSRI's

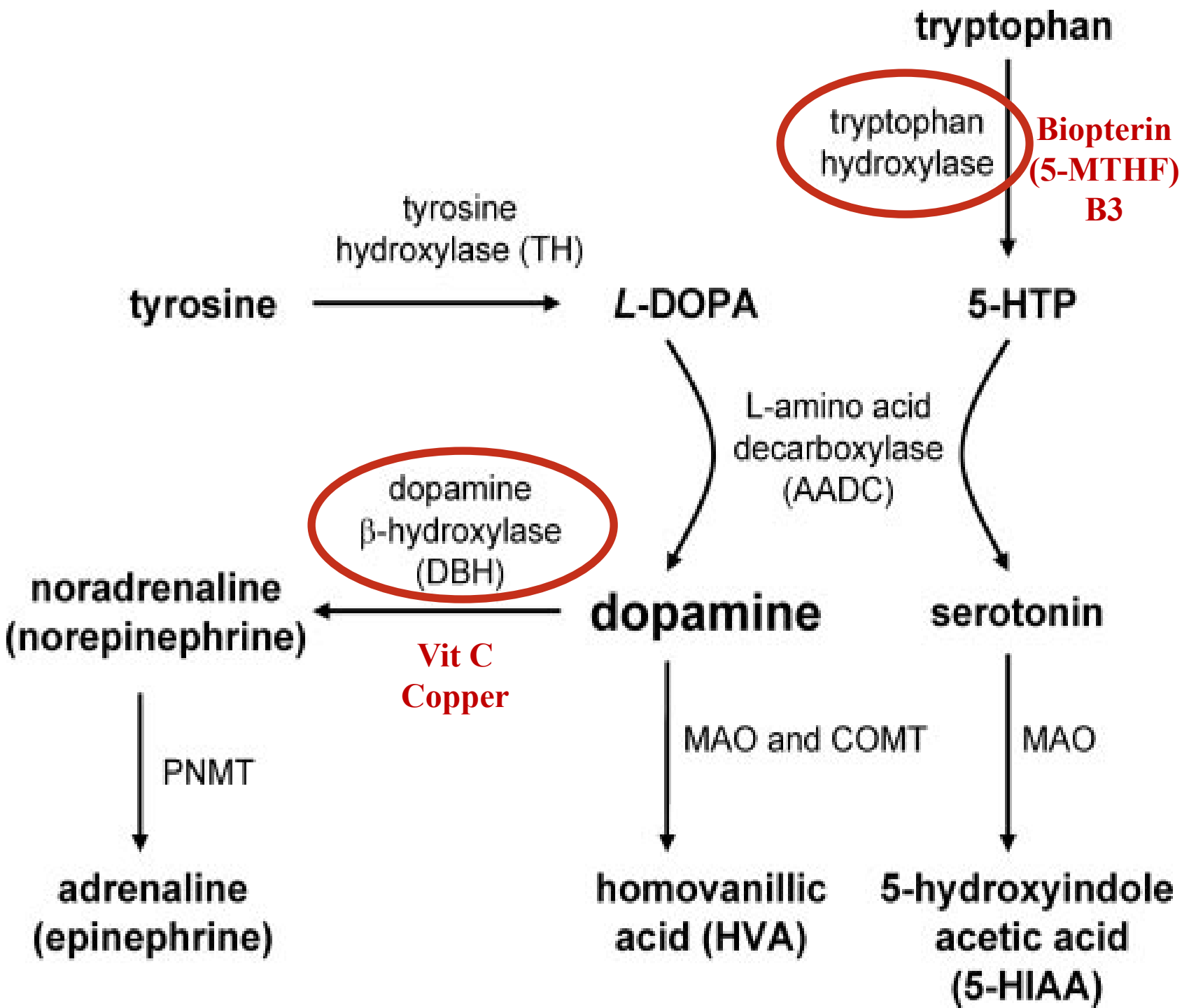
DBH
Dopamine Beta Hydroxylase





DBH
Dopamine Beta Hydroxylase

TPH
Tryptophan Hydroxylase



Important Neurotrophic Protein

- ***BDNF (Brain Derived Neurotrophic Factor) (MAF: .20)***
  - Member of Growth Factor Family
  - Encourages the growth and formation of new neurons and synapses
  - Polymorphism associated with developmental delay, anxiety, various psychiatric disease states, dementia and decreased neuroplasticity
  - **Treatment: Autophagy based (fasting, D-chiro Inositol), exercise and cognitive therapy**

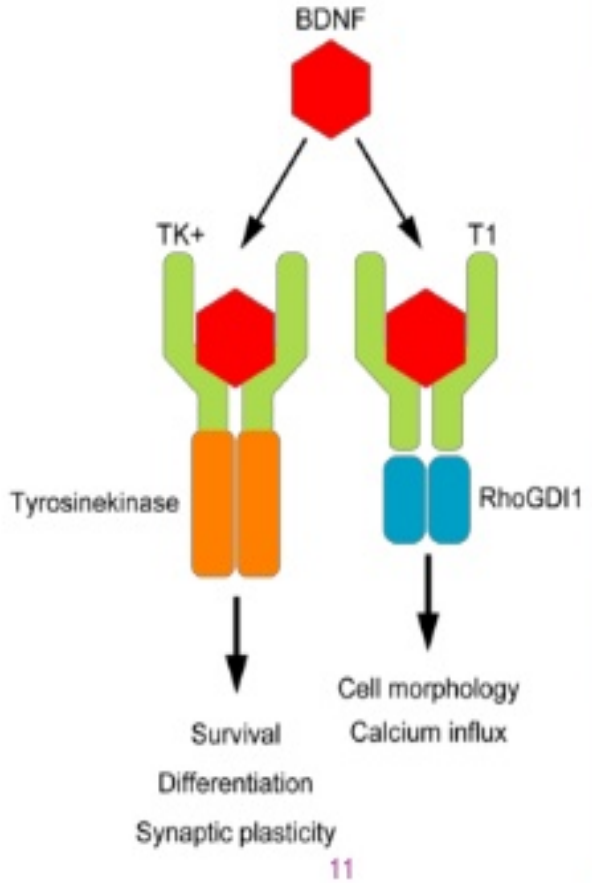
  - **Note: Polymorphism may indicate need for Stem Cell Therapy to assist with recovery**

BDNF
Brain Derived
Neurotrophic
Factor

FUNCTIONS OF BDNF

- BDNF plays critical roles in many aspects of brain development and functions, including

  - Cell survival,
  - Differentiation,
  - Migration,
  - Development,
  - Learning and memory
  - Synaptic plasticity



(Zheng *et al.*, 2012)

Food for Thought

“Many of us will die for science without knowing it.”

Gerhard Kocher

Biochemistry Review

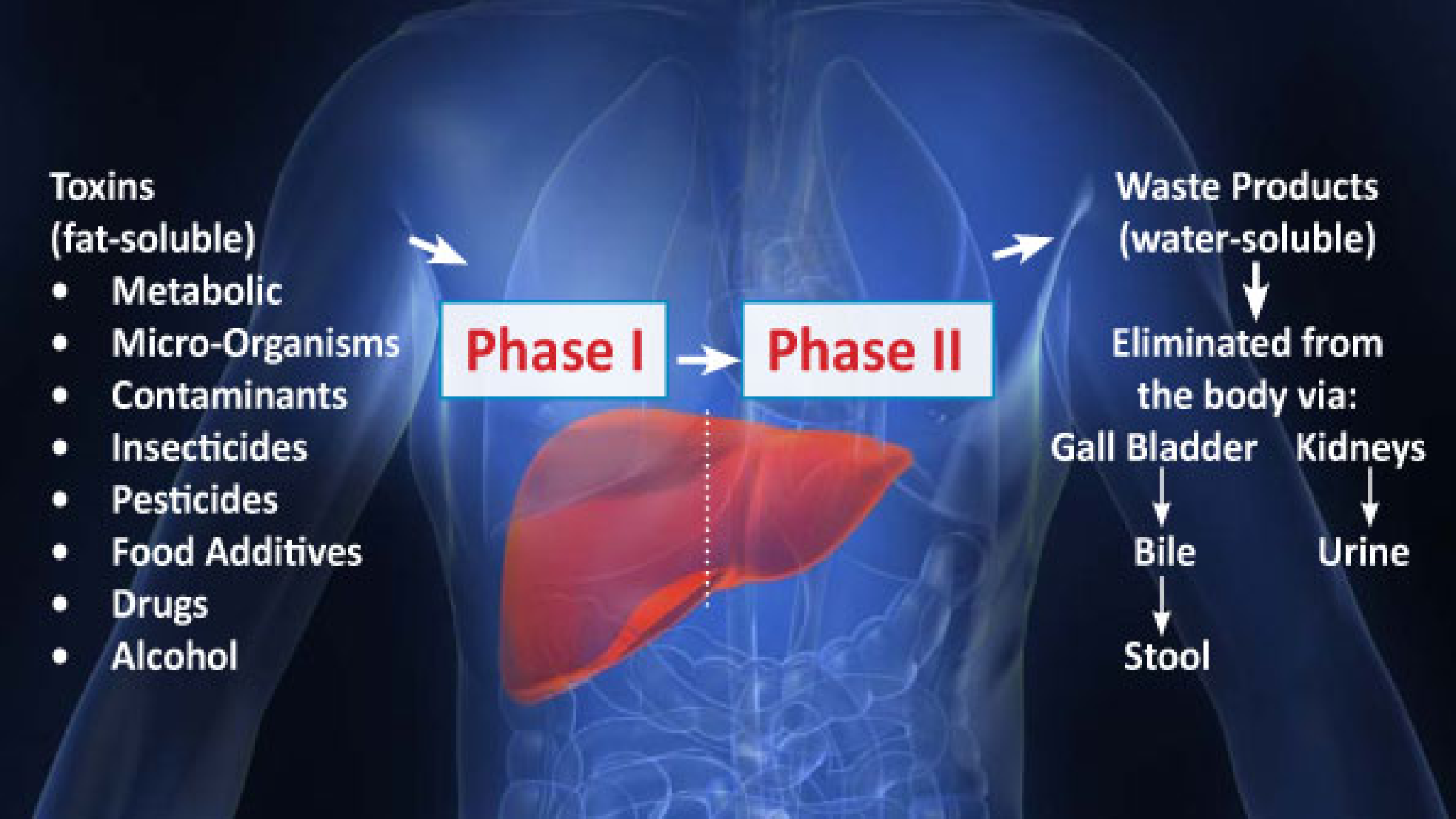
Detoxification

Subtypes of Detoxification

- **Phase I Detoxification**
  - **Cytochrome P450 oxidation and reduction**

- **Phase II Detoxification of Intermediary Metabolites**
  - **Methylation**
  - **Transulfuration**
  - **Acetylation**
  - **Glutathione production and conjugation**

- **Phase III Detoxification of Reactive Molecules**
  - **Peroxide**
  - **Aldehydes**
  - **Reactive oxygen species**


Toxins
(fat-soluble)
• Metabolic
• Micro-Organisms
• Contaminants
• Insecticides
• Pesticides
• Food Additives
• Drugs
• Alcohol
Phase I
Phase II
Waste Products
(water-soluble)
Eliminated from
the body via:
Gall Bladder
Kidneys
Bile
Urine
Stool

Biochemistry Review

Detoxification
Phase I

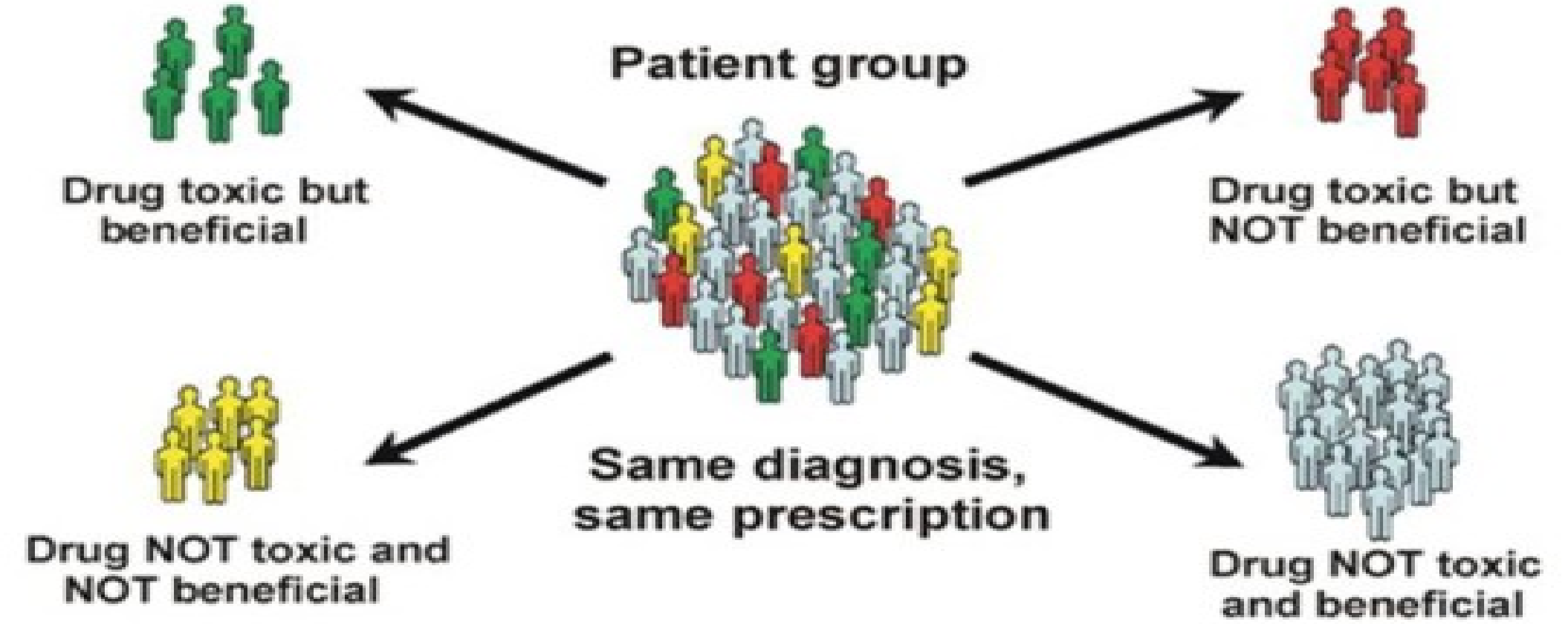
Phase I Detoxification
The Cytochrome Polymorphisms

- **Pharmacogenetics**
- **Hormonal Breakdown**

Detoxification Genetics Report

Gene & Variation	rsID	Alleles	Result
CYP1A1*2C A4889G	rs1048943	TT	-/-
CYP1A1 m3 T3205C	rs4986883	TT	-/-
CYP1A1 C2453A	rs1799814	GG	-/-
CYP1A2 164A>C	rs762551	AA	-/-
CYP1B1 L432V	rs1056836	GG	+/+
CYP1B1 N453S	rs1800440	TT	-/-
CYP1B1 R48G	rs10012	CG	+/-
CYP2A6*2 1799T>A	rs1801272	AA	-/-
CYP2A6*20	rs28399444	II	-/-
CYP2C9*2 C430T	rs1799853	CC	-/-
CYP2C9*3 A1075C	rs1057910	AA	-/-
CYP2C19*17	rs12248560	CT	+/-
CYP2D6 S486T	rs1135840	GG	+/+
CYP2D6 100C>T	rs1065852	AG	+/-
CYP2D6 2850C>T	rs16947	GG	-/-
CYP2E1*1B 9896C>G	rs2070676	CC	-/-
CYP2E1*1B 10023G>A	rs55897648	GG	-/-
CYP2E1*4 4768G>A	rs6413419	GG	-/-
CYP3A4*1B	rs2740574	TT	-/-
CYP3A4*2 S222P	rs55785340	AA	-/-
CYP3A4*3 M445T	rs4986910	AA	-/-
CYP3A4*16 T185S	rs12721627	GG	-/-
GSTP1 I105V	rs1695	AA	-/-
GSTP1 A114V	rs1138272	CC	-/-
SOD2 A16V	rs4880	AG	+/-
NAT1 R187Q	rs4986782	GG	-/-
NAT1 R64W	rs1805158	CC	-/-
NAT2 I114T	rs1801280	TT	-/-
NAT2 R197Q	rs1799930	AA	+/+
NAT2 G286E	rs1799931	GG	-/-
NAT2 R64Q	rs1801279	GG	-/-
NAT2 K268R	rs1208	AA	-/-

Pharmacogenetics is Personalized Medicine for Drugs



FDA Guidance and PGx Testing

- Guidance has included “Black Box” warnings, dosing guidance and recognition that many adverse drug reactions are due to genetically caused decreases in drug metabolism and pharmacological effect.

- More than 130 commonly prescribed medications have labels that include PGx related clinical warnings and precautions

Pharmacokinetics Metabolizer Phenotypes

Phenotype	Active Drug	Prodrug
Poor metabolizer (PM)	• Active drug may accumulate • Require lower dose to avoid toxic accumulation	• Inactive pro-drug may accumulate • Lack of therapeutic response
Intermediate Metabolizer (IM)	• May require reduced doses • May lead to drug-drug interactions with concomitant medications	
Extensive Metabolizer (EM)	• Standard dose appropriate	• Standard dose appropriate
Ultra-Rapid Metabolizer (UM)	• Requires higher dose to offset higher rate of metabolism	• Rapid onset of effect • May require lower dose to prevent excessive accumulation of any active metabolite

Genetics Influence Drug Response by:

Pharmacokinetics

► the body's impact on a drug

- Impacts drug dosage
- 4 metabolic phenotypes:
  - Ultra-rapid
  - Extensive (normal)
  - Intermediate
  - Poor

Pharmacodynamics

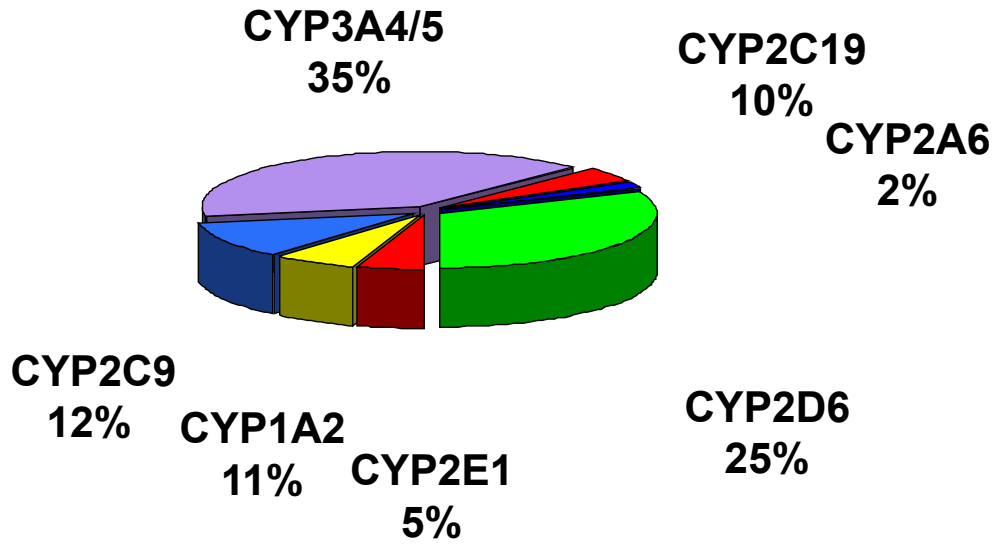
► a drug's impact on the body

- Impacts likelihood of drug producing desired therapeutic effect
- Extremely complex interaction

Pharmacokinetics

Human Cytochromes P450 (CYP) and their Contribution to Hepatic Drug Metabolism

- Approximately 57 types of CYP enzymes
- CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 are responsible for the metabolism of >90% of all drugs
- CYP genetic variation can lead to variability in drug metabolism



Wilkinson, N Engl J Med 2005; 352
Zanger & Schwab, Pharmacol & Therapeutics 2013; 138:103-141
Bertz & Granneman, Clin. PK: 1997

Pharmacokinetics

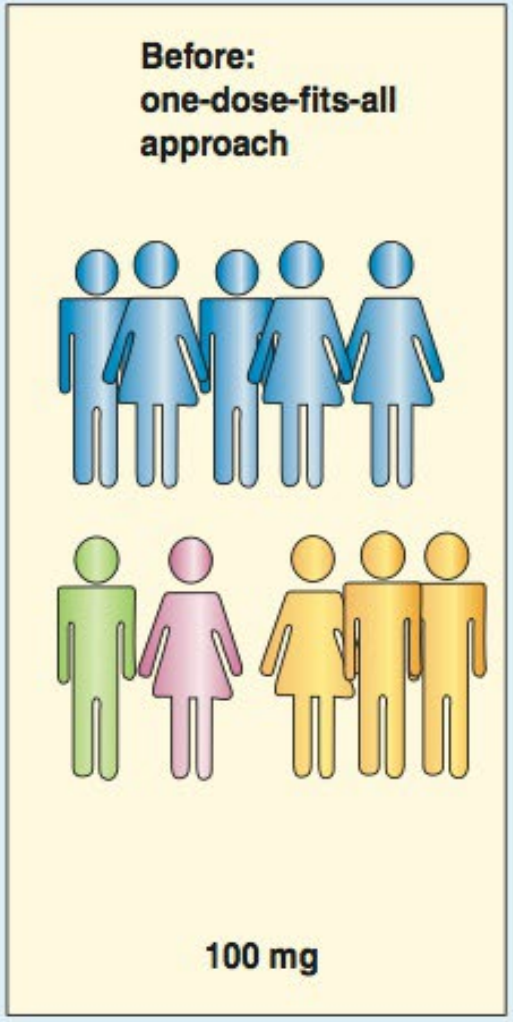
Metabolizer Phenotypes

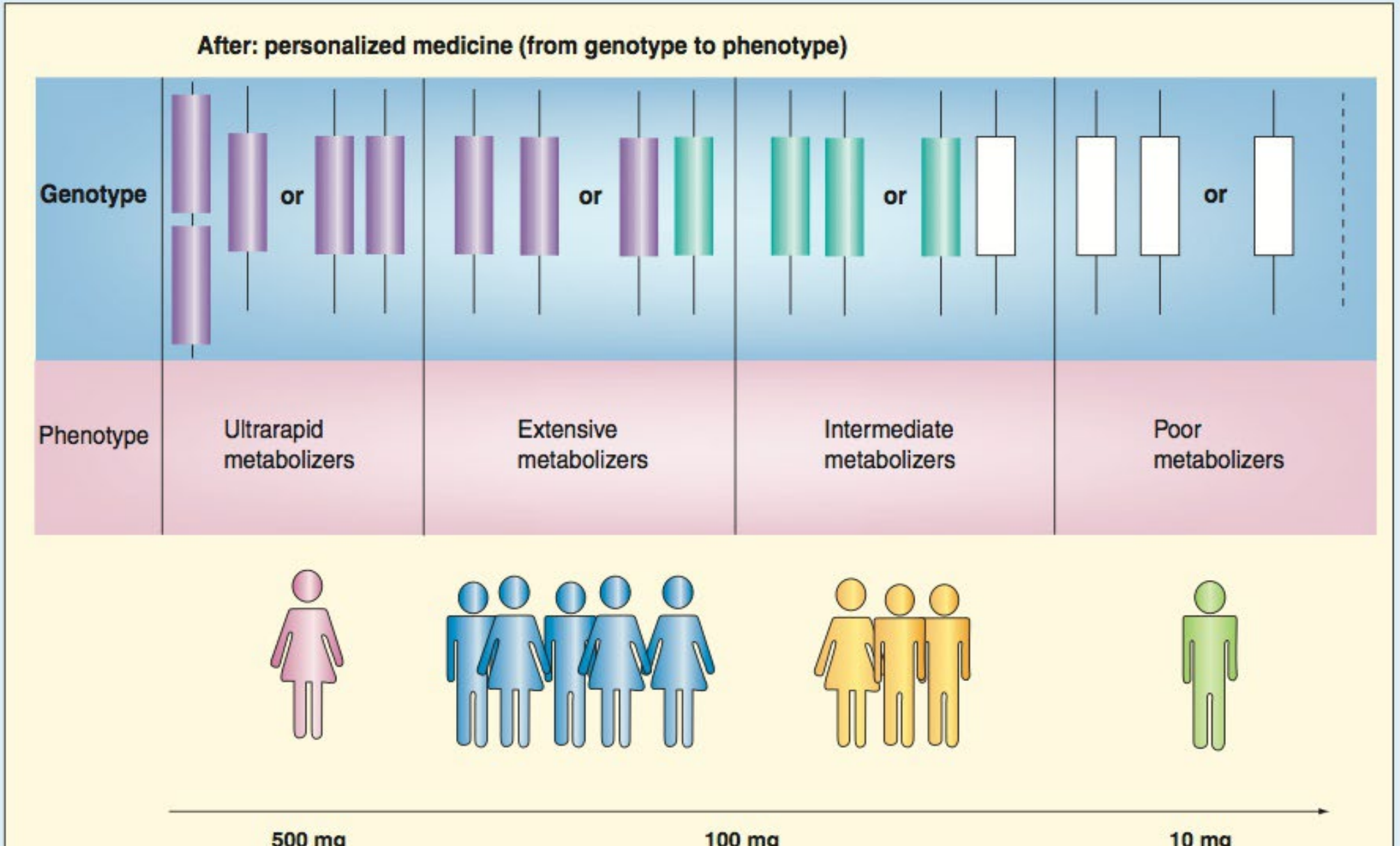
Alleles	Enzyme Activity	Phenotype
Both alleles are non-functional	Little or no enzyme activity	Poor metabolizer (PM)
One allele is non-functional & one allele is functional	Decreased enzyme activity	Intermediate Metabolizer (IM)
Both alleles function normally	Normal enzyme activity	Extensive Metabolizer (EM)
One or more alleles result in increased enzyme function	Increased enzyme activity	Ultra-Rapid Metabolizer (UM)

Pharmacokinetics
Metabolizer Phenotypes

Phenotype	Active Drug	Prodrug
Poor metabolizer (PM)	• Active drug may accumulate • Require lower dose to avoid toxic accumulation	• Inactive prodrug may accumulate • Lack of therapeutic response
Intermediate Metabolizer (IM)	• May require reduced doses • May lead to drug-drug interactions with concomitant medications	
Extensive Metabolizer (EM)	• Standard dose appropriate	• Standard dose appropriate
Ultra-Rapid Metabolizer (UM)	• Requires higher dose to offset higher rate of metabolism	• Rapid onset of effect • May require lower dose to prevent excessive accumulation of any active metabolite

Modify Dose or Avoid based on Metabolizer Phenotype





Xie and Frueh, *Personalized Medicine (2005) 2(4), 325–*

Biochemistry Review

Detoxification
Phase II

Phase II Detoxification Polymorphisms

- **Re-methylation (MTR ,MTRR, MTHFR)**
- **Transmethylation (AHCY)**
- **Trans-sulfuration (CBS, CTH)**
- **Acetylation (NAT2)**
- **Glutathione conjugation (GSTP1, GSTM1/3)**

Important Phase II Detoxification Enzymes

- ***MTR (Methionine Synthase)***
  - *Required for regeneration of methionine from homocysteine*
  - *Requires MTHF and Methyl B12 as a co-factors*
  - *Poor function results in low methionine and high homocysteine*

- ***MTRR (Methionine Synthase Reductase)***
  - *Required for functional methionine synthase*
  - *Essentially regenerates Methyl B12 for Methionine Synthase*

- ***AHCY (Adenosylhomocysteinase)***
  - *Converts adenosylhomocysteine into homocysteine and adenosine*
  - *Results in reduced levels of homocysteine in the pathway*

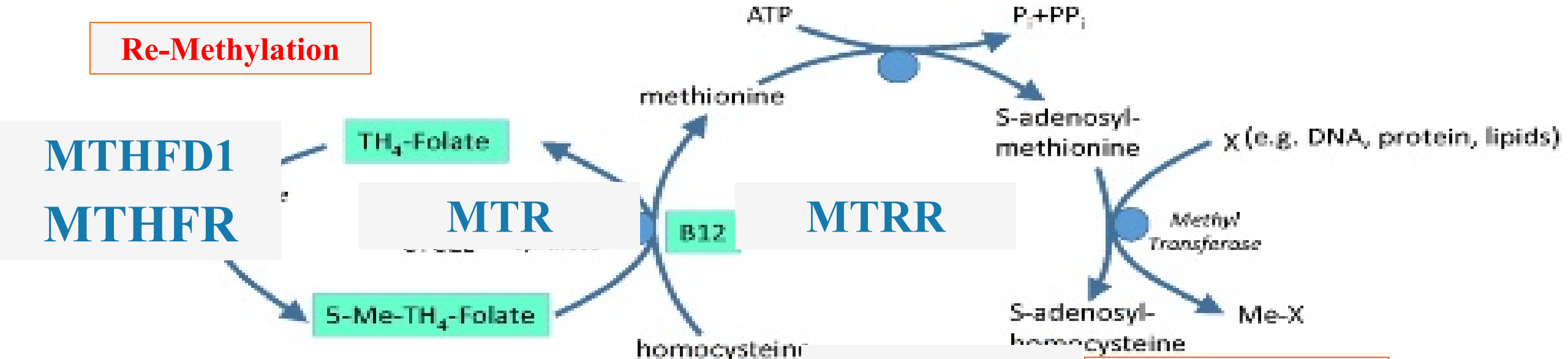
Important Phase II Detoxification Enzymes

- ***MTHFR (Methylenetetrahydrofolate Reductase)***
  - *Required for reconversion of THF to MTHF*

- ***CBS 699 (Cystathionine Beta Synthase)***
  - *Transsulfuration conversion of Homocysteine to Cystathione*
  - *Can cause increased levels of sulfites and ammonia*

- ***CTH (Cystathioninase)***
  - *Enzyme that converts Cystathione to Cysteine*
  - *Important role in glutathione production*

Phase II Detoxification

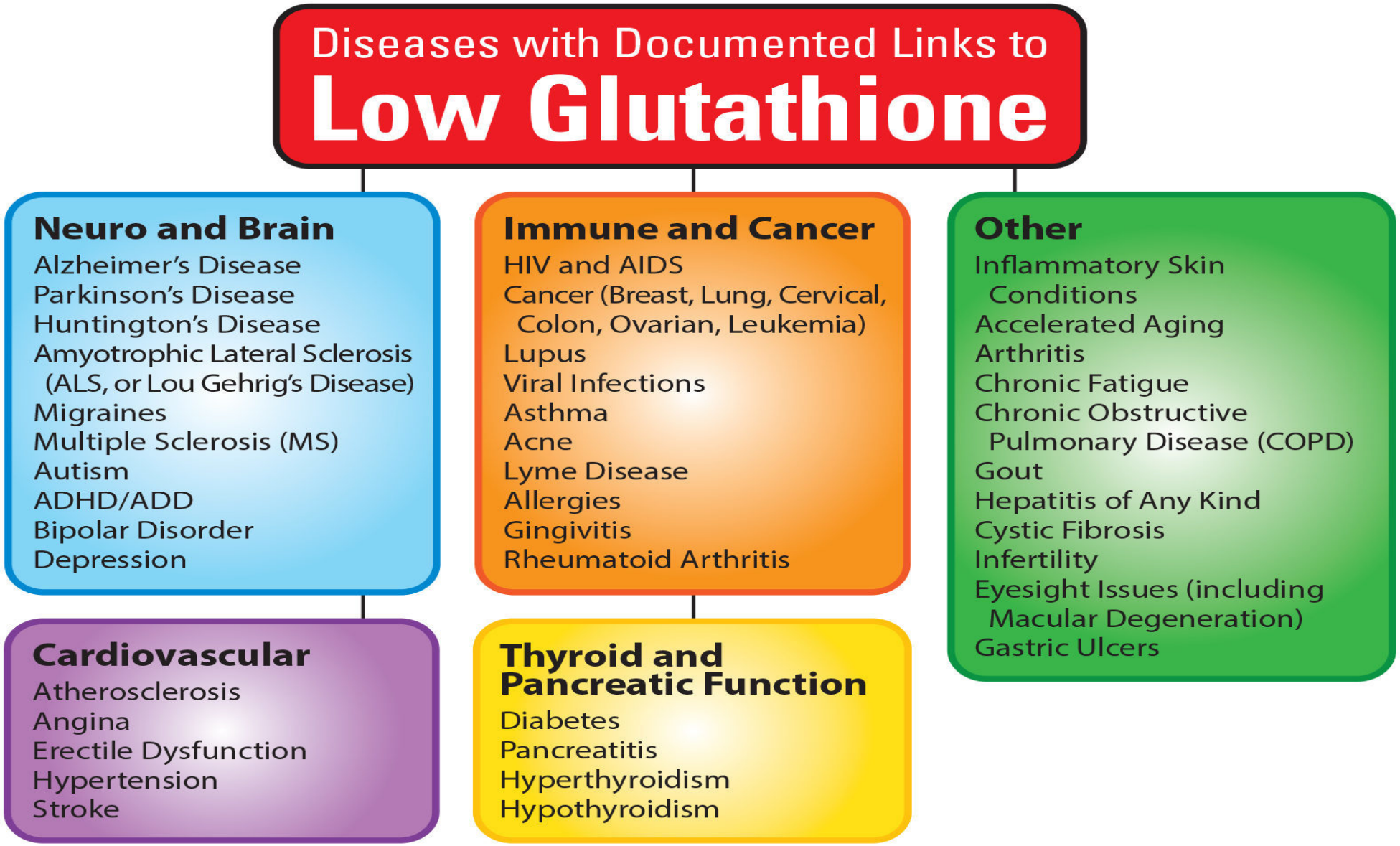


GSTP1

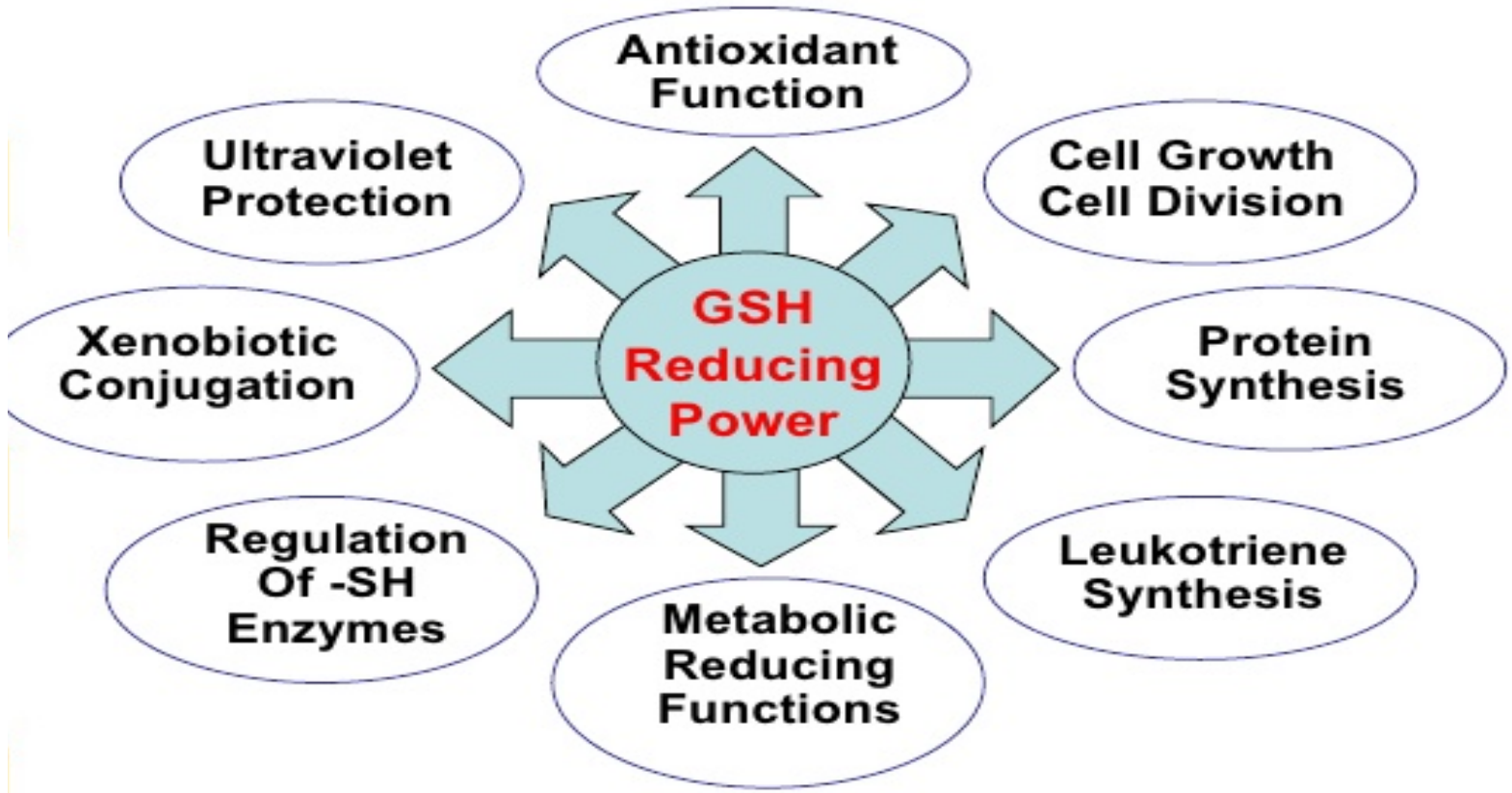
GSTM1

GSTM3

Glutathione Conjugation


Diseases with Documented Links to
Low Glutathione
Neuro and Brain
Alzheimer's Disease
Parkinson's Disease
Huntington's Disease
Amyotrophic Lateral Sclerosis (ALS, or Lou Gehrig's Disease)
Migraines
Multiple Sclerosis (MS)
Autism
ADHD/ADD
Bipolar Disorder
Depression
Immune and Cancer
HIV and AIDS
Cancer (Breast, Lung, Cervical, Colon, Ovarian, Leukemia)
Lupus
Viral Infections
Asthma
Acne
Lyme Disease
Allergies
Gingivitis
Rheumatoid Arthritis
Other
Inflammatory Skin Conditions
Accelerated Aging
Arthritis
Chronic Fatigue
Chronic Obstructive Pulmonary Disease (COPD)
Gout
Hepatitis of Any Kind
Cystic Fibrosis
Infertility
Eyesight Issues (including Macular Degeneration)
Gastric Ulcers
Cardiovascular
Atherosclerosis
Angina
Erectile Dysfunction
Hypertension
Stroke
Thyroid and Pancreatic Function
Diabetes
Pancreatitis
Hyperthyroidism
Hypothyroidism

Roles of Glutathione



Detoxification Phase II - MTRR

- ***Methionine Synthase Reductase (MTRR)***
  - Hetero / Homo = **decreased activity**
  - Regenerates B12 for use in Methionine Synthase
  - Typically causes a high homocysteine (<12) and low methionine
  - Can cause hypomethylation of neurotransmitters, DNA and drug substrates
  - **Treatment: 5-MTHF / Leucovorin, MB12, Methionine**

Detoxification Phase II - AHCY

- ***Adenosylhomocysteinase (AHCY)***
  - Homozygous = **decreased activity**
  - Typically causes a very low homocysteine (<5) and high methionine
  - Can cause hypomethylation of neurotransmitters, DNA and drug substrates
  - Overall result is substantial decrease in all downstream substrates including Glutathione
  - **Treatment: N-Acetyl-Cysteine, Glutathione**

Detoxification Phase II - CTH

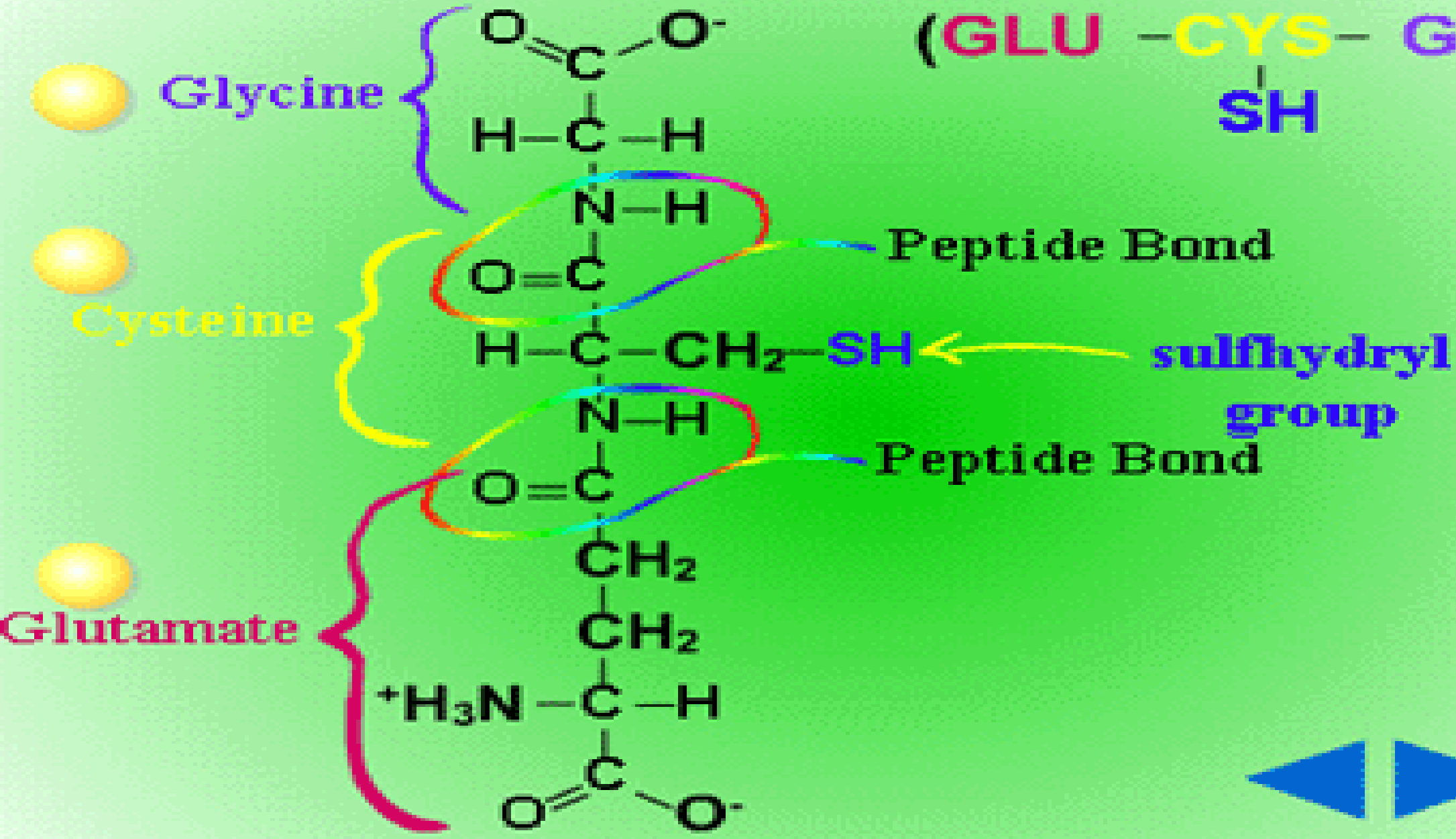
- **Cystathioninase (*CTH*)**
  - Homozygous = **decreased activity**
  - Converts Cystathione into Cysteine
  - Results in low level of Cysteine and high levels of Cystathione
  - Overall result is substantial decrease in all downstream substrates including Glutathione
  - **Treatment: N-Acetyl-Cysteine, Glutathione**

Detoxification Phase II - GST

- **Glutathione-s-Transferase (*GST*)**
  - Hetero / Homo = **decreased activity**
  - Catalyze the conjugation of chemicals to glutathione
  - Can compromise up to 10% of cytosolic proteins in some cells
  - Primary enzyme combination to remove xenobiotics
  - Treatment: High dose glutathione (IV or suppository), Low dose targeted glutathione, N-Acetyl-Cysteine

Reduced glutathione ((-Glutamylcysteinylglycine)

(GLU –CYS– GLY)



Detoxification Phase II -Glutathione Conjugation

- ***GSTP1*** *(Glutathione-s-Transferase pi) (33% of population)*
  - Detoxifies hydrophobic and electrophilic intermediates
  - Removes cytotoxic and carcinogenic agents from extracellular tissue
  - Present in mucousal membranes and skin (bowel, lungs, bladder, sinuses, skin)
  - Associated with **eczema, asthma, chronic sinusitis, IBS, cystitis**

- ***GSTM1*** *(Glutathione-s-Transferase mu 1) (9% of population)*
  - Detoxifies hydrophobic and electrophilic intermediates
  - Removes cytotoxic and carcinogenic agents from intracellular spaces
  - Associated with increased risk of **various cancers and joint inflammation**

- ***GSTM3*** *(Glutathione-s-Transferase mu 3) (brain) (16% of population)*
  - Detoxifies hydrophobic and electrophilic intermediates
  - Removes cytotoxic and carcinogenic agents from brain and nervous system
  - Associated with increased risk of **dementia, neuropathies, radiculopathies, etc.**

Biochemistry Review

Detoxification
Phase III

Phase III Detoxification Polymorphisms

- **Detoxification of Reactive Molecules**
  - **Free Radicals (*SOD2, SOD3*)**
  - **Peroxides (*GPX3*)**
  - **Sulfites (SUOX)**

Phase III Detoxification
SOD1 (Cytoplasm), SOD 2 (Mitochondrial)

- **Superoxide Dismutase (SOD1, SOD2)**
  - Hetero / Homo significance = **Decreased activity**
  - Converts Oxygen radicals into H2O2
  - Reduces free radical oxidative stress in respective areas
  - Correlated with increased risk of cancer, hearing loss, grey matter shrinkage and motor neuron disease
  - **Treatment: NRF2 activators (Tumeric, polyphenols, catechins, Pterostilbene (resveratrol) , sulforaphane (broccoli), black pepper extract, quercetin**

Phase III Detoxification - GPX3

- **Glutathione Peroxidase 3 (*GPX3*)**
  - Homozygous significance = decreased activity
  - Catalyzes the reduction of hydrogen peroxides and hydroperoxides into water and oxygen
  - Warning: Must be cautious with Ozone and IV Vit C therapy
  - **Treatment: Glutathione**

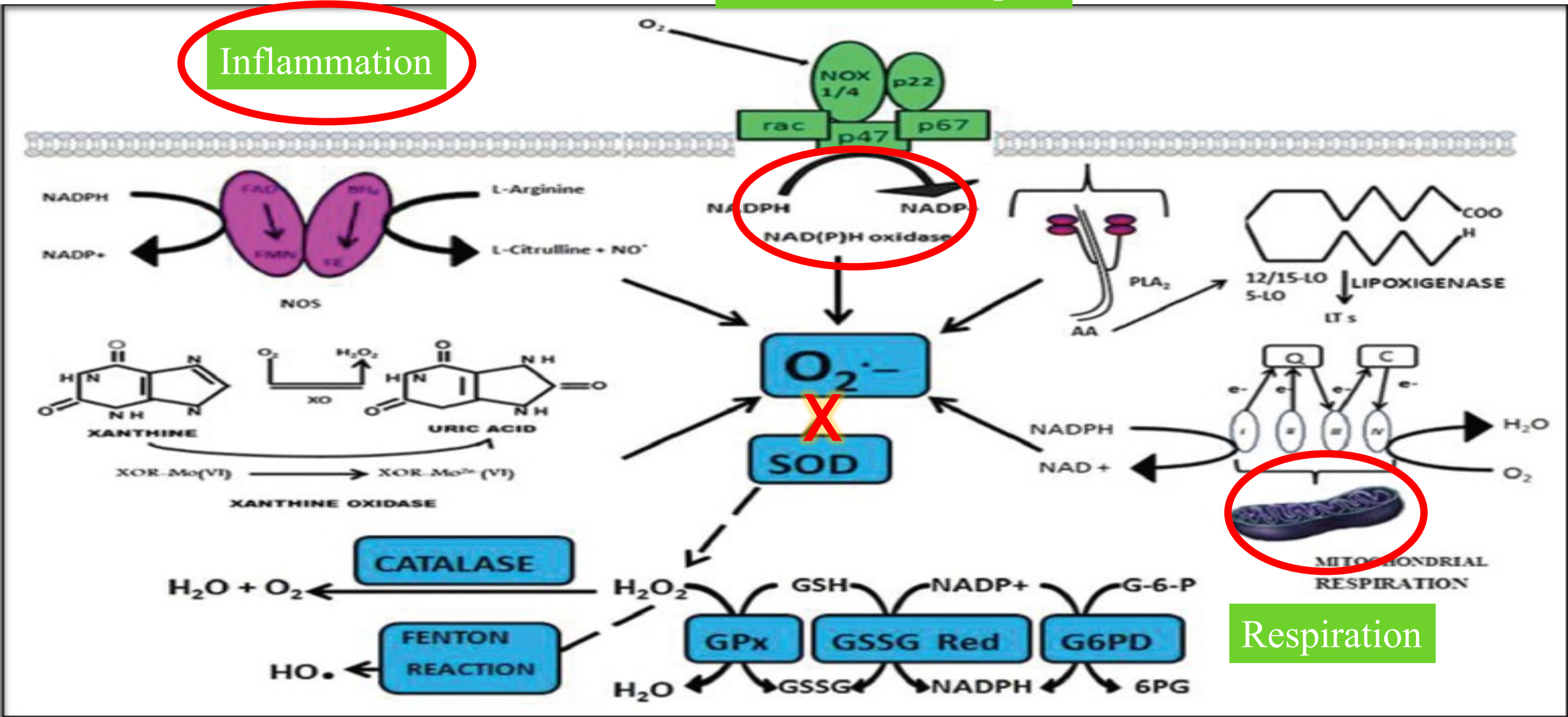
Phase III Detoxification - SUOX

- **Sulfur Oxidase (SUOX)**
  - Homozygous significance = **decreased activity**
  - Catalyzes proteins that contain sulfur (methionine and cysteine)
  - Converts sulfites (toxic) to sulfates (non-toxic)
  - Treatment: Low Protein Diet

Oxygen Free Radicals

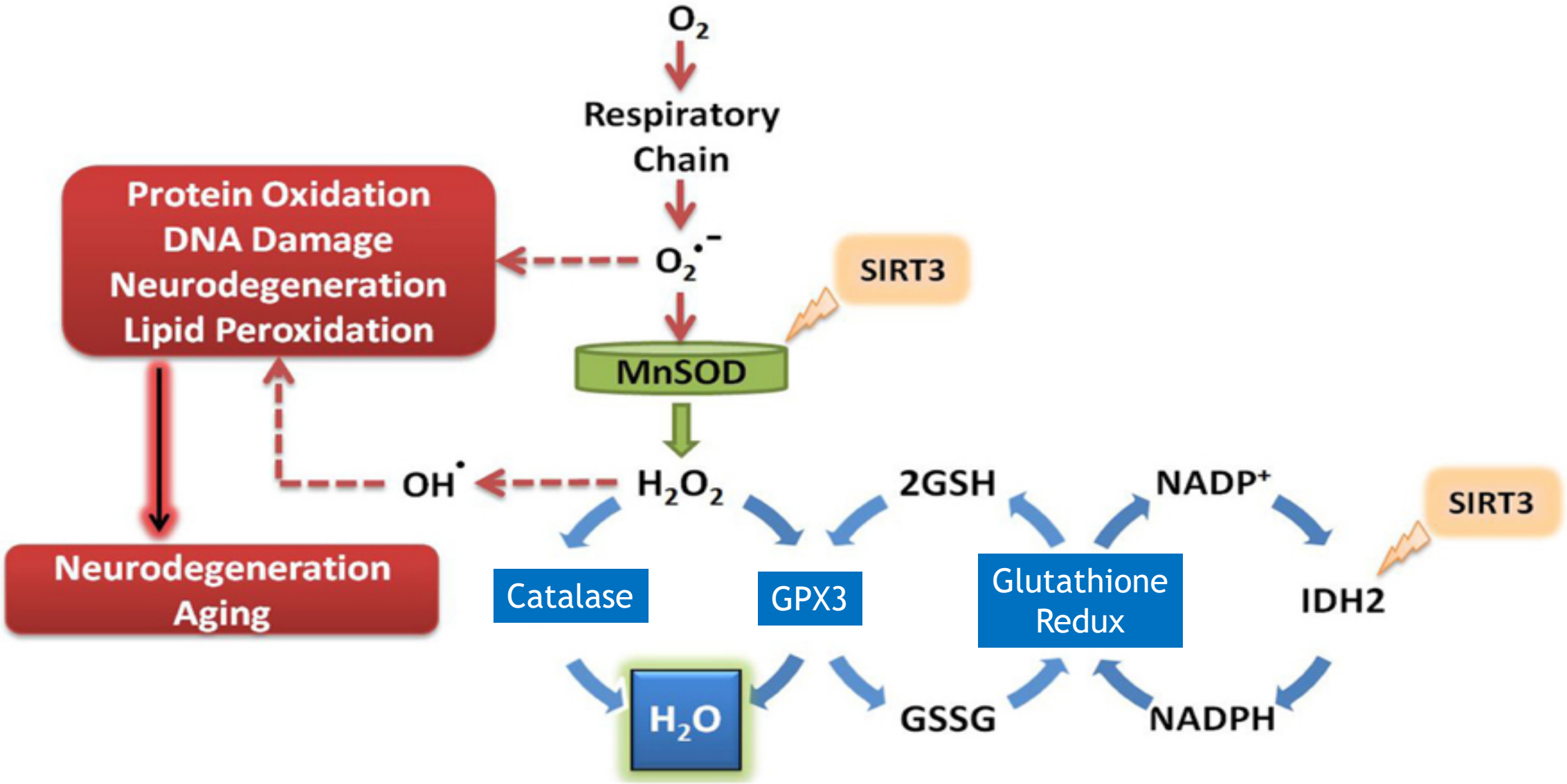
Membrane Transport

Inflammation

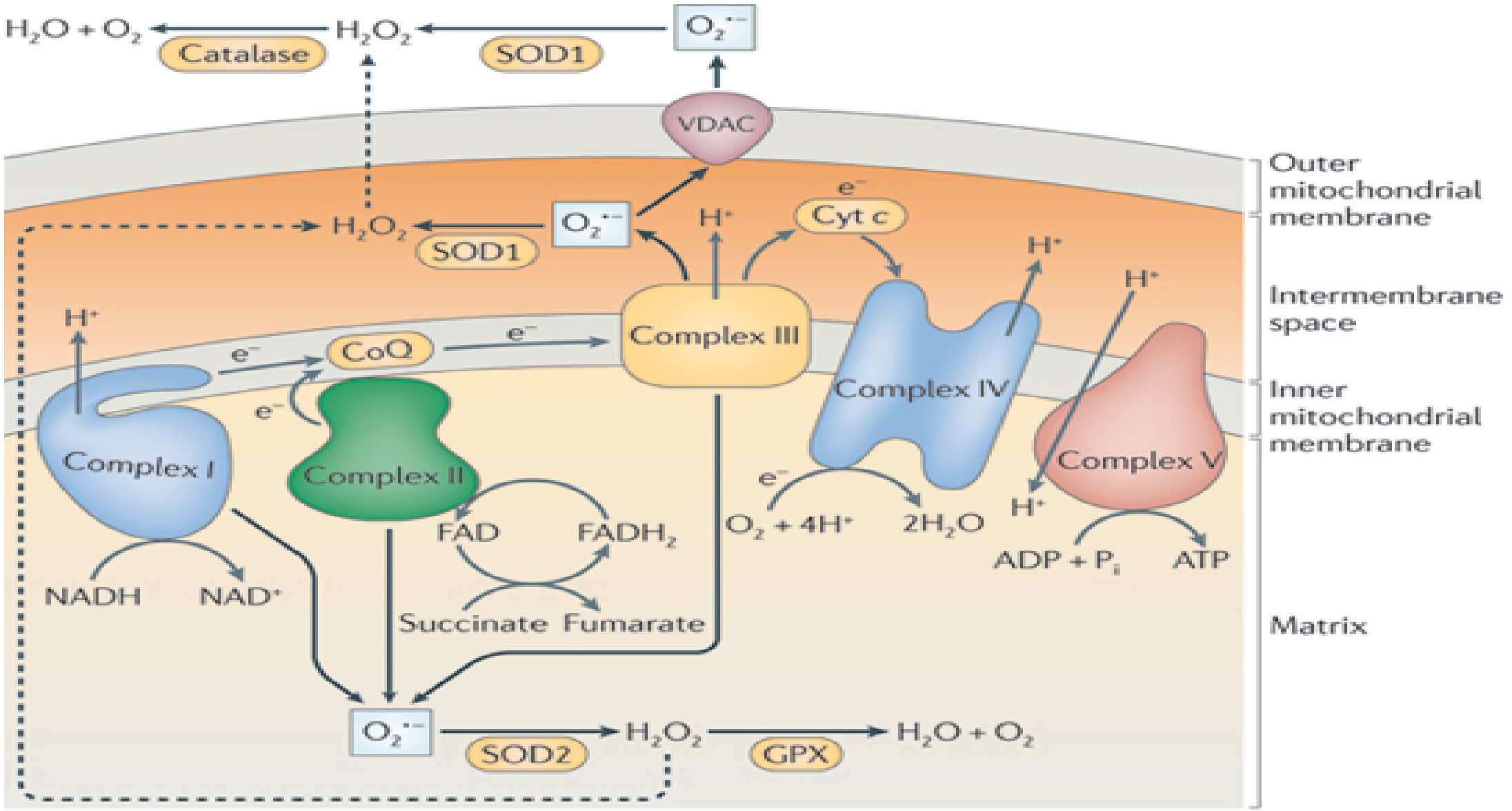


Respiration

SOD and GPX3
Oxygen Free Radicals



SOD and Mitochondria



Biochemistry Review

Vitamin and Minerals

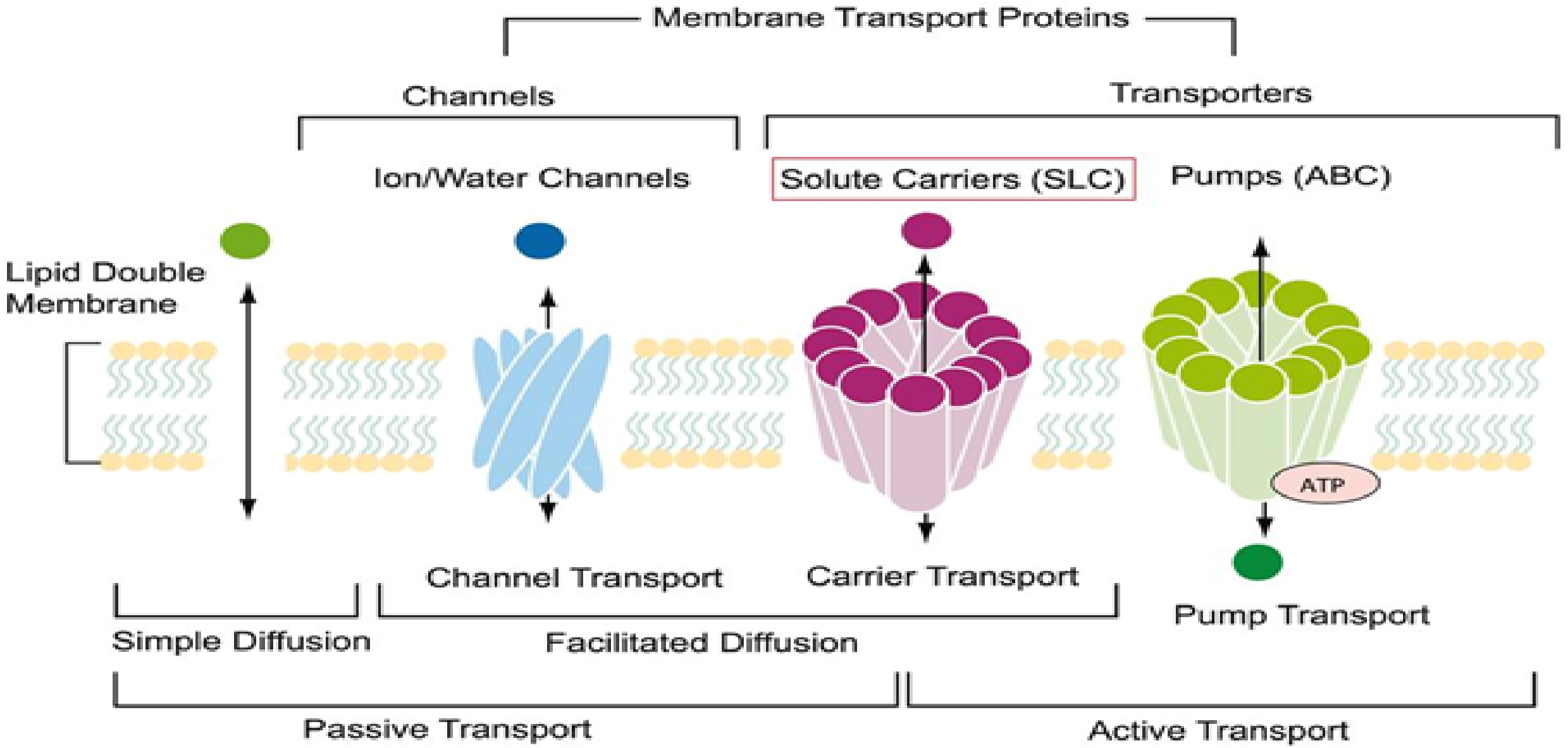
Important Vitamin / Mineral SNPs

- ***SLC30A8 (Solute Carrier Family – Zinc) (MAF .26)***
  - *Responsible for Zinc efflux from cell*
  - *Mutation allows for toxic build-up of intracellular Zinc concentration*
  - *Treatment: Reduce Zinc intake*

- ***SLC23A1 (Solute Carrier Family – Vit C) (MAF: .035)***
  - *Functions as Vit C transporter*
  - *Treatment: High Dose Vit. C*

- ***SLC5A6 (Solute Carrier Family Biotin / Pantothenate) (MAF .47)***
  - *Functions as transporter for pantothenate (B5) and Biotin (B7)*
  - *Treatment: High dose Biotin and Pantothenic Acid*

Solute Carrier Family



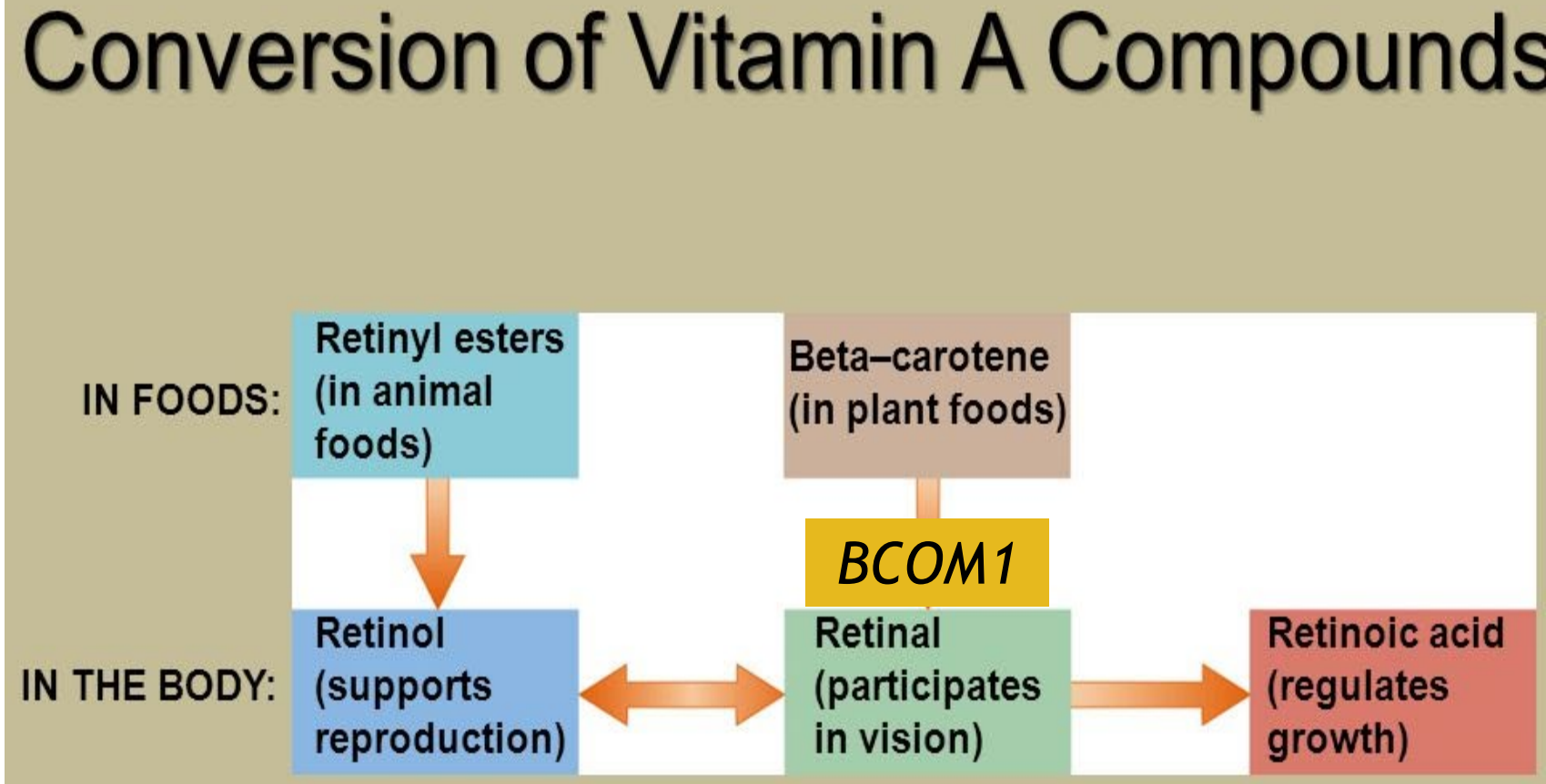
Important Vitamin SNPs

- ***BCOM1 (Beta Carotene Oxygenase 1) (MAF .16 and .22)***
  - *Two separate SNPS*
  - *Both SNPs = 69% reduction If one SNP = 32% reduction*
  - *Responsible for conversion of Beta Carotene to Retinol*
  - *Treatment: Retinol (Vit A)*

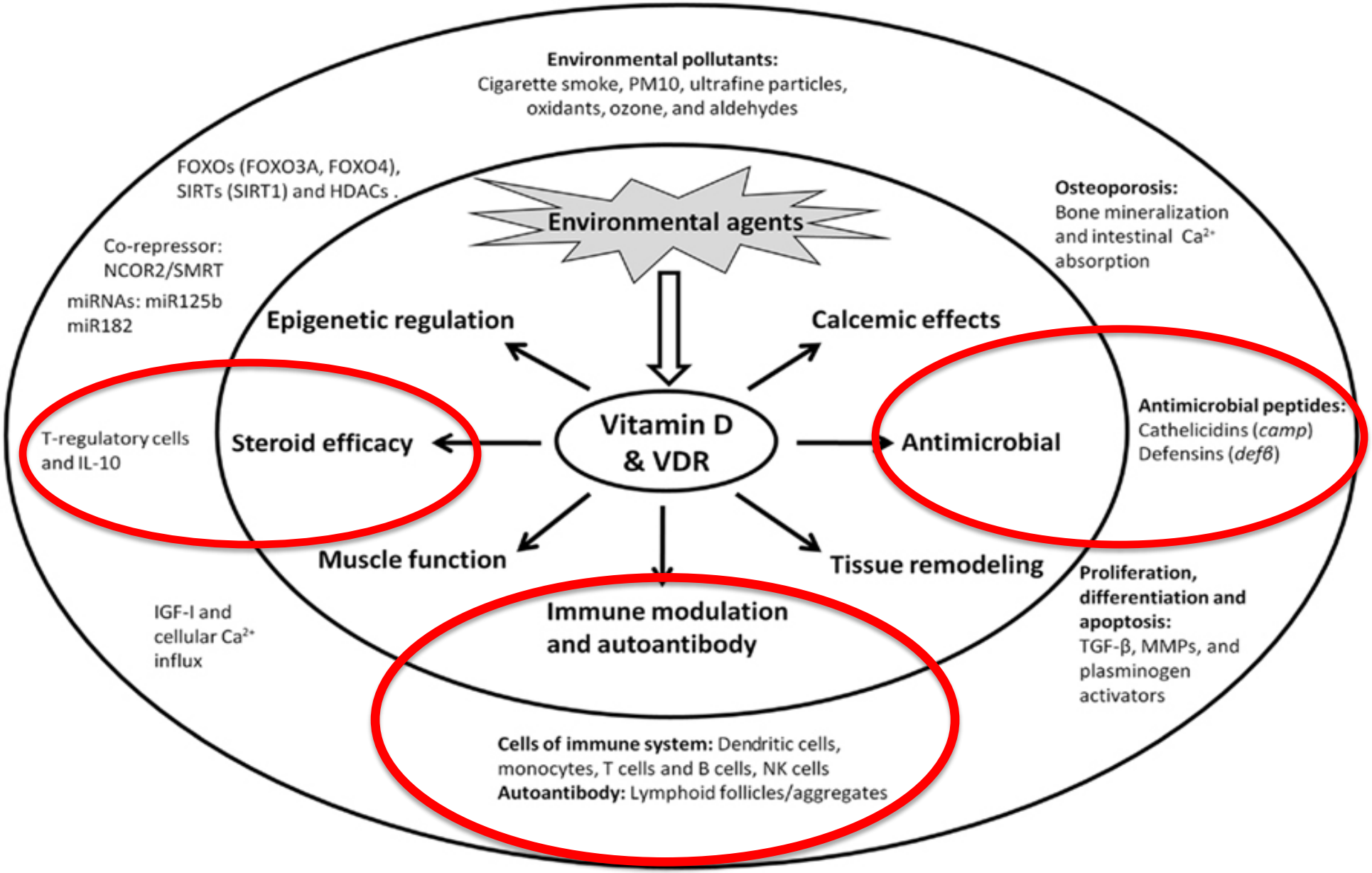
- ***VDR–taq and DBP (Vit D Binding Protein) (MAF .20)***
  - *Responsible for Binding and Transporting Vit D*
  - *Most Vit D in blood is bound to DBP*
  - *Polymorphism reduces both binding capability and response to Vit D therapy*
  - *Treatment: High Dose Vit. D + K*

- ***CoQ2 (Ubiquinone Synthase) (MAF: .35)***
  - *Results in CoQ10 deficiency*
  - *Treatment: High Dose Ubiquinone and PQQ*
  - *Must Avoid Statin Usage if possible*

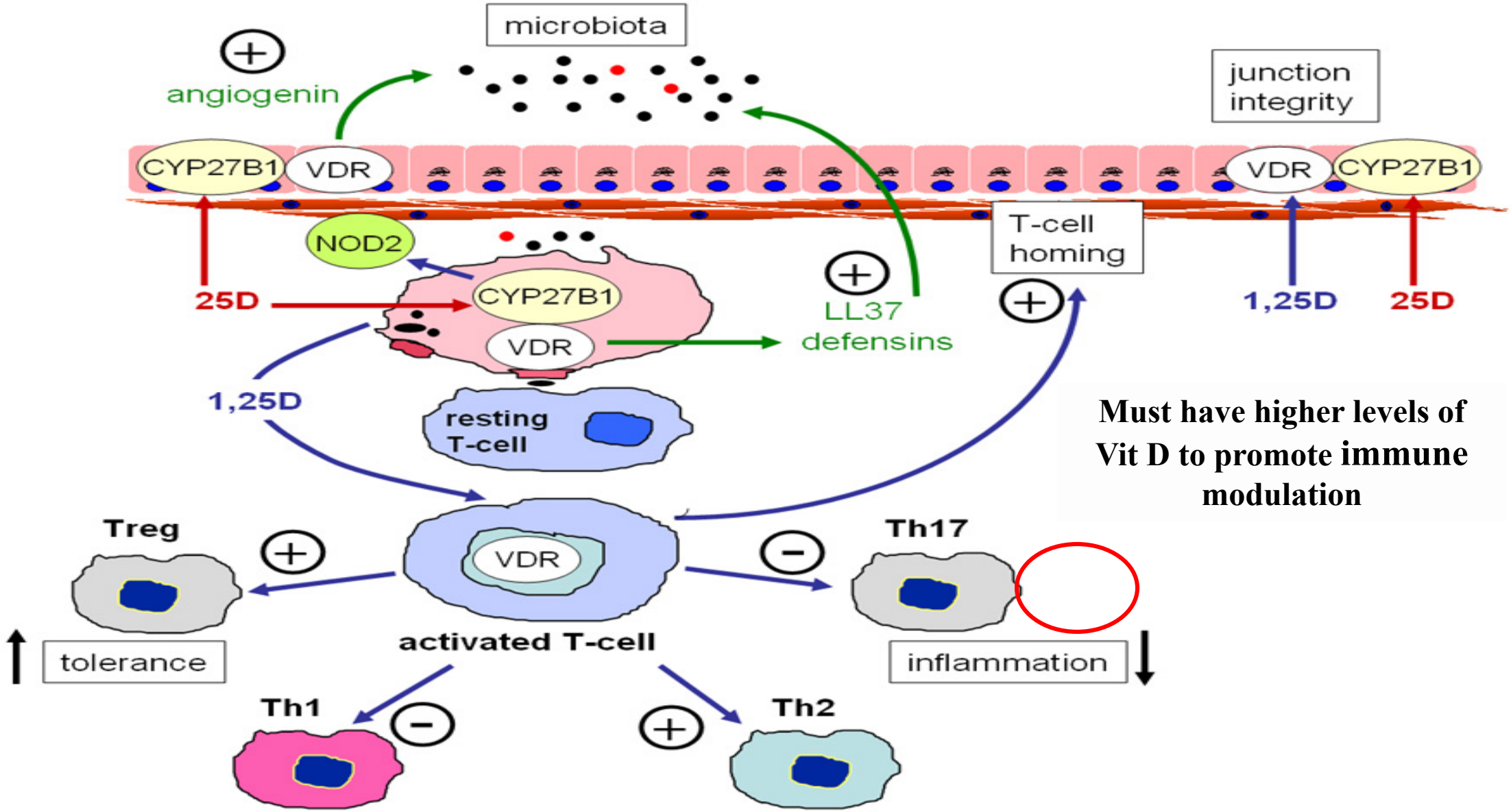
BCOM1
Beta Carotene Dioxygenase 1



Vitamin D Functions

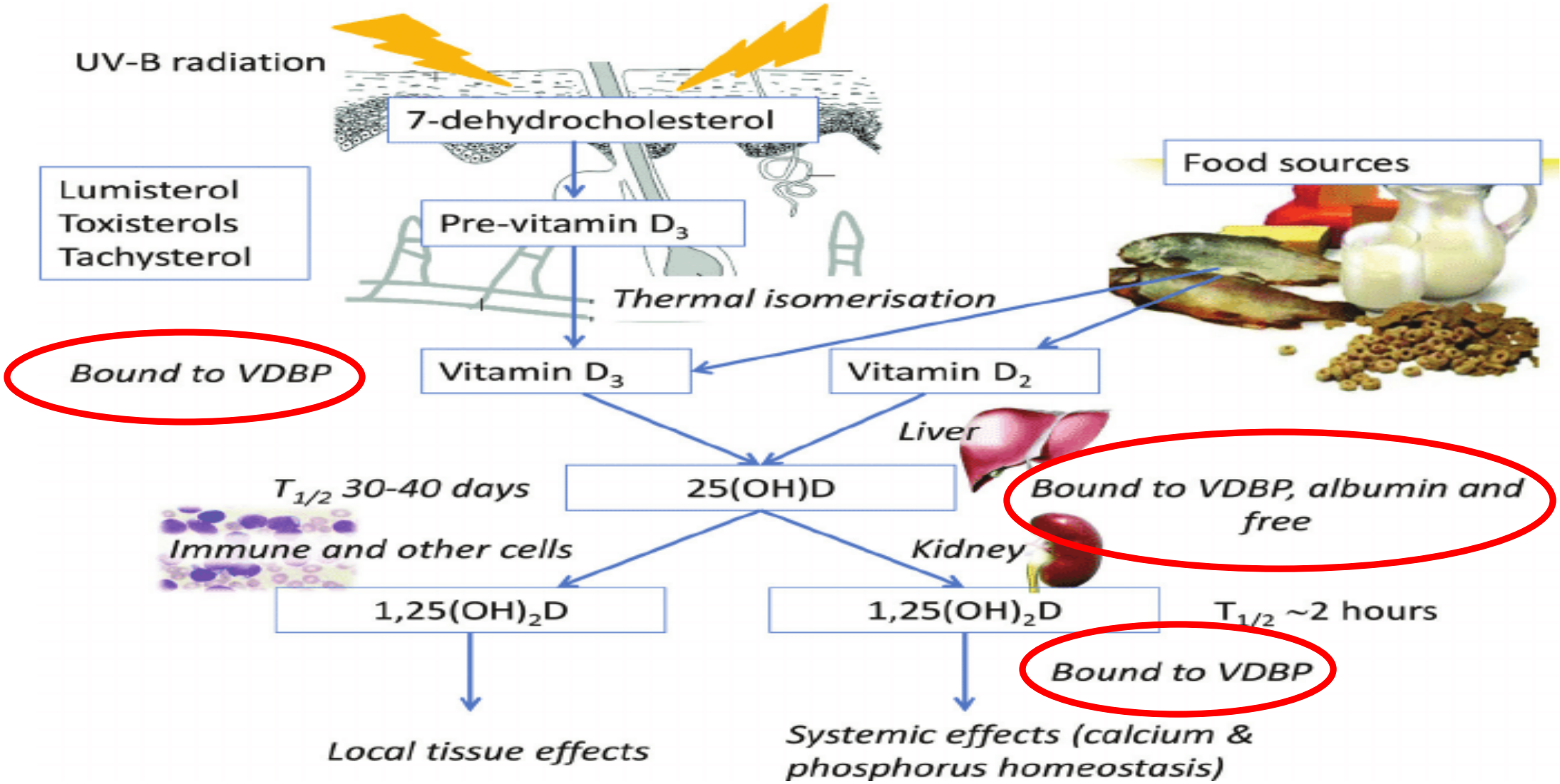


VDR (Vitamin D Receptor)
Immune Modulation

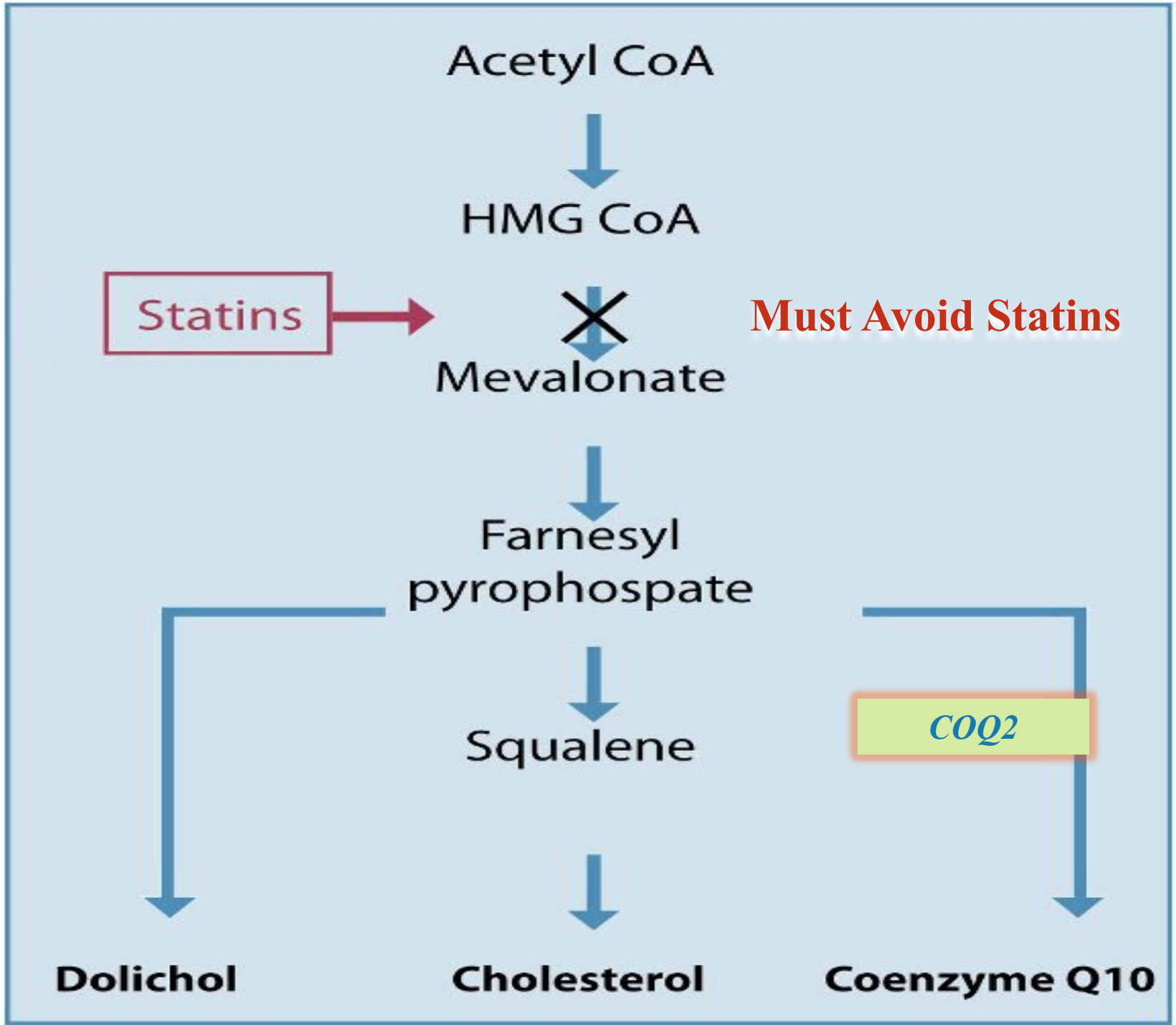


Must have higher levels of Vit D to promote immune modulation

Vitamin D Biochemistry
DBP (Vit D Binding Protein)



COQ2
Ubiquinol Synthase



Biochemistry Review

Women's Hormones

Important Hormone Related SNPs
Estrogen

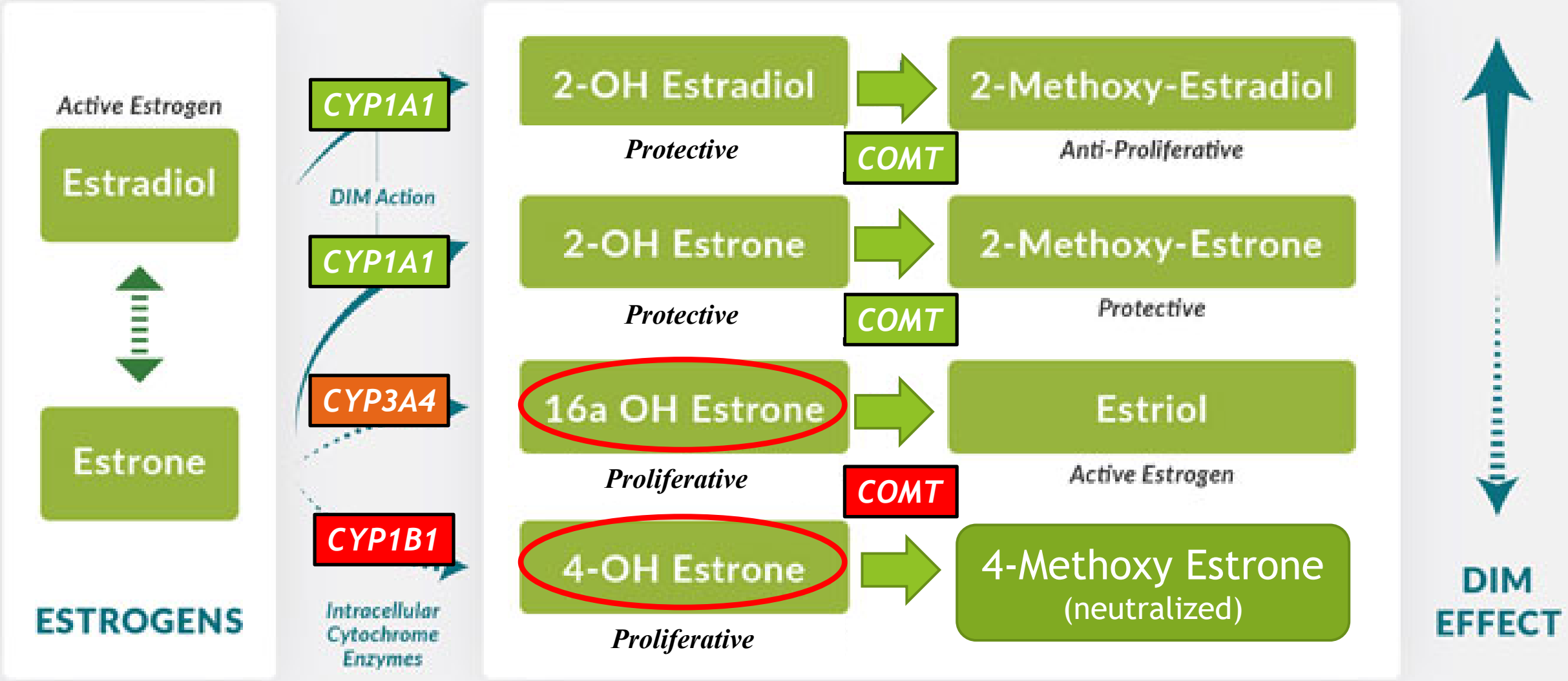
- ***CYP1B1 (Cytochrome 1B1)***
  - Converts E1/E2 to 4-Hydroxyestrone (pro-carcinogenic)
  - Homo = **Up Regulation** (higher production of 4-OHE1)

- ***CYP1A1 (Cytochrome 1A1)***
  - Converts E1/E2 to 2-Hydroxyestrone
  - Homo = **Reduced Function** (lower production of 2-OHE1)

- ***COMT (Catecholamine-O-Methyltransferase)***
  - Converts 4-OHE1 (pro-carcinogenic) to 4-MeE1 (neutralized)
  - Converts 2-OHE1 to 2-methoxyE1 (protective)
  - Homo = **Reduced Function** (lower production of 4-MeE1 and 2-MeE1)

- **GSTP1 (Glutathione-s-transferase Pi1)**
  - Responsible for Phase 2 clearance of mercapturates (carcinogenic quinones)
  - Homo = **Poor clearance**

Estrogen Metabolism



Important Hormone Related SNPs
Men and Women

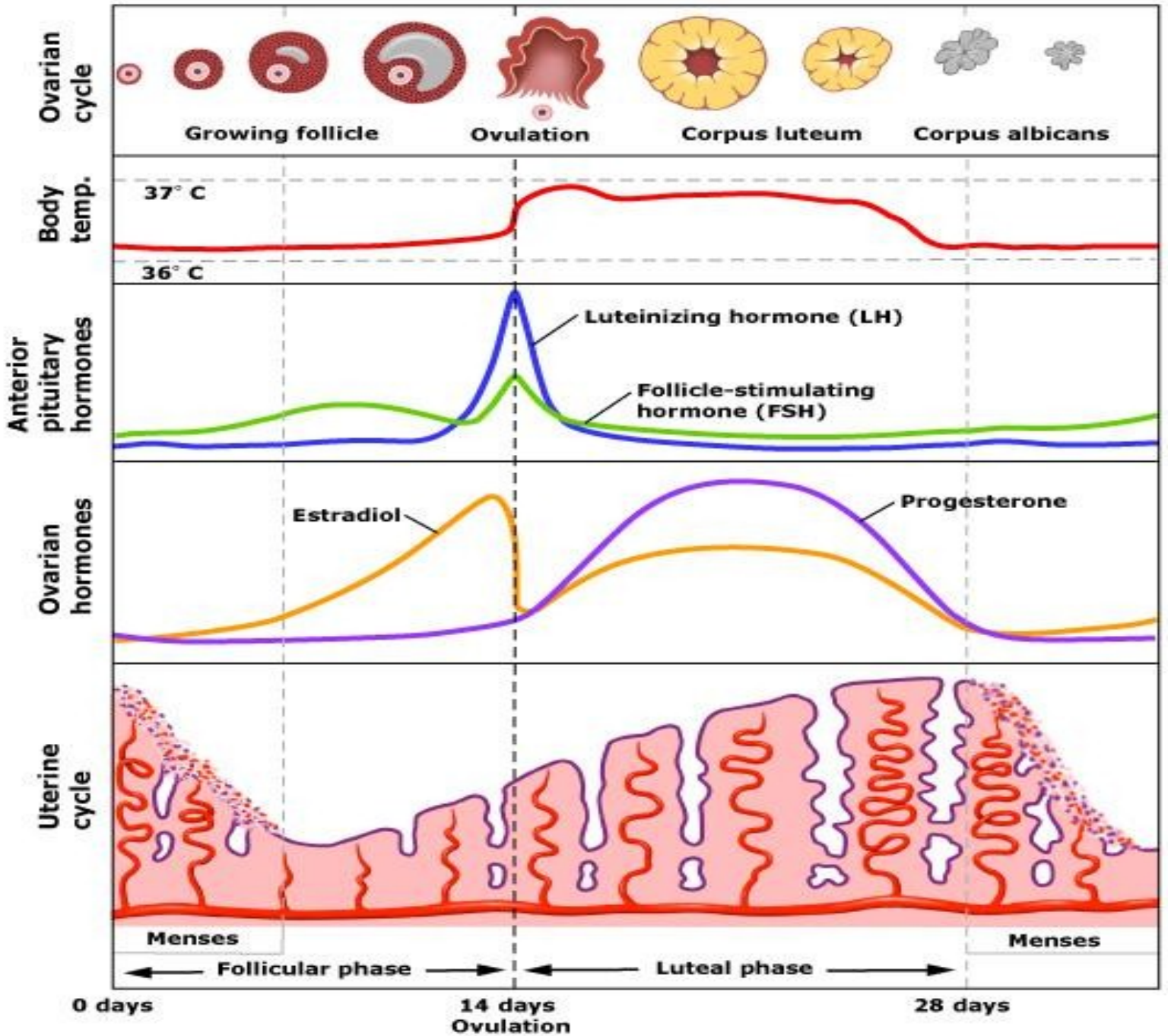
- ***FSHR (Follicular Stimulating Hormone Receptor)***
  - Homo = **Reduced Sensitivity**
  - Higher risk of Premature Ovarian Failure and lower response rate to ovarian stimulation
  - Will probably need hormone supplementation

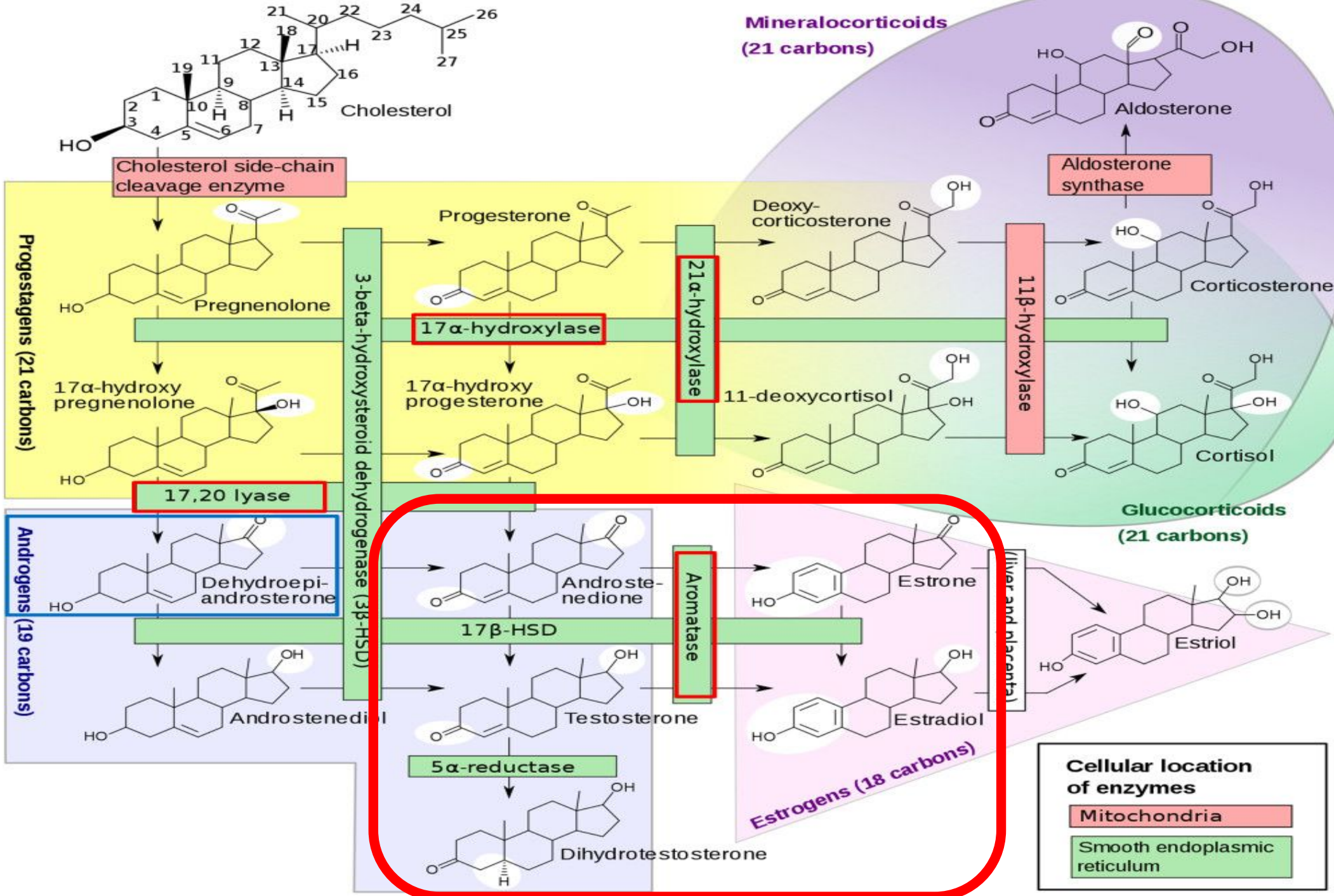
- ***CYP19A1 (Cytochrome 19A1)***
  - Also known as **Aromatase**
  - Converts Androstenedione and Testosterone to Estrone and Estradiol respectively
  - Homo = **Increased Function** (higher levels of Estrone and Estradiol)
  - Associated with increased risk of endometriosis and estrogen dominance
  - Consider IC3 (indole 3 carbinol), Aromatase inhibitor or DIM (Di-Indoyl Methane)

Follicular Stimulating Hormone (FSH)

and

Luteinizing Hormone (LH)



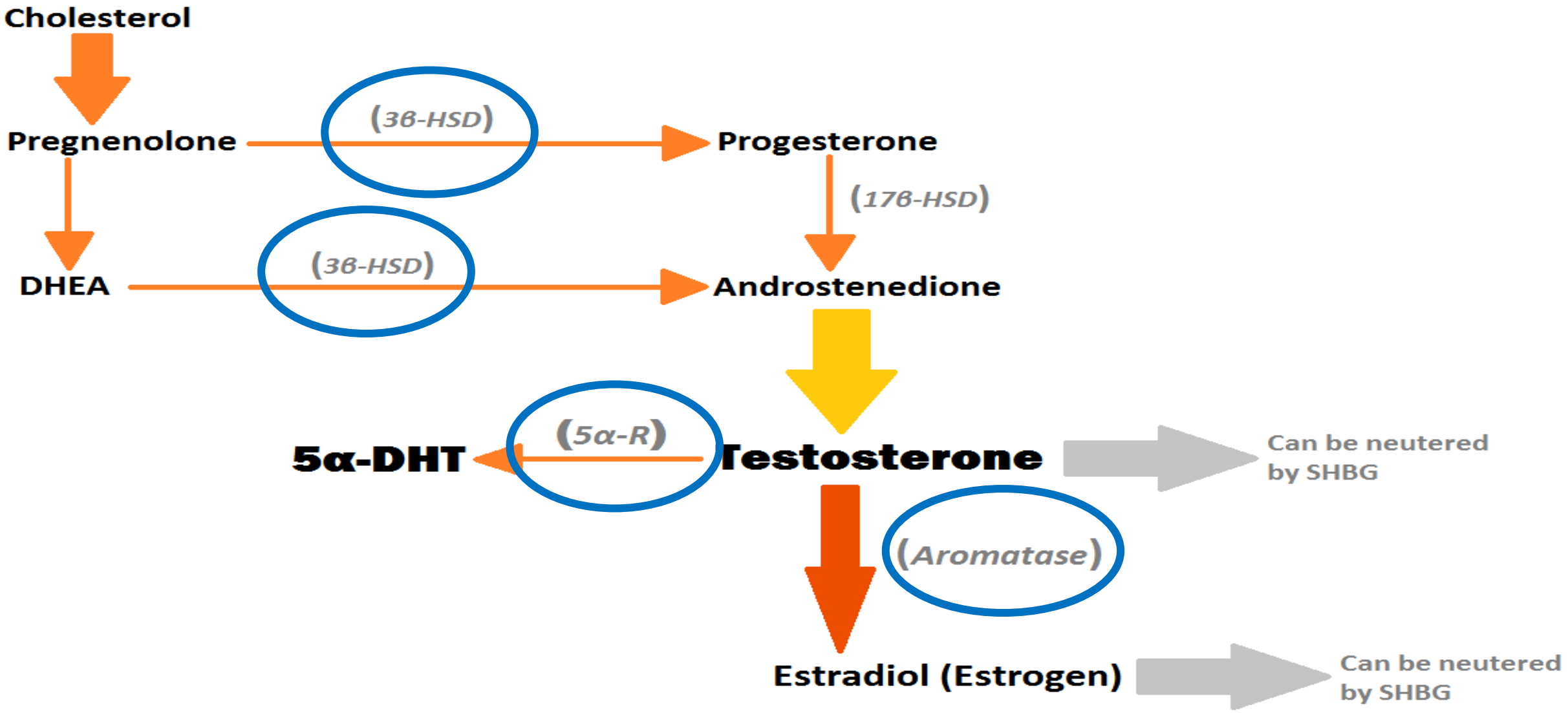

Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
Progesterone
17α-hydroxylase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
21α-hydroxylase
Deoxy-corticosterone
11β-hydroxylase
Corticosterone
Aldosterone synthase
Aldosterone
Mineralocorticoids
(21 carbons)
17α-hydroxy pregnenolone
17α-hydroxy progesterone
11-deoxycortisol
Cortisol
Glucocorticoids
(21 carbons)
17,20 lyase
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Androstenedi
Testosterone
5α-reductase
Dihydrotestosterone
Aromatase
Estrone
Estradiol
Estriol
(liver and placenta)
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Important Hormone Related SNPs
Men and Women

- ***HSD3B2 (3-Beta-Hydroxysteroid Dehydrogenase Type II)***
  - Utilized in conversion of all ketosteroid hormones
  - Hetero / Homo = **Reduced Function**
  - Polymorphism causes deficiency in all ketosteroids
  - Associated with increased risk of Gonadal and Adrenal insufficiency
  - Will need significant hormonal assistance

- **SRD5A (Steroid 5 Alpha Reductase)**
  - Converts testosterone to Di-hydrotestosterone (DHT)
  - Hetero / Homo = **Increased Function**
  - Increased Risk of Androgenic Symptoms
  - Recommend measuring DHT levels
  - Consider DHT blockers (Beta Sitosterol(Saw Palmetto), Stinging Nettle, Spironolactone)

Testosterone Metabolism



Food for Thought

"Be skeptical, ask questions, demand proof. Demand evidence. Don't take anything for granted. But here's the thing; When you get proof, you need to accept the proof. And we're not good at doing that."

Michael Specter

End of Day 1

DAN PURSER MD

CHANGING THE MATH ON YOUR HEALTH

BY DAN PURSER MD

CASE #8: HOMOZYGOUS C677T MTHFR & 0THER GENETIC ERRORS

GENETIC SNPS OR ERRORS DISCUSSED

Homozygous C677T MTHFR

FOLR2

MTHFD1

MTRR A66G

GAD1

SLC19A1

MAO-B

COMT V158M

COMT H62H

IL5

SOD2

FOXE1

ACE

LESSON 1
INTRODUCTION

WHO AM I?

DAN PURSER - an MD

Occasionally think I’m a Naturopath

Endocrinology Research

Currently in a Cosmetic Surgery Group

Deal with complex wound issues and get to the root causes

Practice is in Lindon Utah

World Educator and Speaker

Also an Author…

ALSO, I EDUCATE ALL OVER THE WORLD

This selfie was taken in Tokyo near my hotel.

I’ver spoken to fans in over 50 countries and every state (more than once).

Search online Dan Purser MD in (say) Borneo (or Brisbane) and see what comes up.

This year my goal is to educate physicians.

I’ve partnered with WorldLink Medical, LLC and some really big software companies to accomplish this.

So get ready.

FULL AMA (AMERICAN MEDICAL ASSOCIATION) DISCLOSURE

I’m a 30 year member of the AMA and am my county’s rep for the Utah Medical Association for 12 years.

I have also written books on the genetic medical errors.

All this is my own medical opinion

Not selling any products.

END LESSON 1

LESSON 1:
A MEDICAL PARADIGM SHIFT

FIRST

NO MORE BANDAIDS

Like giving an amphetamine for Chronic Fatigue Syndrome

What’s the actual cause of the fatigue?

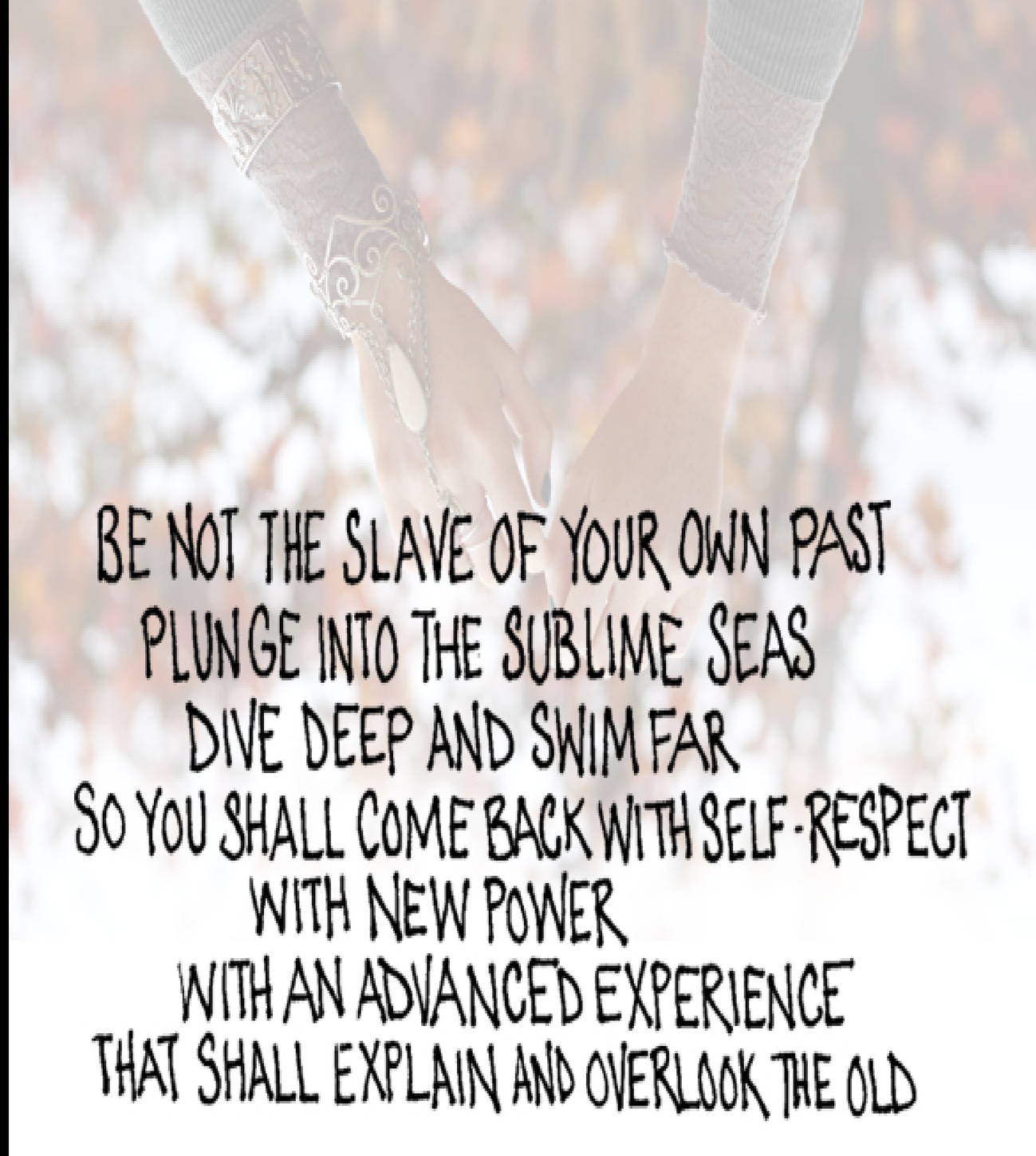
THEN

Start Practicing Root Cause Medicine

Get it? From here on out, you're going to look for that root cause of the fatigue…

PLEASE TAKE THE TIME

TO DIVE OR DIG DEEPER, TO REALLY QUESTION THE WHY...



LANDMARK 1998 STANFORD STUDY PUBLISHED IN JAMA

JAMA. 1998 May 20;279(19):1548-53.

https://jamanetwork.com/journals/jama/fullarticle/187543

Why patients use alternative medicine: results of a national study.

Astin JA[1].

Author information

[1]Stanford Center for Research in Disease Prevention, Stanford University School of Medicine, Palo Alto, Calif 94304-1583, USA. astin@scrdp.stanford.edu

Abstract

CONTEXT: Research both in the United States and abroad suggests that significant numbers of people are involved with various forms of alternative medicine. However, the reasons for such use are, at present, poorly understood.

OBJECTIVE: To investigate possible predictors of alternative health care use.

METHODS: Three primary hypotheses were tested. People seek out these alternatives because (1) they are dissatisfied in some way with conventional treatment; (2) they see alternative treatments as offering more personal autonomy and control over health care decisions; and (3) the alternatives are seen as more compatible with the patients' values, worldview, or beliefs regarding the nature and meaning of health and illness. Additional predictor variables explored included demographics and health status.

DESIGN: A written survey examining use of alternative health care, health status, values, and attitudes toward conventional medicine. Multiple logistic regression analyses were used in an effort to identify predictors of alternative health care use.

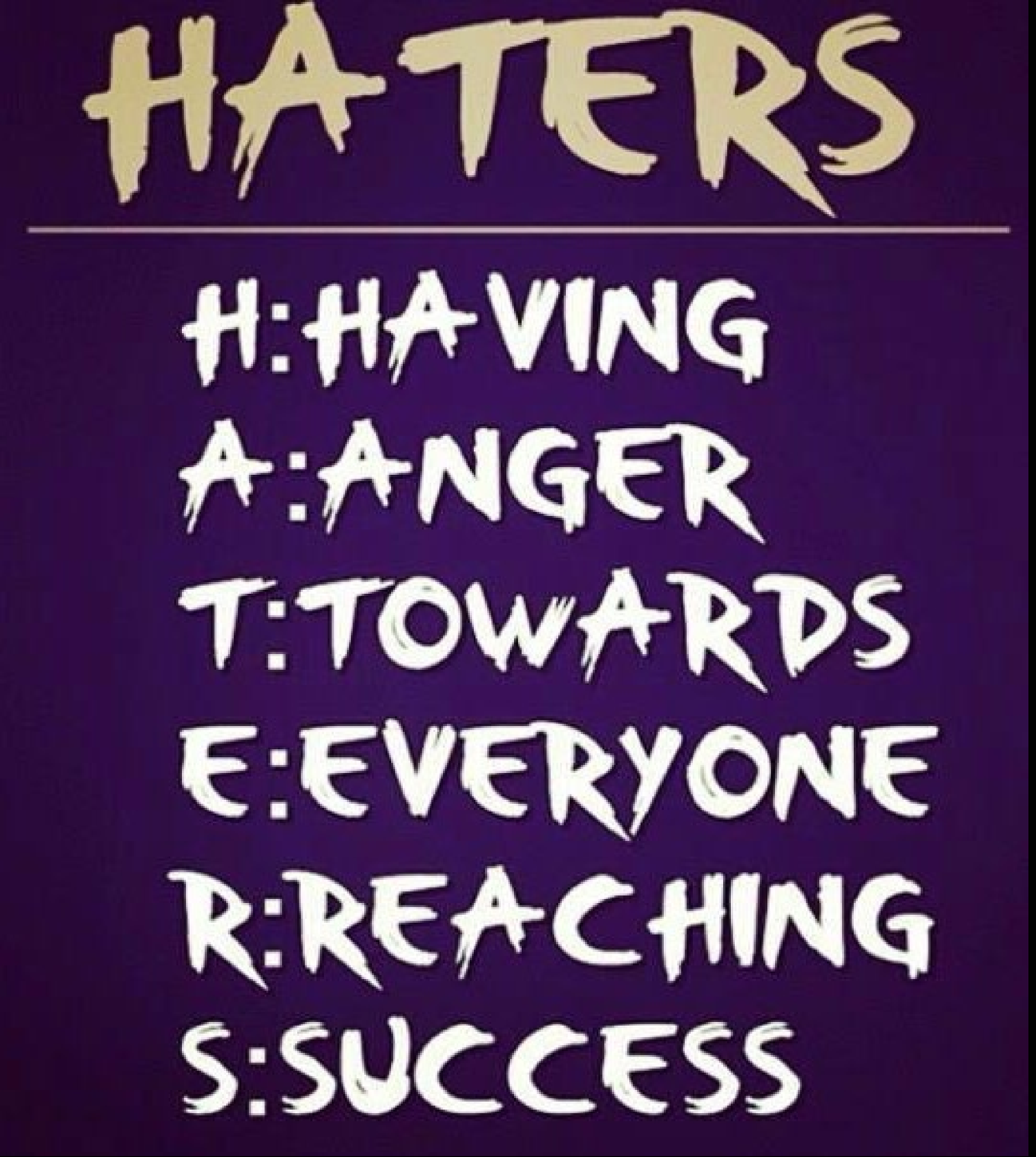
SETTING AND PARTICIPANTS: A total of 1035 individuals randomly selected from a panel who had agreed to participate in mail surveys and who live throughout the United States.

MAIN OUTCOME MEASURE: Use of alternative medicine within the previous year.

RESULTS: The response rate was 69%. The following variables emerged as predictors of alternative health care use: more education (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1-1.3); poorer health status (OR, 1.3; 95% CI, 1.1-1.5); a holistic orientation to health (OR, 1.4; 95% CI, 1.1-1.9); having had a transformational experience that changed the person's worldview (OR, 1 .8; 95% CI, 1 .3-2.5); any of the following health problems: anxiety (OR, 3.1; 95% CI, 1.6-6.0); back problems (OR, 2.3; 95% CI, 1 .7-3.2); chronic pain (OR, 2.0; 95% CI, 1.1 -3.5); urinarytract problems (OR, 2.2; 95% CI, 1.3-3.5); and classification in a cultural group identifiable by their commitment to environmentalism, commitment to feminism, and interest in spirituality and personal growth psychology (OR, 2.0; 95% CI, 1.4-2.7). Dissatisfaction with conventional medicine did not predict use of alternative medicine. Only 4.4% of those surveyed reported relying primarily on alternative therapies.

CONCLUSION: Along with being more educated and reporting poorer health status, the majority of alternative medicine users appear to be doing so not so much as a result of being dissatisfied with conventional medicine but largely because they find these health care alternatives to be more congruent with their own values, beliefs, and philosophical orientations toward health and life.

69%
WANTED
MORE
NATURAL
THERAPY
OPTIONS
1998



NAYSAYERS

LIKE DR NEAL ROUZIER SAYS,
THERE ARE ALWAYS HATERS

DON'T BILL INSURANCE —
THOUGH IT'S NOT, THEY'LL TRY
TO CALL IT FRAUD OR QUACKERY

REMEMBER SIMMELWEISS

MAKING THEIR DISSATISFIED
PATIENTS HAPPY WILL MAKE
OTHER DOCTORS MAD AT YOU

PATIENTS WILL LOVE YOU
THOUGH

NAYSAYERS

INSURANCE COMPANIES

CLEVELAND CLINIC

https://health.clevelandclinic.org/2013/09/a-genetic-test-you-dont-need/

A Genetic Test You Don't Need

Testing MTHFR is usually unnecessary

September 27, 2013 / By Charis Eng, MD, PhD

As a geneticist and researcher, I believe in the power of genetic testing. By identifying genetic mutations, we can improve care and save lives.

But just because we *can* test something doesn't always mean we *should*.

Take the *MTHFR* gene, for example. *MTHFR* codes for an enzyme that helps your body convert homocysteine into an amino acid that processes proteins. People with mutations or variations of *MTHFR* may end up with homocystinuria, a disorder that affects the eyes, joints and other parts of the body. High homocysteine levels also have been connected to heart disease and strokes.

There is a genetic test for *MTHFR* variations. But there's also a cheaper and more accurate way to test for whether *MTHFR* variations are causing disease. We simply check the levels of homocysteine in the blood. If levels are high, we can react appropriately. If homocysteine levels are normal — even if there is an *MTHFR* variation — then nothing needs to be done clinically.

In other words, the homocysteine levels determine our actions, not the *MTHFR* test results.

"Keeping an eye on which tests truly improve care and which ones may waste money is more important than ever."

Charis Eng, MD, PhD

Founding Chairwoman of the Genomic Medicine Institute

Words from an ignorant person whose never seen a SpectraCell.

Simple test, simple solutions

Not only is the test for homocysteine levels simple, but so are the solutions. People with high homocysteine levels typically respond well to supplementation with vitamins such as B6, B12, and folate or folic acid.

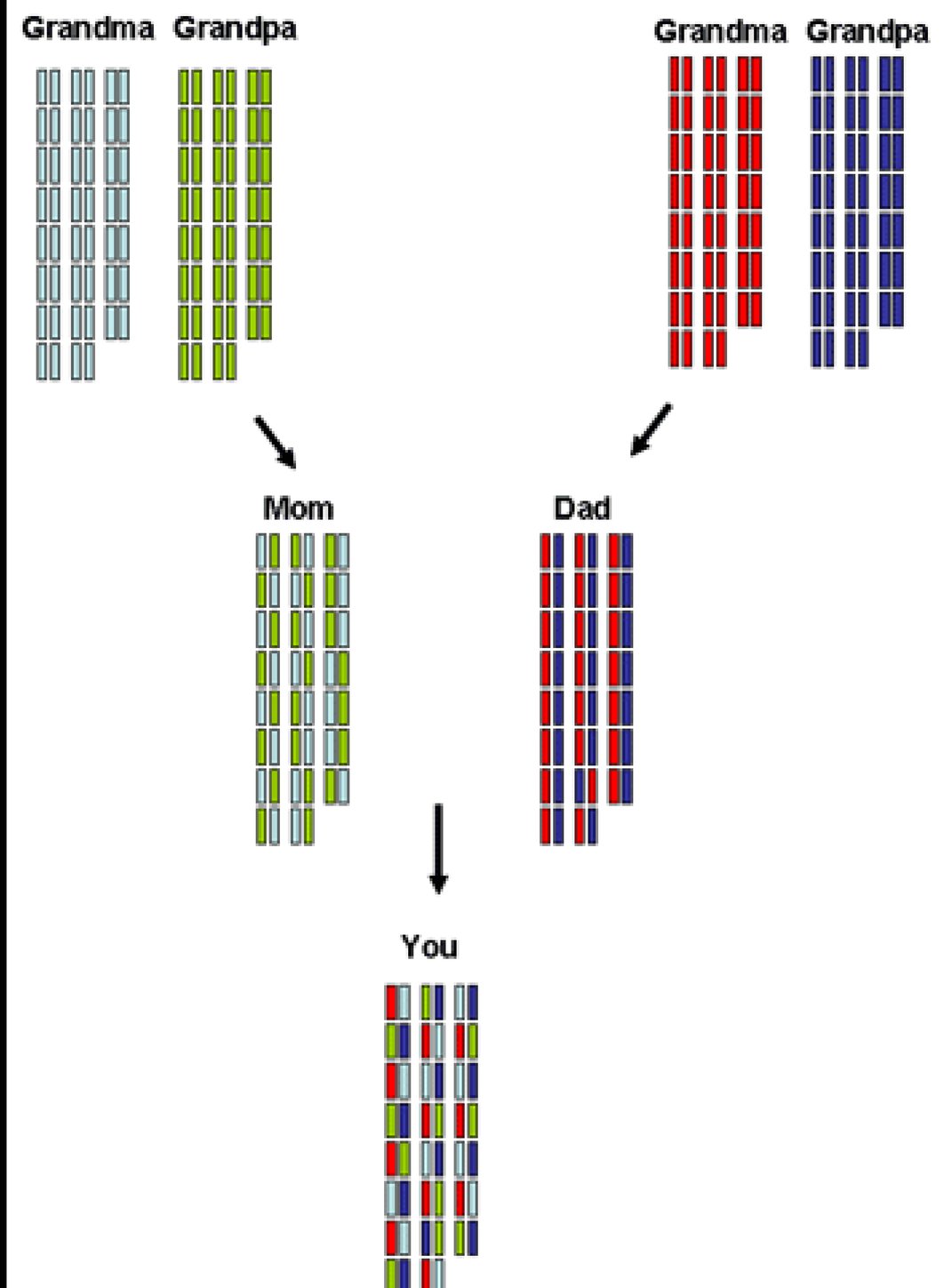
The same is true of other disorders that might be related to *MTHFR*. For example, mutations in *MTHFR* have been associated with some neural tube defects in babies. But rather than having an unnecessary test for *MTHFR* gene variations, pregnant women should simply take prenatal vitamins that contain higher folate.

https://health.clevelandclinic.org/a-genetic-test-you-dont-need/

CONFUSING: THE BIG BOYS SAY THE FUTURE IS GENETIC MEDICINE, BUT THEN THEY SAY IT'S NOT. WHICH IS IT?

Maybe it's just the type of genetic medicine that they control or can do — not what the average primary care can do…

What I am going to teach you is about specific genetic errors that have been passed down to you from hundreds of generations ago when the mutation first occurred – and how these genetic errors affect your body's ability to function properly physiologically.



GENETIC ERRORS YOU CARRY AFFECT YOU

These are not mutations, what you carry are “transcription errors”.

You carry errors passed down from many generations ago (when they originally occurred – this was the original MUTATION).

So these are copies of mutations from hundreds or thousands of years ago.

Your ancestors have all carried these too.

These were transcribed over and over until your parents gave them to you.

Now the world and our diet habits have changed – we live longer too. So we can suffer more too. But our ancestors were tough – and we just don’t know how much and how they suffered every day.

END LESSON 2

LESSON 3:

TERMINOLOGY & DEFINITIONS

“A rose by any other name would smell as sweet.”

— WILLIAM SHAKESPEARE, ROMEO AND JULIET

MTHFR

An acronym

Stands for “MethyleneTetraHydroFolate Reductase (Enzyme Deficiency Disease)” so should be MTHFREDD (but???!!?).

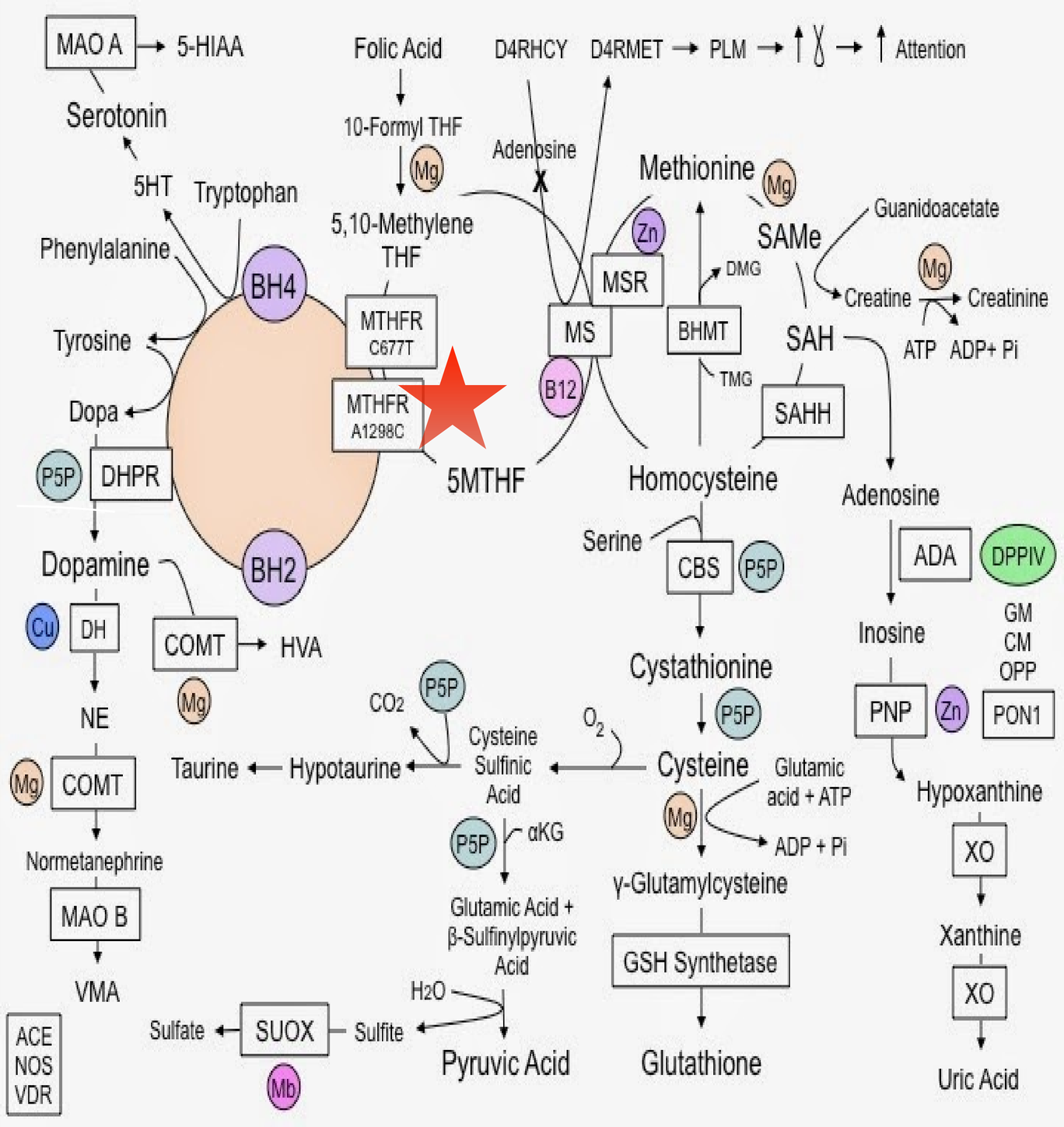
Technically NOT a mutation.

Technically A Replication Error.

Some viking 600-1,000 generations back had the original mutation.

YOU just have the ERROR (lucky you).

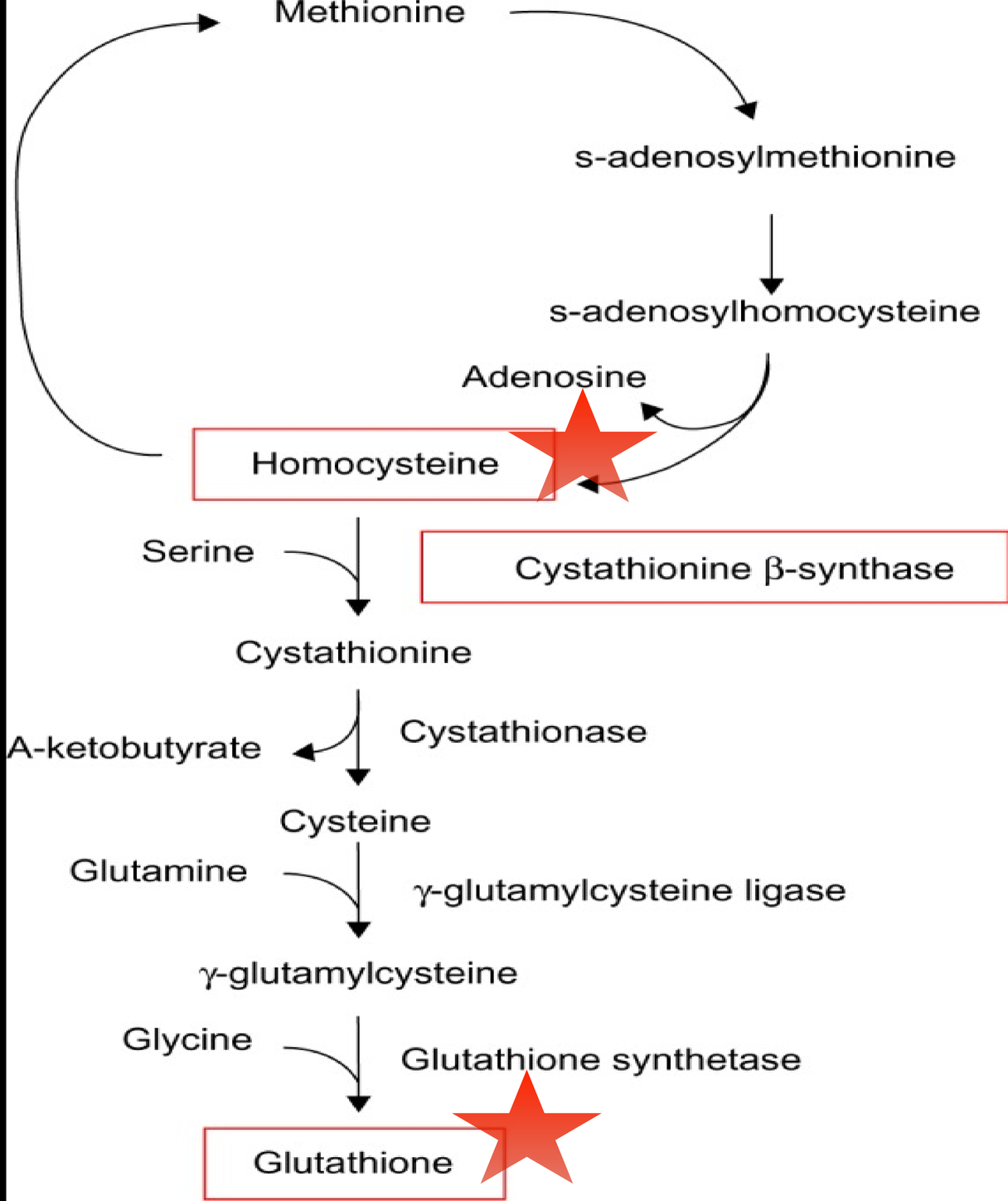
On its surface just a deficiency of 5, 10-methylenetetrahydrofolate reductase enzyme.

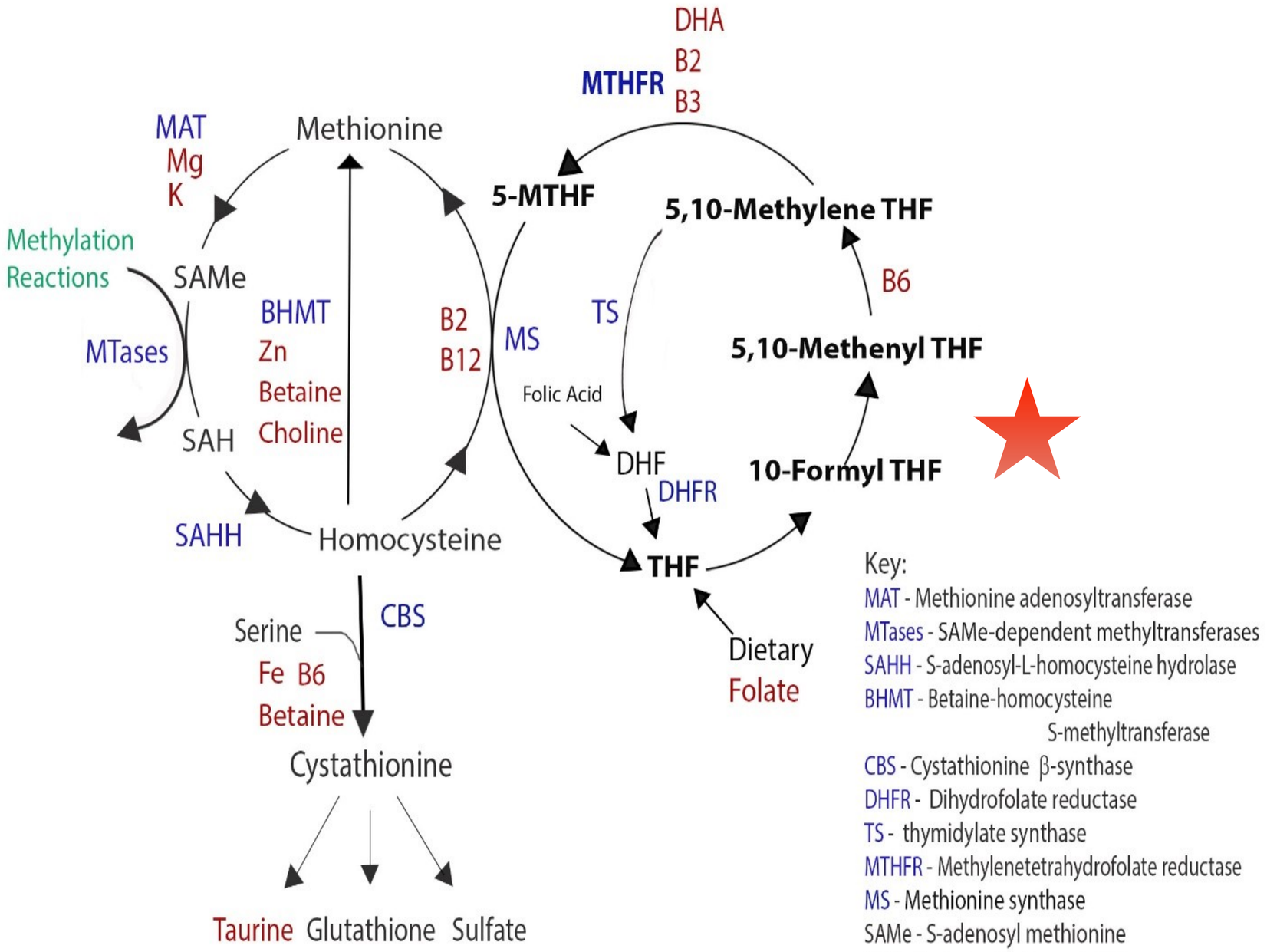


THIS MAKES MORE MEDICAL SENSE

MTHFR ERRORS PREVENT CONVERSION OF HOMOCYSTEINE TO GLUTATHIONE.

HIGH HOMOCYSTEINE IS DIAGNOSTIC OF MTHFR AND VERY BAD.





Key:
MAT - Methionine adenosyltransferase
MTases - SAMe-dependent methyltransferases
SAHH - S-adenosyl-L-homocysteine hydrolase
BHMT - Betaine-homocysteine S-methyltransferase
CBS - Cystathionine β-synthase
DHFR - Dihydrofolate reductase
TS - thymidylate synthase
MTHFR - Methylenetetrahydrofolate reductase
MS - Methionine synthase
SAMe - S-adenosyl methionine
SAH - S-adenosyl-L-homocysteine
THF - Tetrahydrofolate
DHF - Dihydrofolate
5-MTHF - L-5-methyltetrahydrofolate

The genetic errors we are discussion are each known to specifically decrease the functionality of certain enzymes – this decrease can be in the amount produced, or in the percentage of functional versions of the enzymes created.

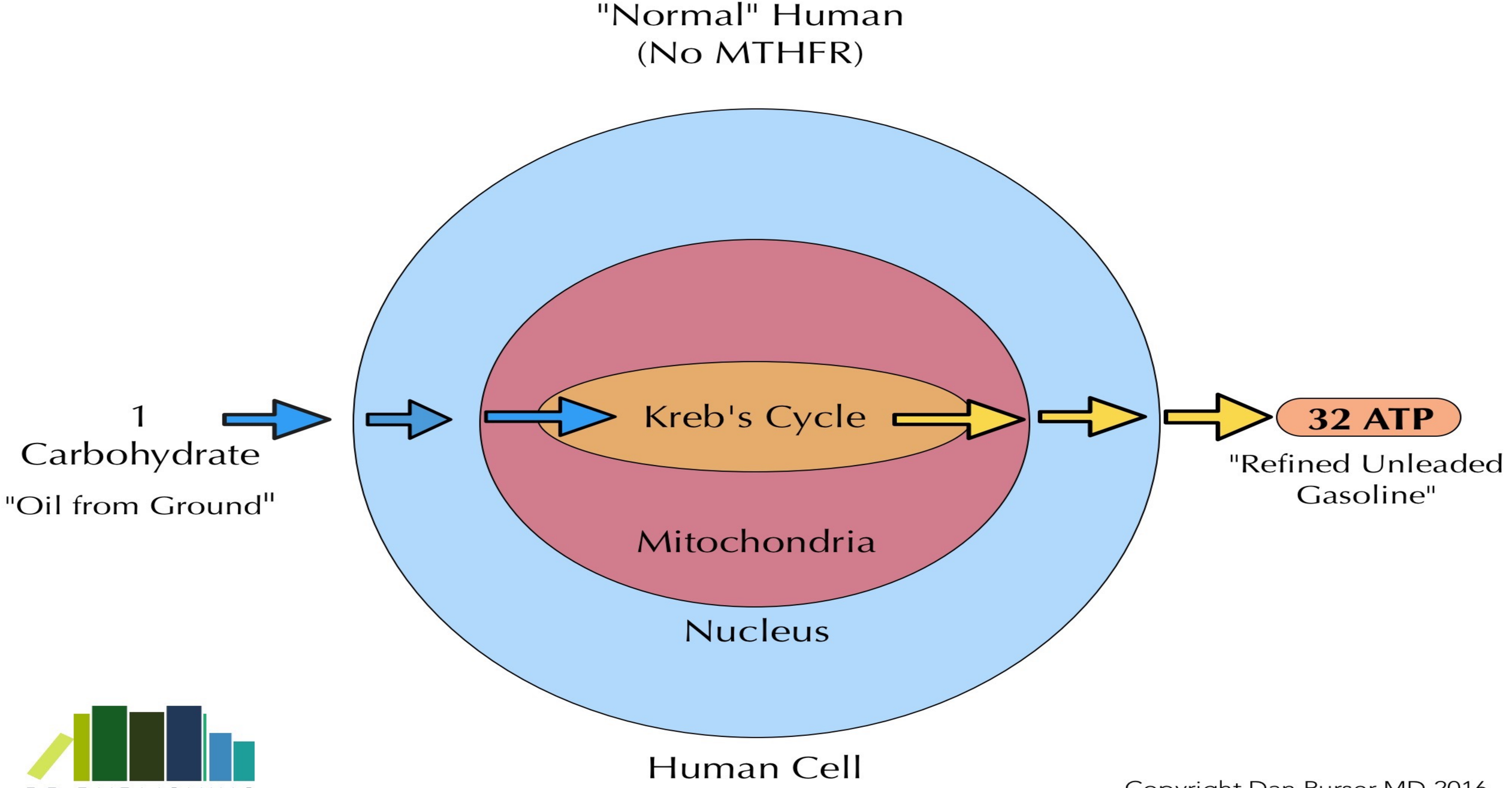
AT THE BASIC LEVEL WE'RE DISCUSSING SYMPTOMATOLOGY

#1 SYMPTOM OF MTHFR?

FATIGUE

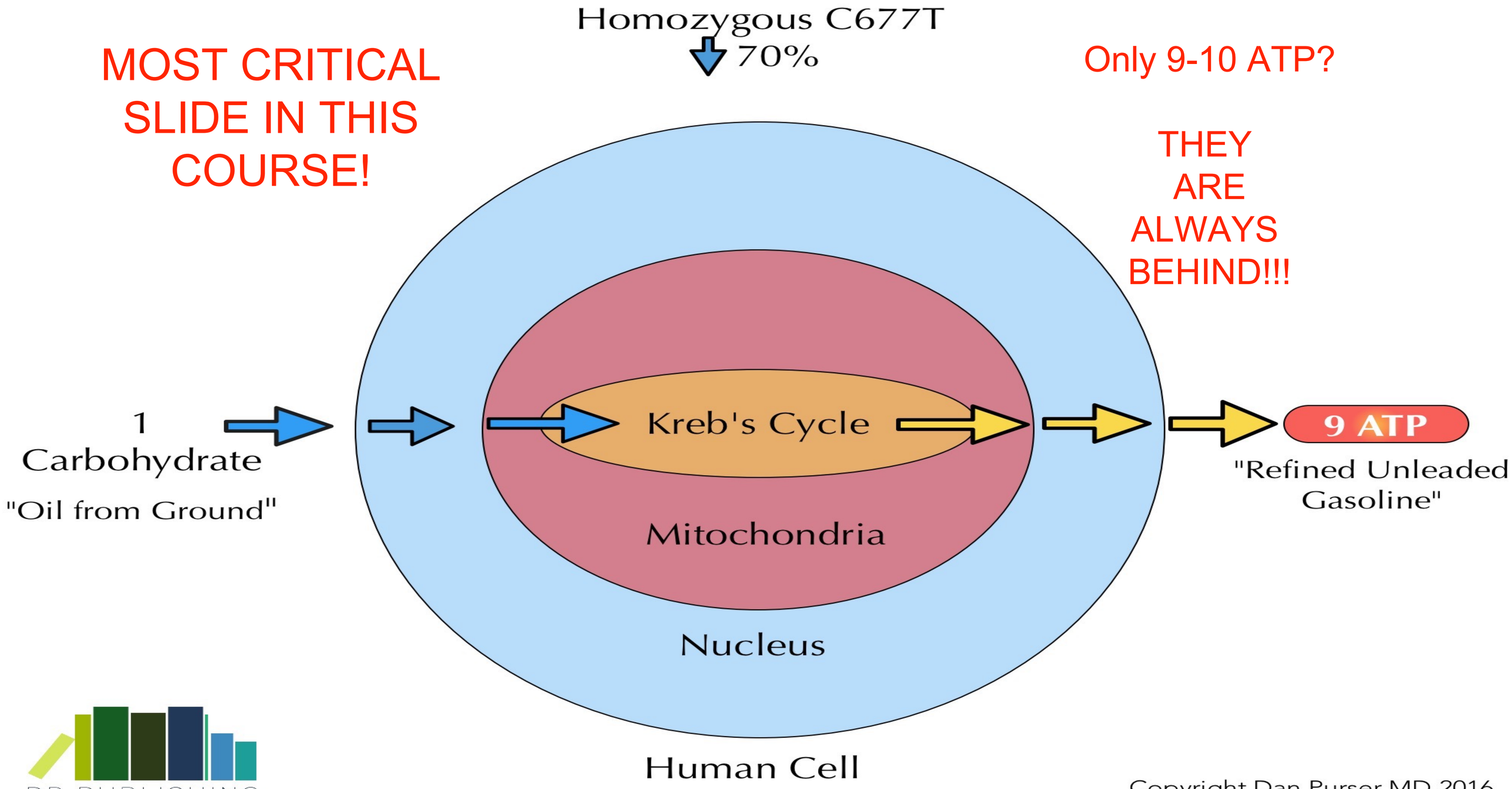

So MTHFR is about NEVER having enough energy.
TIRED ALL THE TIME!
THUS THE POPULARITY OF FIVE HOUR ENERGY DRINKS

WHY YOU MIGHT BE TIRED...



DP PUBLISHING

MOST CRITICAL SLIDE IN THIS COURSE!



DP PUBLISHING

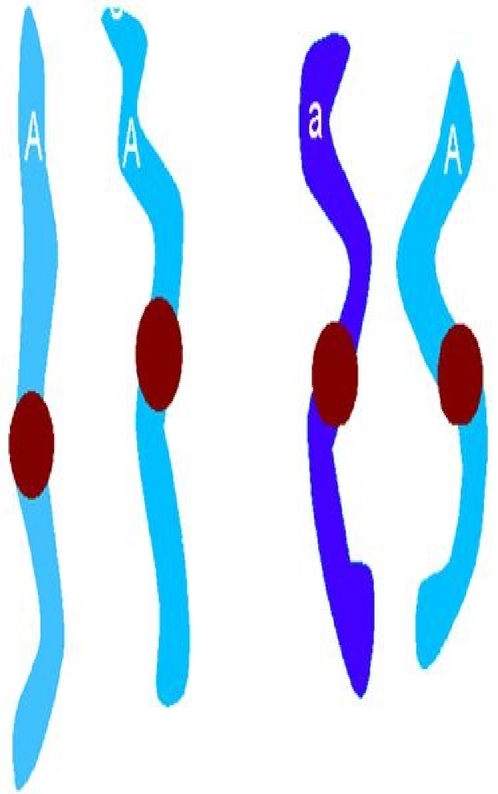
HETEROZYGOUS

Only one SNP (allele) is present

(Not as bad as two or HOMOZYGOUS errors)

Answer

- **Homozygous** - Having identical alleles for a trait. 2) Carrying two copies of the same allele. Compare to heterozygous. (i.e. A homozygous plant could have the genotype ***RR*** or ***rr***).
- **Heterozygous** - Having different alleles for a trait. 2) Carrying two different alleles. Compare to homozygous. (i.e. The heterozygous plant has the genotype ***Rr***).



https://biodifferences.com/difference-between-homozygous-and-heterozygous.html

https://www.frontiersin.org/articles/10.3389/fgene.2015.00179/full

Genotype and phenotype in homozygous

Genotype is what is inside (eg. AA, Aa, aa)

Phenotype is what we see (eg. Blue eyes, brown hair)

Talking about homozygous:

If we cross one homozygous dominant with another homozygous dominant, the result will always be the same, 100% of genotypic ratio of having the same. And equal with the phenotype. And with the recessive ones always happens the same. Lets see the punnet square to understand this:

AA/AA	A	A
A	AA	AA
A	AA	AA

aa/aa	a	a
a	aa	aa
a	aa	aa

HOMOZYGOUS

Means the genetic error is fully realized.

Two of the errors are present, one from each parent.

C677T

On GENE 1. At 677 position the Cytosine has been replaced with a Thymine.

Most common MTHFR error.

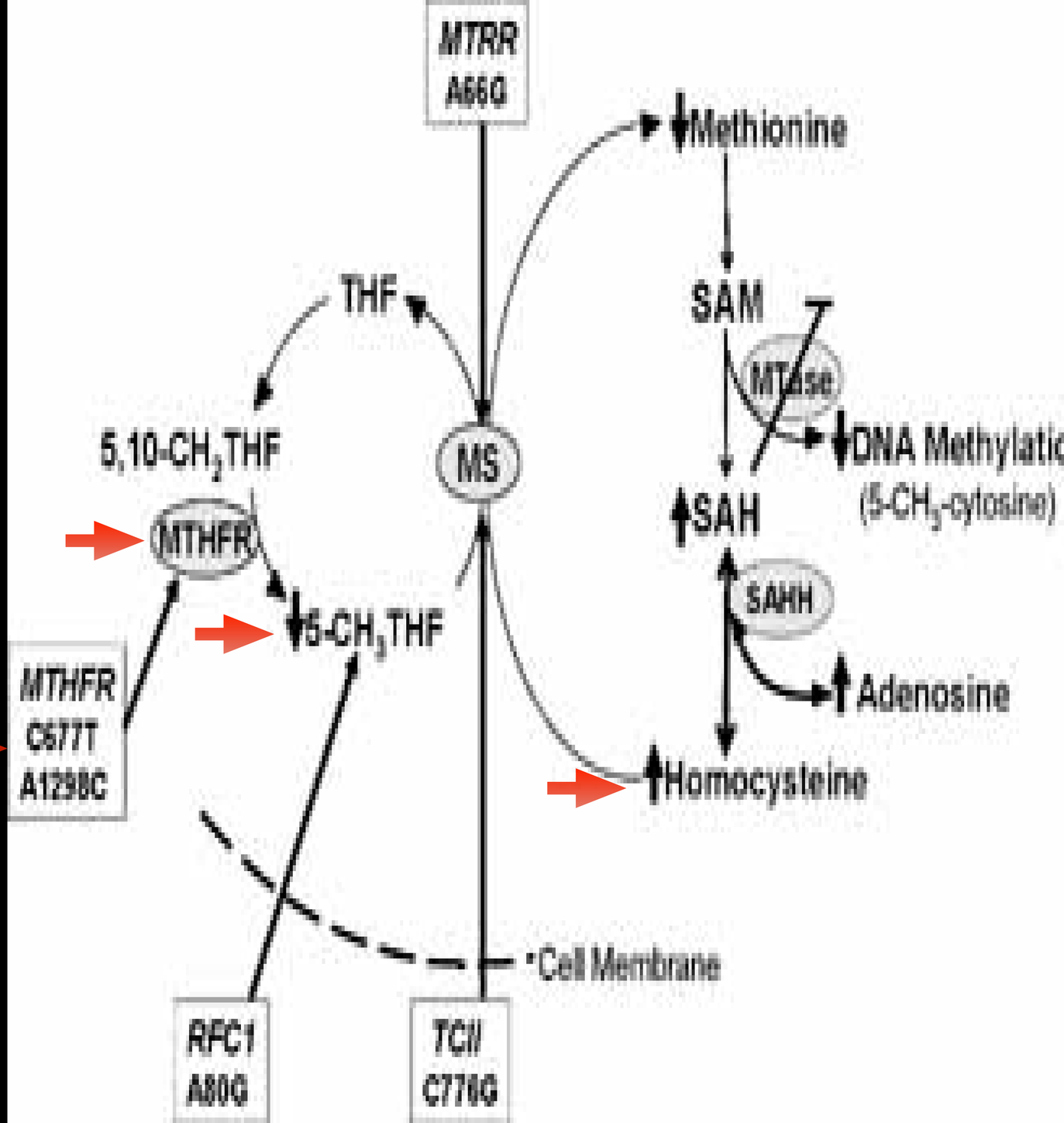
Having one error (HETEROZYGOUS) reduces production by 30% of the 5,10-MTHFR (MethyleneTatraHydraFolate) Reductase Enzyme.

Having one error means they have only 23 ATP per carbohydrate vs usual 32 ATP. (ATP is unleaded gas for humans.)

Causes a reduction in production of 5-methyltetrahydrofolate (5-CH3-THF).

Error most associated with HYPERHOMOCYSTINEMIA.

See the pathway to the right.



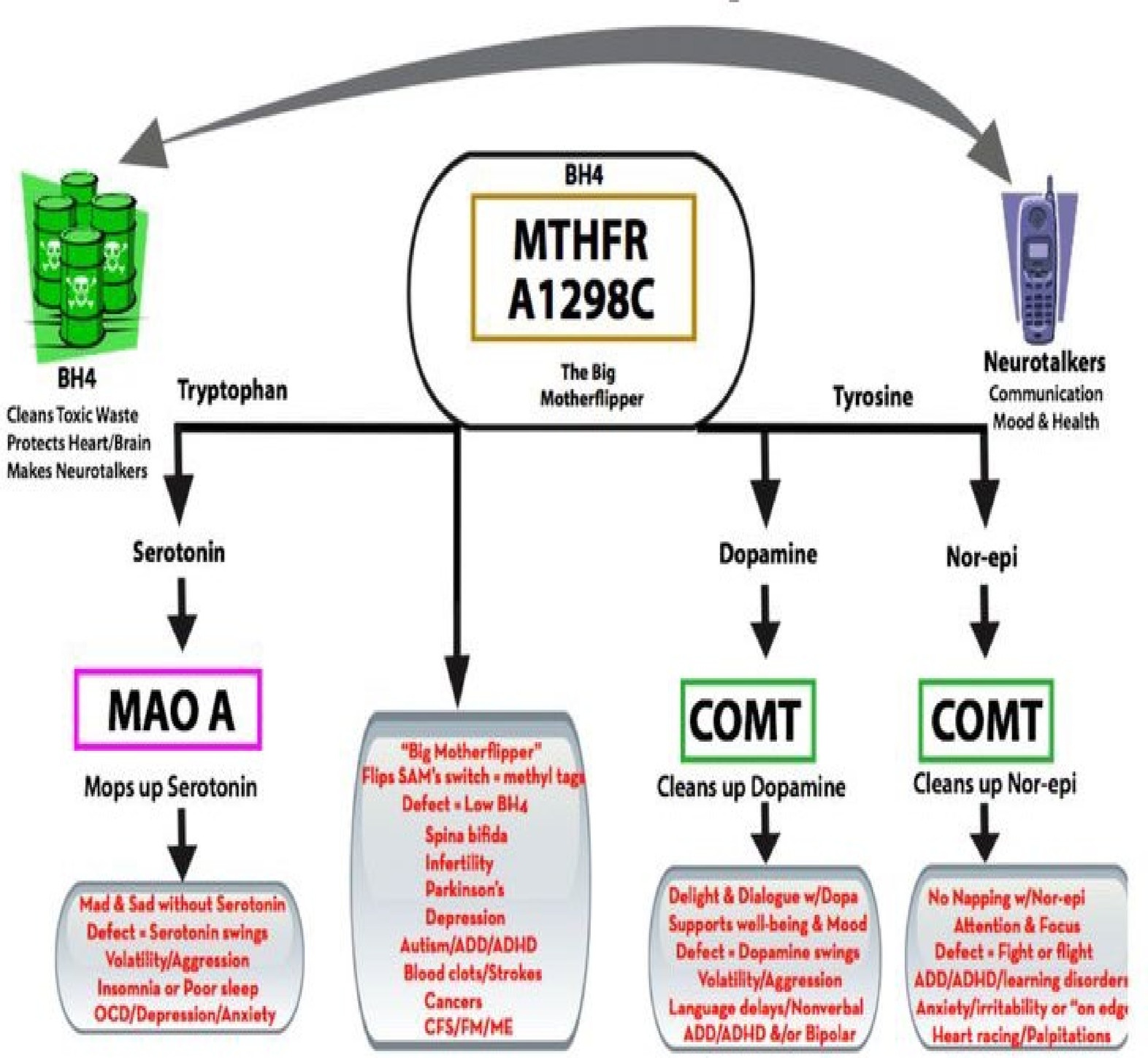
A1298C

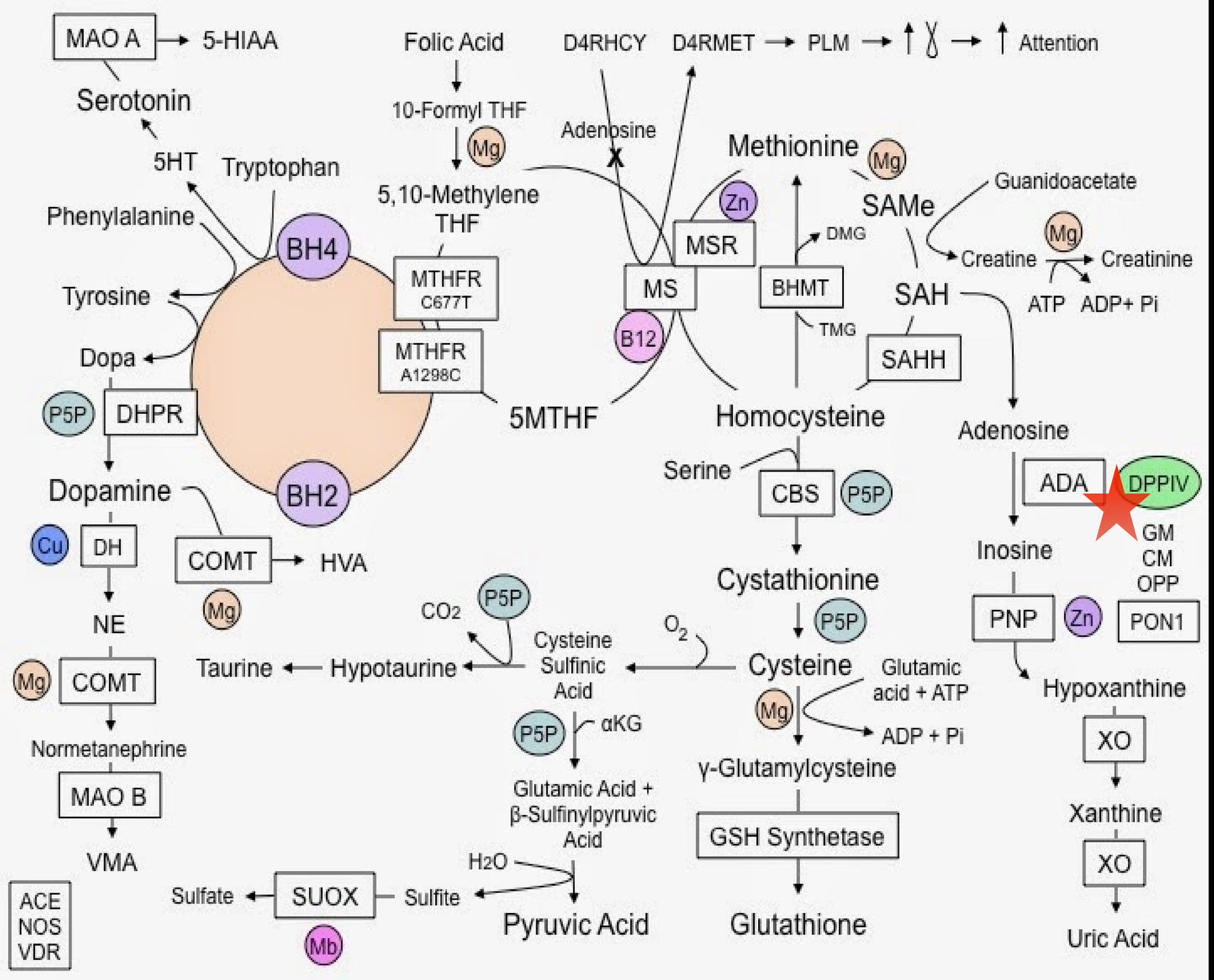
Having one is not supposed to affect methylation — WRONG!

Reduces BH4, too.

Causes neuro-transmitter problems.

Causes anxiety. Associated with schizophrenia when they can't turn their brains off due to TOO MUCH NorEpinephrine.





COMT H62H & COMT V158M

COMT, when functional, cleans up excess Dopamine & Norepinephrine.

Cannot break these neurotransmitters down if carries or Homozygous.

These people tend to have very high levels of neurotransmitters.

Brains cannot shut down.

Tend to be OCD (Obsessive Compulsive).

Tend to have anxiety and cannot sleep well.

Much worse with Homozygous MAO-A R297R

Can give small doses of Lithium Orotate 5mg to increase COMT production.

MTRR ERRORS

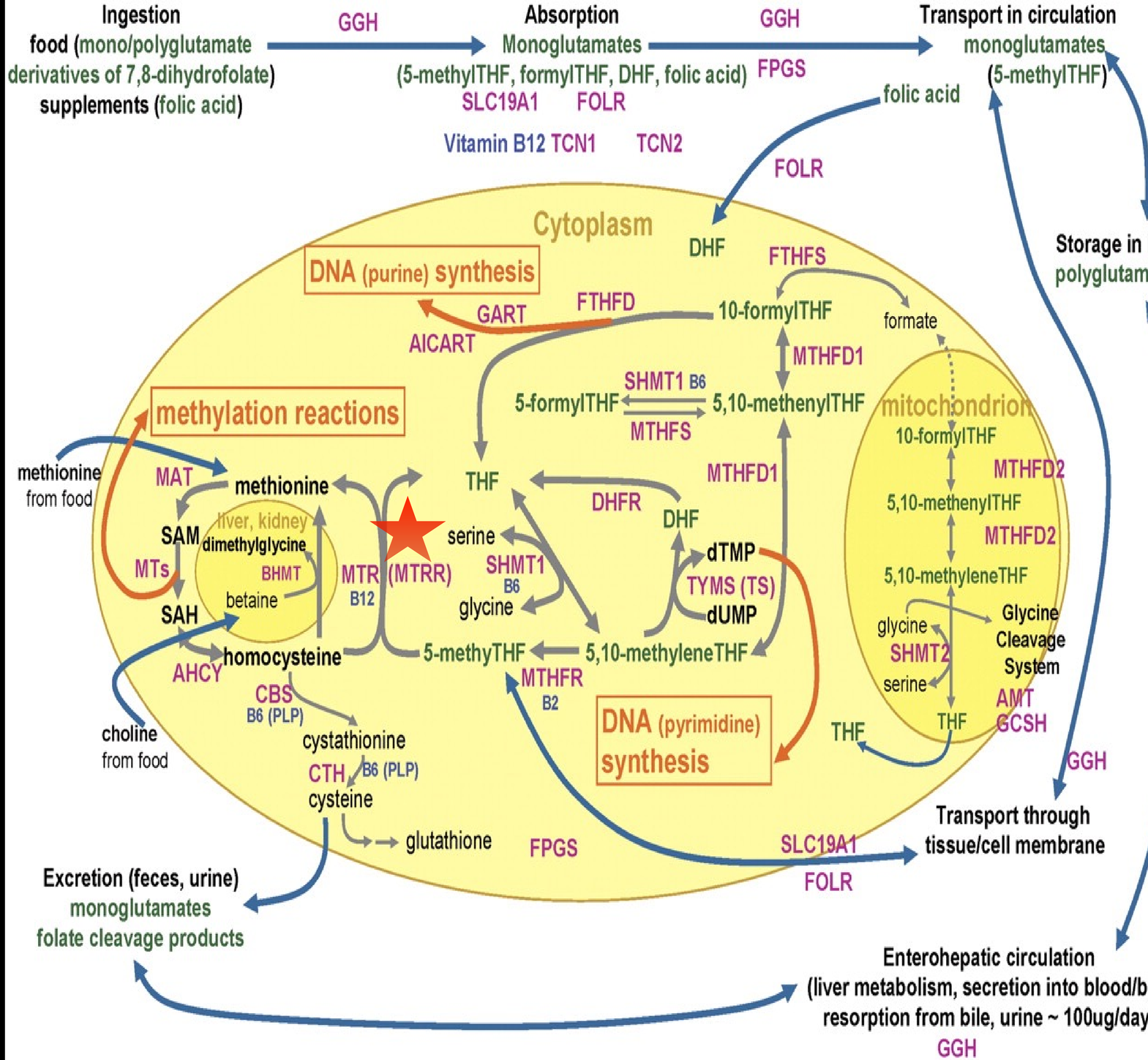
Key in the methylation cycle.

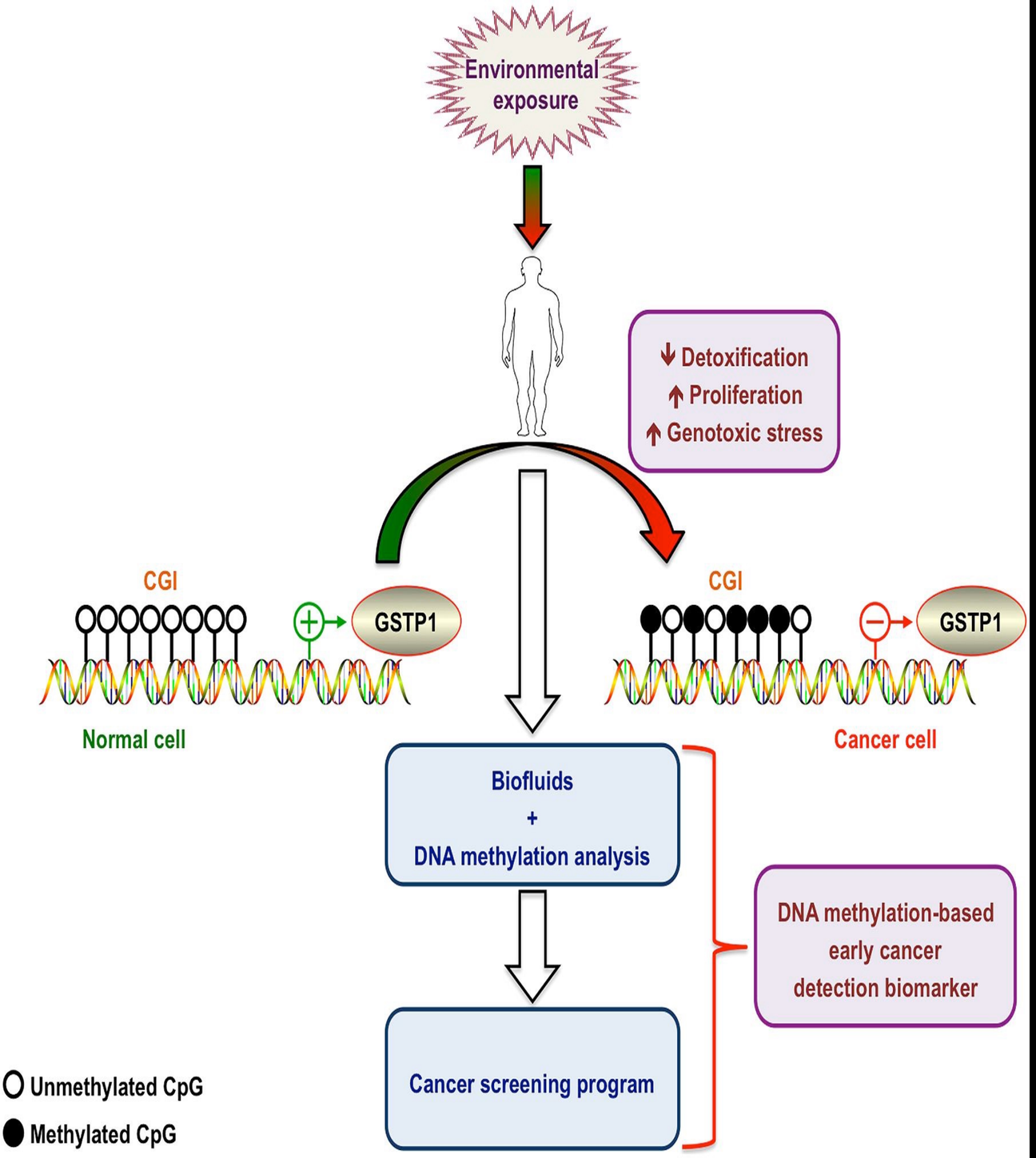
These are necessary to regenerate Methyl-B12 for use by MTR.

Mutation can cause shortage, suggesting a need for more B12.

Treat with ADDITIONAL Methylcobalamin 1000-5000 mcg.

This also multiplies the severity of MTHFR errors.





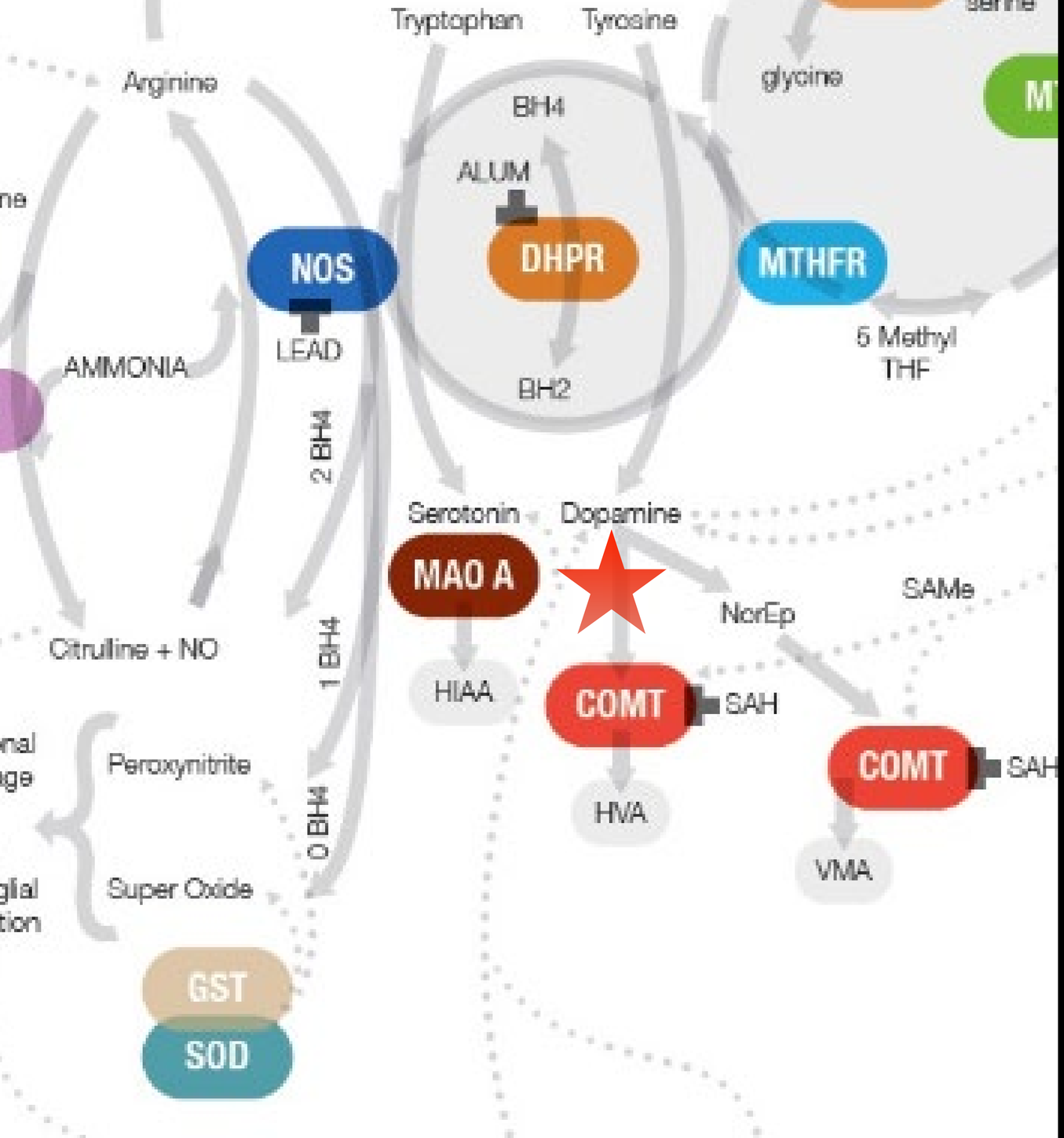
GTSP1 I105V

Especially if HOMOZYGOUS can cause you to use up your reduced glutathione (GSH) too quickly and so will always be low.

Lack of glutathione increases toxin and metal loads.

Increases risk for cancer.

I might just be the top knowledge on clinical use of glutathione in the world – I have been awarded two glutathione patents and we have a glutathione product going through FDA approval as an OTC med.



MAO-A R297R

Also called the Warrior Gene because of potential for increased agitation.

Slows breakdown of Serotonin.

Can lead to high levels of neurotransmitters.

The healthy enzyme requires B2 (Riboflavin) in sufficient levels to function (so use in treatment).

Associated with mood swings, aggressive behavior, depression, anxiety, OCD.

Treat with progesterone.

MAO-A R297R

Intolerance of methylfolate (which increases neurotransmitters that can't be broken down by MAO A, causing feelings of overstimulation).

Treat with Riboflavin, compounded natural progesterone.

Try lithium orotate 5-10 mg a day.

Try Rauwolfia Serpentina 60 mg QID too.

A great website/blog regarding this topic: https://selfhacked.com/2014/12/07/about-mao-a-and-what-to-do-if-you-have-the-warrior-gene/

MAO Enzyme

- MAO exists in tow forms coded by separate genes
  - MAO-A: has substrate preference for 5-HT and is the main target for antidepressant MAOIs
  - MAO-B: has substrate pereference for phenylethylamine
- Both enzymes act on NA and dopamine
- Mutation in the MAO-A gene causes increased brain accumulation of 5-HT and NA in the brain leading to mental retardation and aggressive behaviour

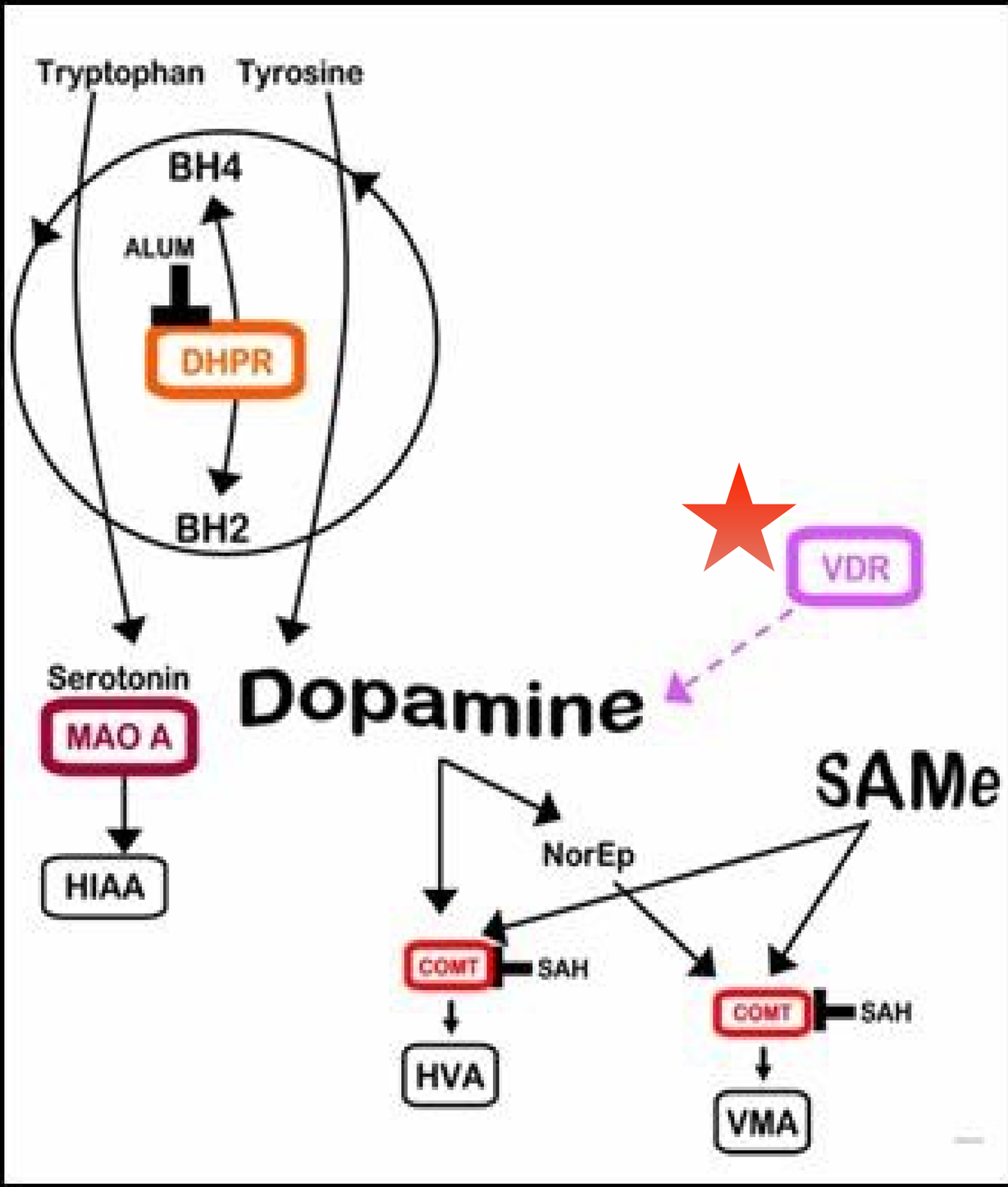
VDR Taq (or Tak)

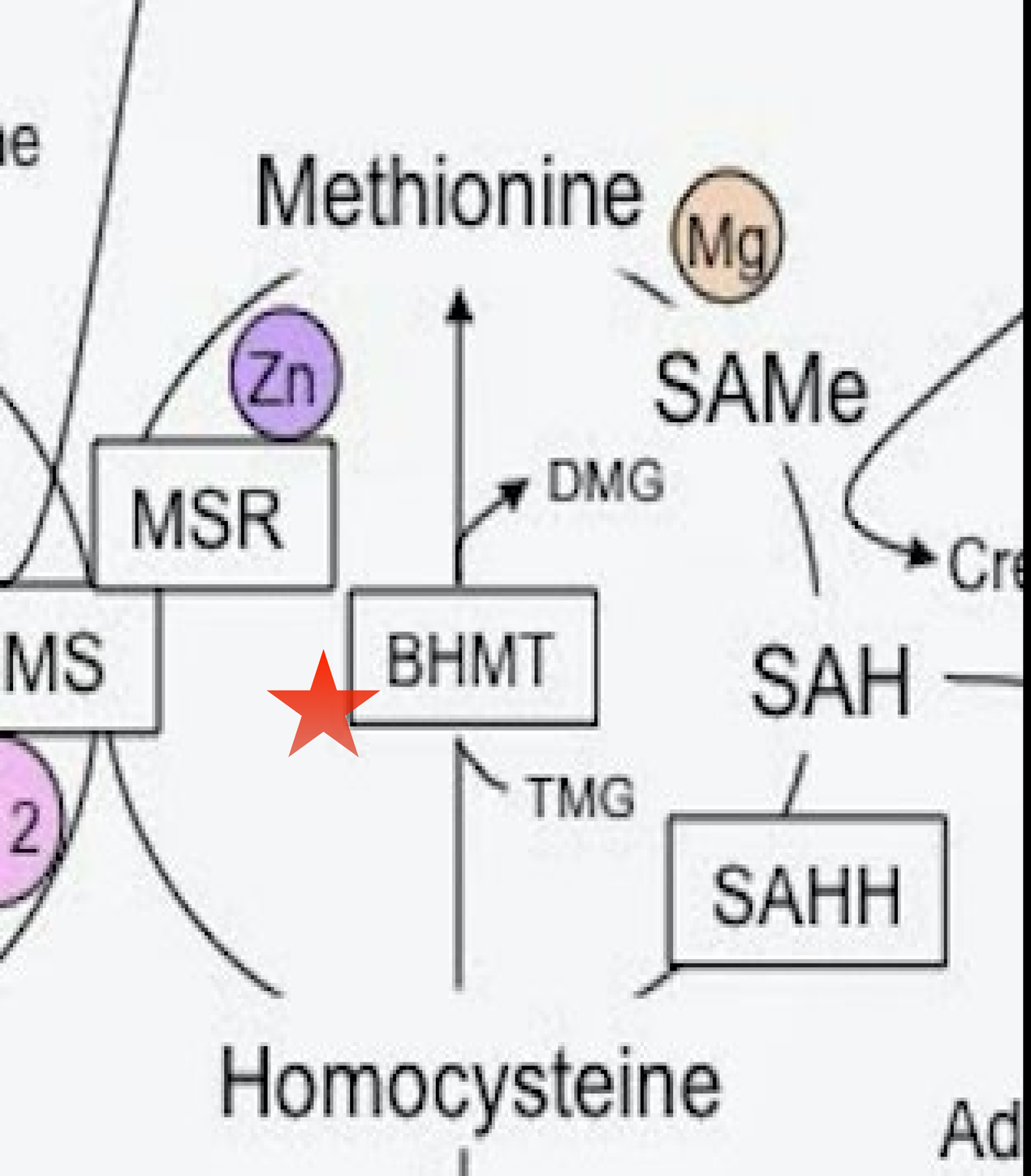
VDR Fok is involved with blood sugar regulation.

VDR mutations oppose COMT mutations in the regulation of dopamine levels.

A VDR mutation means that a person is less sensitive to methyl group supplement levels (mood swings).

Supplement with D3. Watch serum levels.





BHMT-02, BHMT-04, BHMT-08

BHMT genes are central to helping to converting homocysteine to methionine.

The activity of this gene can be affected by STRESS, by CORTISOL levels.

Dr. Amy Yasko believes that BHMT-02 and BHMT-04 play a role in the gut environment.

Yasko also believes that BHMT-08 is related to the impact that psychological stress has on a patient's attention levels.

END LESSON 3

LESSON 4
GX SCIENCE CASE #8

SIGNS & SYMPTOMS – 52 Y/O MALE

Fatigue.

Unexplained low testosterone.

Confusion, insomnia, BAD anxiety, life long weight problem.

Depression.

Problem with alcoholism and addictions – now controlled.

Worried about sons with similar problems.

Takes no supplements.

1600_41713
Aesthetica Preventive Med
383 West 600 North
Lindon UT 84042
(801) 796-7667

LABORATORY REPORT

MSCL
MountainStar Clinical Laboratories
MSCL
1140 East 3900 South , Salt Lake City UT 84124

Patient Name	Sex	Age
	M	50

Patient Birth Date	Patient SSN	Patient Phone Number	Physician
7/19/1966		(801) 362-9230	AESTHETICA PREVENTIVE ME

Accession No	Client Accession Number	Collection Date & Time	Report Date & Time	REPORT STATUS
H8521425		6/8/2017 9:45 AM	6/10/2017 4:36 AM	FINAL

TEST	IN RANGE	OUT OF RANGE	REFERENCE RANGE	UNITS	SITE CODE
Lipid Profile (CONTINUED)					
Two Times AVG Risk	7.1		9.6		
Four Times AVG Risk	11.0		24.0		
Insulin-Like Growth Factor 1	148.5	Low (250-320)	121-237	ng/mL	01
Testos, Tot/Free (Adult Male)					
Free Testosterone (Adult Male)	9.0		4.3-30.4	pg/mL	01
Testosterone, Total	361	Low (800-1200)	193-740	ng/dL	01

NOTE:

'01' refers to site: PAML
110 W Cliff Ave
Spokane WA 99204

'MH' refers to site: St Mark's Hospital
1200 East 3900 South
Salt Lake City UT 84124

>> END REPORT <<

361 ng/dl

Dan Purser MD

NATURAL AND MODERN

Gene Comprehensive Nutrigenomic Report

Accession Number:
Report Generated: January 24, 2019
Specimen Received: January 22, 2019
Created For:
DOB: 07/19/1966
Male

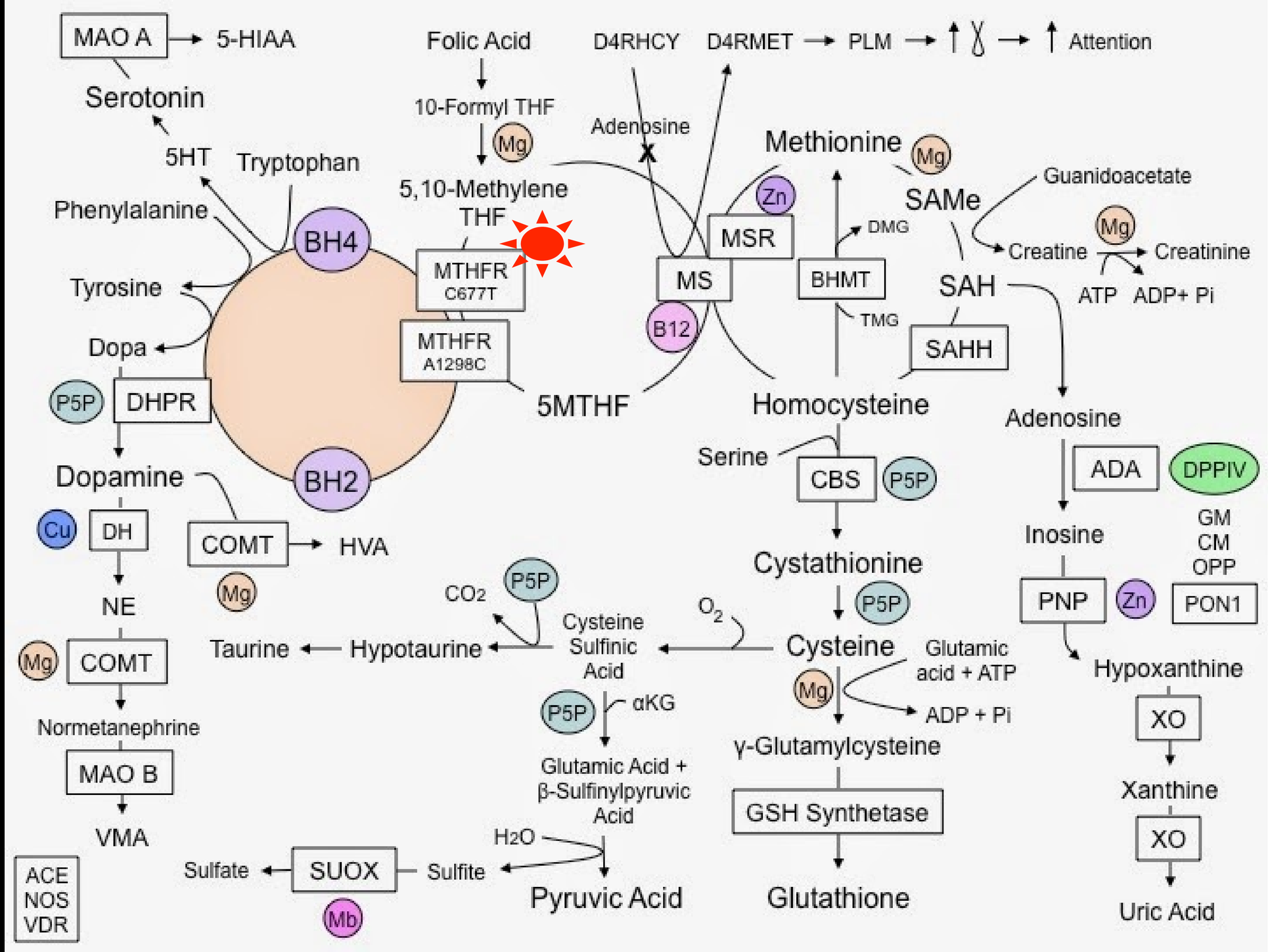
Do not make any decisions about your health solely based on the information contained in this report. Always consult with a licensed and experienced health practitioner when you receive this report.

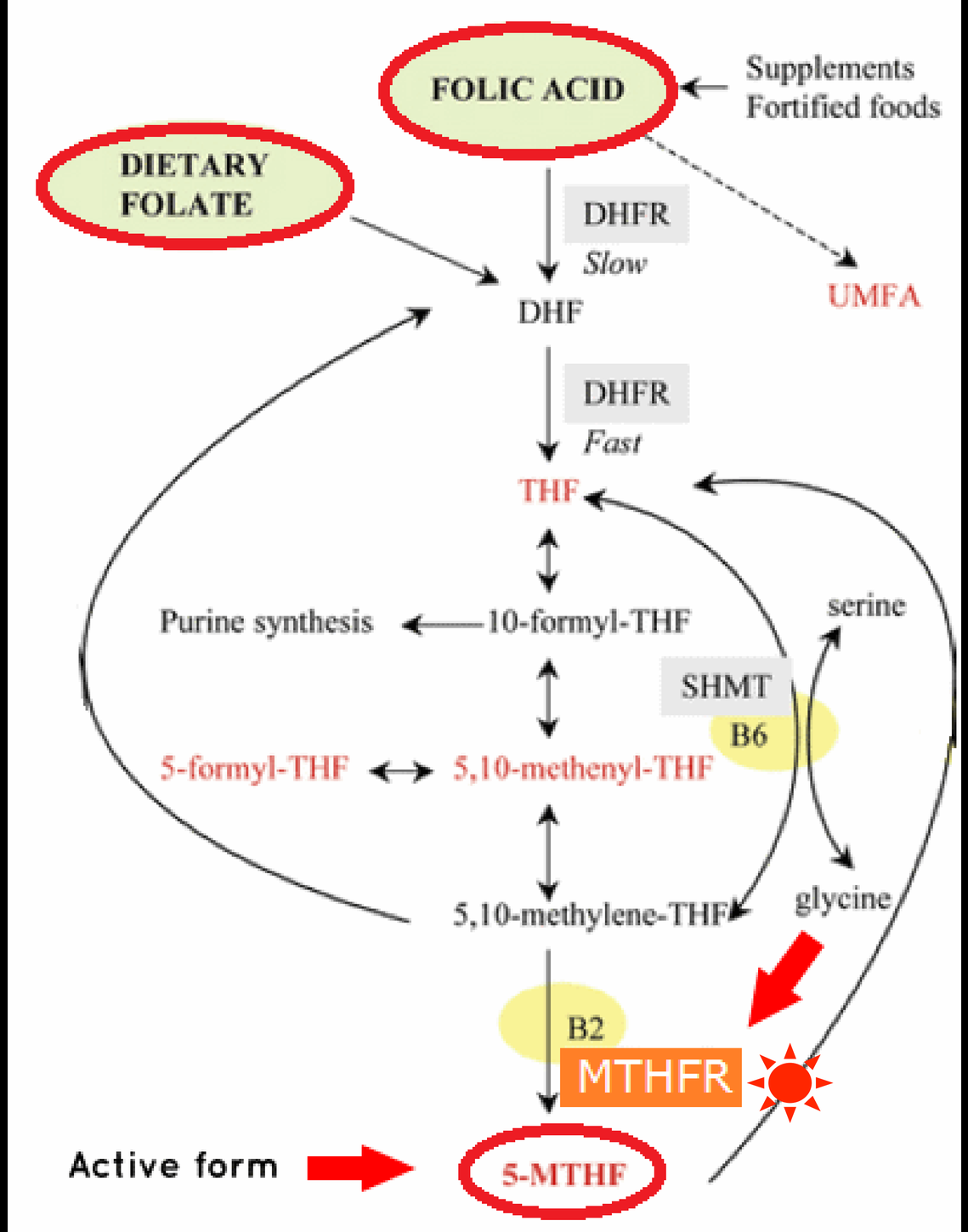
rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	Highly Recommended Therapeutics	Provider Discretion: As Needed Formula Recommendations	Lifestyle Recommendations	Laboratory Recommendations
METHYLATION							
rs2071010	FOLR1	-/-	Methyltetrahydrofolate (5-MTHF)	Physician Designed MTHFR Support™			Consider Checking For High Plasma Folate
rs651933	FOLR2	+/+					
rs1643649	DHFR	+/-					
rs1076991	MTHFD1	+/+					
rs1801133	MTHFR C677T	+/+					
rs1801131	MTHFR A1298C	-/-					
rs1802059	MTRR A664A	+/-	Methyl B12, Adenosyl B12	Physician Designed MTHFR Support Plus™			Consider Checking Plasma B12 Level
rs1801394	MTRR A66G	+/+					
rs526934	TCN1	-/-					
rs1801198	TCN2	+/-					
rs558660	GIF	-/-					

HOMOZYGOUS C677T

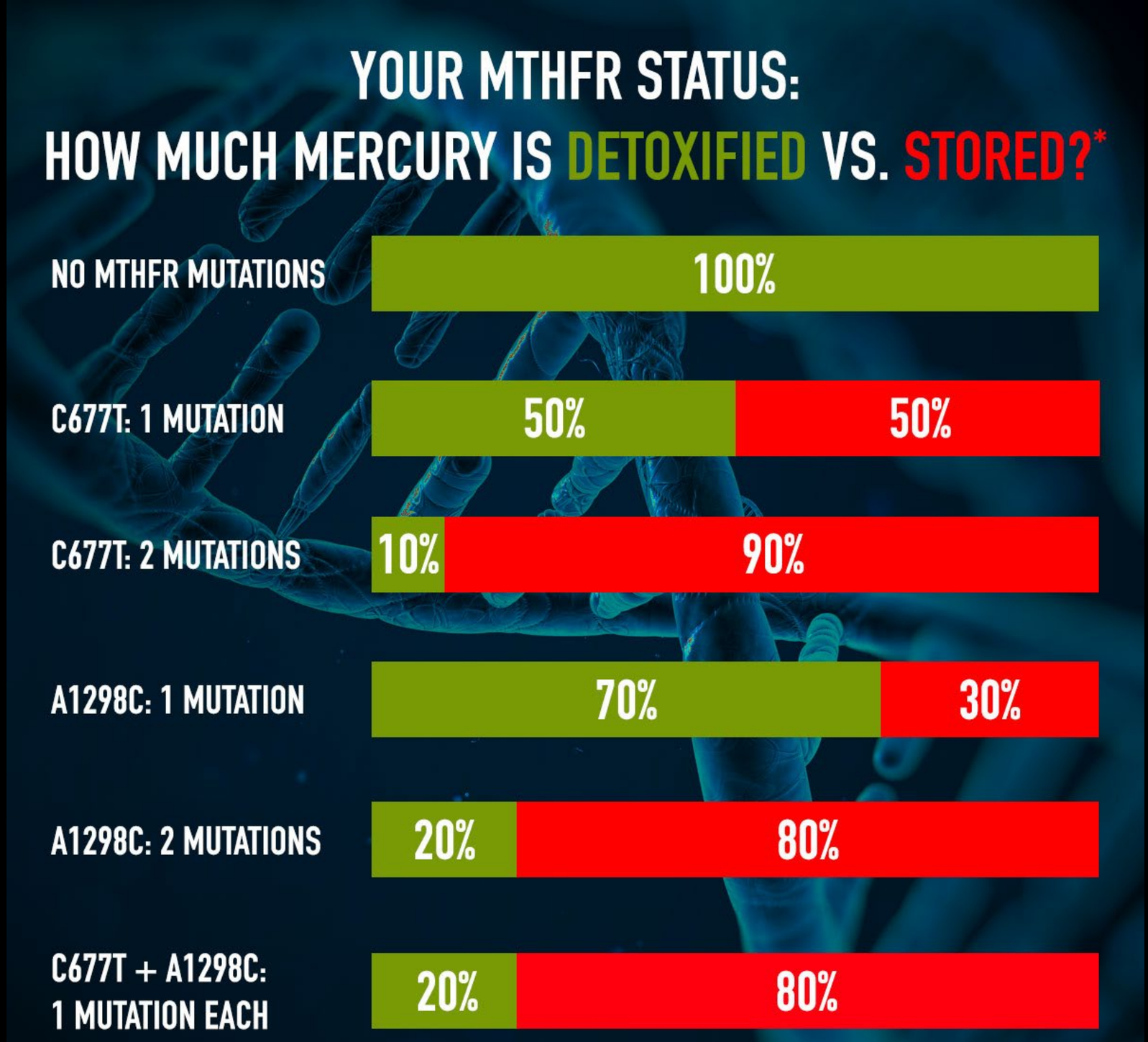
PubMed lists over 3,000 studies linking rs1801133 to a long list of disorders in various populations across the world, of which only some are mentioned above. Considering the central role of MTHFR in folate metabolism and in control of homocysteine levels this is not surprising. A nice summary of the pathological significance of elevated homocysteine levels could be found in this article. However, despite the evidence that folic acid and other vitamins can reduce homocysteine levels, a review of 8 clinical trials concluded that the supplements provided no benefit in terms of decreasing blood clots, heart disease, cancer or overall mortality.[PMID 21069462]

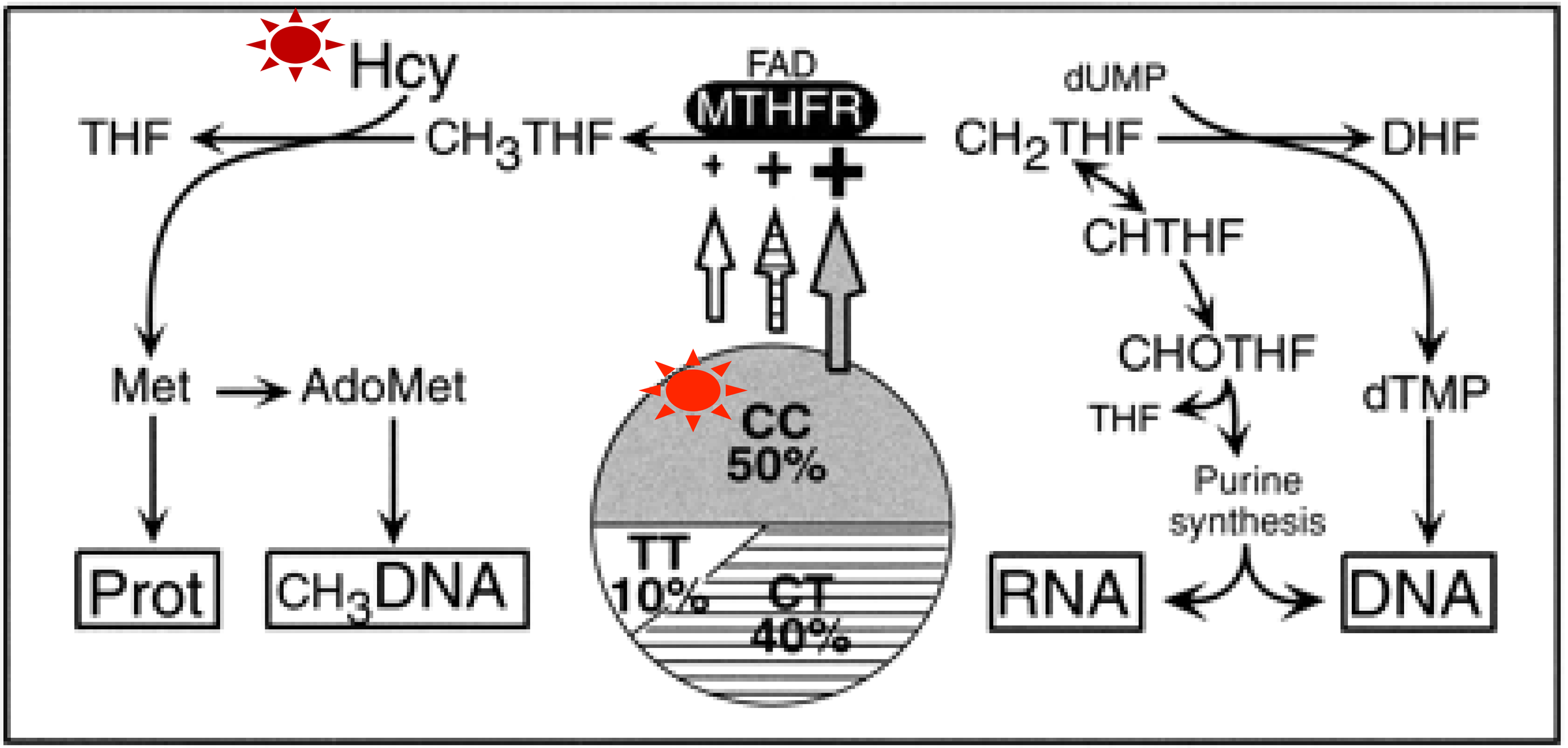
HA HAHAHAHAHAHAHAHA! Really?


MAO A
5-HIAA
Serotonin
5HT
Tryptophan
Phenylalanine
Tyrosine
Dopa
P5P
DHPR
Dopamine
Cu
DH
NE
Mg
COMT
Normetanephrine
MAO B
VMA
ACE
NOS
VDR
COMT
HVA
Mg
BH4
BH2
Folic Acid
10-Formyl THF
Mg
5,10-Methylene THF
MTHFR C677T
MTHFR A1298C
5MTHF
Adenosine
D4RHCY
D4RMET
PLM
Attention
Methionine
Mg
Zn
MSR
MS
B12
BHMT
DMG
TMG
SAMe
Guanidoacetate
Creatine
Mg
Creatinine
ATP
ADP+ Pi
SAH
SAHH
Homocysteine
Serine
CBS
P5P
Cystathionine
P5P
Cysteine
Glutamic acid + ATP
Mg
ADP + Pi
γ-Glutamylcysteine
GSH Synthetase
Glutathione
O2
CO2
P5P
Cysteine Sulfinic Acid
Taurine
Hypotaurine
P5P
αKG
Glutamic Acid + β-Sulfinylpyruvic Acid
H2O
Pyruvic Acid
Sulfate
SUOX
Sulfite
Mb
Adenosine
ADA
DPPIV
GM
CM
OPP
PON1
Inosine
PNP
Zn
Hypoxanthine
XO
Xanthine
XO
Uric Acid


FOLIC ACID
Supplements
Fortified foods
DIETARY FOLATE
DHFR
Slow
UMFA
DHF
DHFR
Fast
THF
Purine synthesis
10-formyl-THF
serine
SHMT
B6
5-formyl-THF
5,10-methenyl-THF
5,10-methylene-THF
glycine
B2
MTHFR
Active form
5-MTHF

YOUR MTHFR STATUS:
HOW MUCH MERCURY IS DETOXIFIED VS. STORED?*




Hcy
FAD
MTHFR
THF
CH3THF
CH2THF
dUMP
DHF
CHTHF
CHOTHF
THF
Purine
synthesis
Met
AdoMet
Prot
CH3DNA
CC
50%
TT
10%
CT
40%
dTMP
RNA
DNA

HOMOZYGOUS C677T MTHFR

Most severe form of MTHFR

70-80% decline in Methylation

Worse symptoms of fatigue, depression, and anxiety.

Cellular malnourishment then causes low testosterone in men and women.

Associated with high homocysteine levels (CAD Strokes).

Usually associated with weight issues (obesity).

These people eventually just become TIRED.

Neuroendocrinology Letters Volume 33 No. 5 2012

The relationship between the C677T polymorphism of the MTHFR gene and serum levels of luteinizing hormone in males with erectile dysfunction

Omar Šerý [1,2], Taťána Šrámková [3], Jitka Klempová [1], František Šťastný [1], Jan Lochman [1], Naim Akhtar Khan [4]

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2 Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic, Brno, Czech Republic
3 Trauma Hospital of Brno, Department of Clinical Psychology and Psychiatry, Brno, Czech Republic
4 UPRES EA4183 "Lipides & Signalisation Cellulaire", Université de Bourgogne, Dijon, France;

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Laboratory of Neurobiology and Molecular Psychiatry,
Department of Biochemistry, Faculty of Science, Masaryk University,
Kotlářská 2, 611 37 Brno, Czech Republic.
TEL: +420 549 497 312; FAX: +420 542 213 827; E-MAIL: omarsery@sci.muni.cz

Submitted: 2012-05-31 *Accepted: 2012-07-17* *Published online: 2012-10-02*

Key words: **MTHFR; C677T polymorphism; follicle-stimulating hormone; luteinizing hormone; erectile dysfunction**

Neuroendocrinol Lett 2012; **33**(5):499–504 **PMID:** 23090267 NEL330512A02

Abstract

OBJECTIVES: The methylenetetrahydrofolate reductase (MTHFR) enzyme activity plays an important role in the metabolism of folate within methionine-homocysteine pathway and, consequently, in the development of vascular diseases. The C677T polymorphism (rs1801133) of the *MTHFR* gene affects the MTHFR activity, modifies the homocysteine plasma concentration and, among others, increases the risks for idiopathic male infertility, including erectile dysfunction (ED). As this sexual dysfunction is related to sex hormone levels, we investigated a possible relationship between the C677T polymorphism of the *MTHFR* gene and plasma concentrations of follicle-stimulating hormone (FSH) as well as luteinizing hormone (LH) in male patients with ED.

METHODS: We conducted our study on 90 healthy men with ED between the age of 32 and 61 (mean age was 51.1 ± 11.5) years. The subjects were genotyped and their FSH and LH plasma levels were analysed.

RESULTS: The analysis results of ED patients and their genotypes of the *MTHFR* gene did not provide evidence supporting any causal association of T allele in CT and TT genotypes with studied clinical parameters. However, we found that patients with the CC genotype had significantly higher plasma levels of LH than patients with the CT and/or TT genotypes.

CONCLUSIONS: Our observations suggest that the C677T polymorphism of *MTHFR* gene has no direct relationship to erectile dysfunction, but does exhibit a relationship between this rs1801133 polymorphism and plasma LH concentrations.

https://www.ncbi.nlm.nih.gov/pubmed/23090267

ORIGINAL ARTICLE

In summary: C677T errors are associated with low LH and LOW TESOSTERONE (In both sexes actually.)

Aliases for FOLR2 Gene

Aliases for FOLR2 Gene

- Folate Receptor Beta [2 3 3 5]
- Folate Receptor, Fetal/Placental [3 4]
- Placental Folate-Binding Protein [3 4]
- Folate Receptor 2 (Fetal) [2 3]
- FBP [3 4]
- Folate-Binding Protein, Fetal/Placental [3]
- Folate Receptor 2 [4]
- BETA-HFR [3]
- FBP/PL-1 [3]
- FR-BETA [3]
- FR-Beta [4]
- FR-P3 [3]

External Ids for FOLR2 Gene

HGNC: 3793 Entrez Gene: 2350 Ensembl: ENSG00000165457 OMIM: 136425 UniProtKB: P14207

Previous GeneCards Identifiers for FOLR2 Gene

GC11U990040, GC11P073467, GC11P072150, GC11P071654, GC11P071605, GC11P071927, GC11P068220

Search aliases for FOLR2 gene in PubMed and other databases

PLOS | ONE

RESEARCH ARTICLE

MTHFR 677C>T Polymorphism Increases the Male Infertility Risk: A Meta-Analysis Involving 26 Studies

Mancheng Gong[1,2], Wenjing Dong[3], Tingyu He[4], Zhirong Shi[5], Guiying Huang[6], Rui Ren[2], Sichong Huang[2], Shaopeng Qiu[1]*, Runqiang Yuan[2]*

1 Department of Urology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, China, **2** Department of Andrology, Zhongshan Affiliated Hospital of Sun Yat-sen University, Zhongshan, Guangdong, 528403, China, **3** Department of Oncology, Zhongshan Affiliated Hospital of Sun Yat-sen University, Zhongshan, Guangdong, 528403, China, **4** Department of Reproductive Center, Zhongshan Affiliated Hospital of Sun Yat-sen University, Zhongshan, Guangdong, 528403, China, **5** Department of Pharmacy, The Second People's Hospital of Zhuhai, Zhuhai, Guangdong, 519020, China, **6** The Second General Department, Zhongshan Affiliated Hospital of Sun Yat-sen University, Zhongshan, Guangdong, 528403, China

* medicinegd@163.com (SPQ); yuanrunqiang2013@163.com (RQY)

OPEN ACCESS

Citation: Gong M, Dong W, He T, Shi Z, Huang G, Ren R, et al. (2015) *MTHFR* 677C>T Polymorphism Increases the Male Infertility Risk: A Meta-Analysis Involving 26 Studies. PLoS ONE 10(3): e0121147. doi:10.1371/journal.pone.0121147

Academic Editor: W. Steven Ward, John A. Burns School of Medicine, UNITED STATES

Received: July 12, 2014

Accepted: February 10, 2015

Published: March 20, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors have no support or funding to report.

Abstract

Background and Objectives

Methylenetetrahydrofolate reductase (*MTHFR*) polymorphism may be a risk factor for male infertility. However, the epidemiologic studies showed inconsistent results regarding *MTHFR* polymorphism and the risk of male infertility. Therefore, we performed a meta-analysis of published case-control studies to re-examine the controversy.

Methods

Electronic searches of PubMed, EMBASE, Google Scholar and China National Knowledge Infrastructure (CNKI) were conducted to select eligible literatures for this meta-analysis (updated to June 19, 2014). According to our inclusion criteria and the Newcastle-Ottawa Scale (NOS), only high quality studies that observed the association between *MTHFR* polymorphism and male infertility risk were included. Crude odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association between the *MTHFR* polymorphism and male infertility risk.

Results

Twenty-six studies involving 5,575 cases and 5,447 controls were recruited. Overall, *MTHFR* 677C>T polymorphism showed significant associations with male infertility risk in both fixed effects (CT+TT vs. CC: OR = 1.34, 95% CI: 1.23–1.46) and random effects models (CT+TT vs. CC: OR = 1.39, 95% CI: 1.19–1.62). Further, when stratified by ethnicity

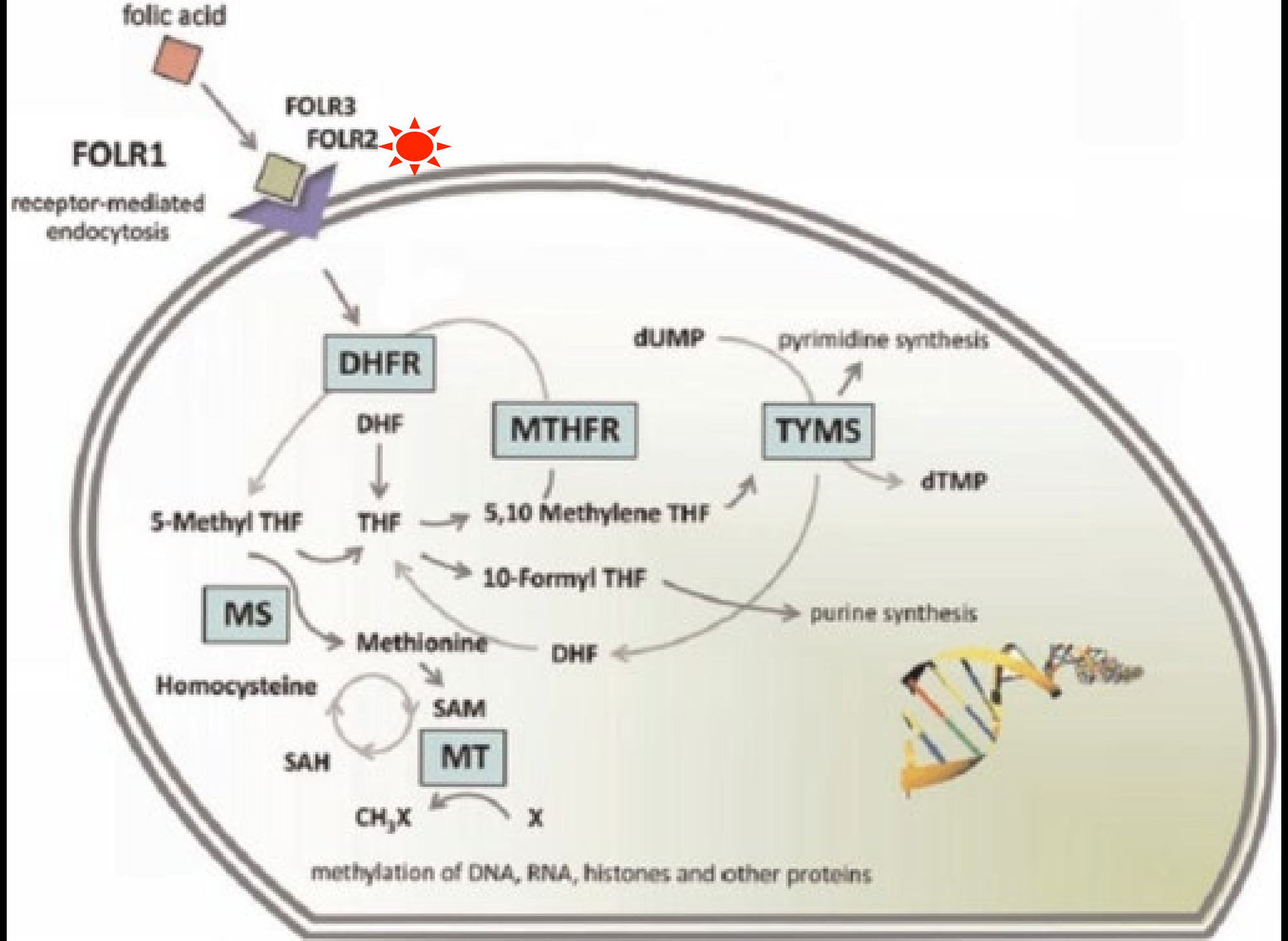
FOLR2 folate receptor beta [*Homo sapiens* (human)]

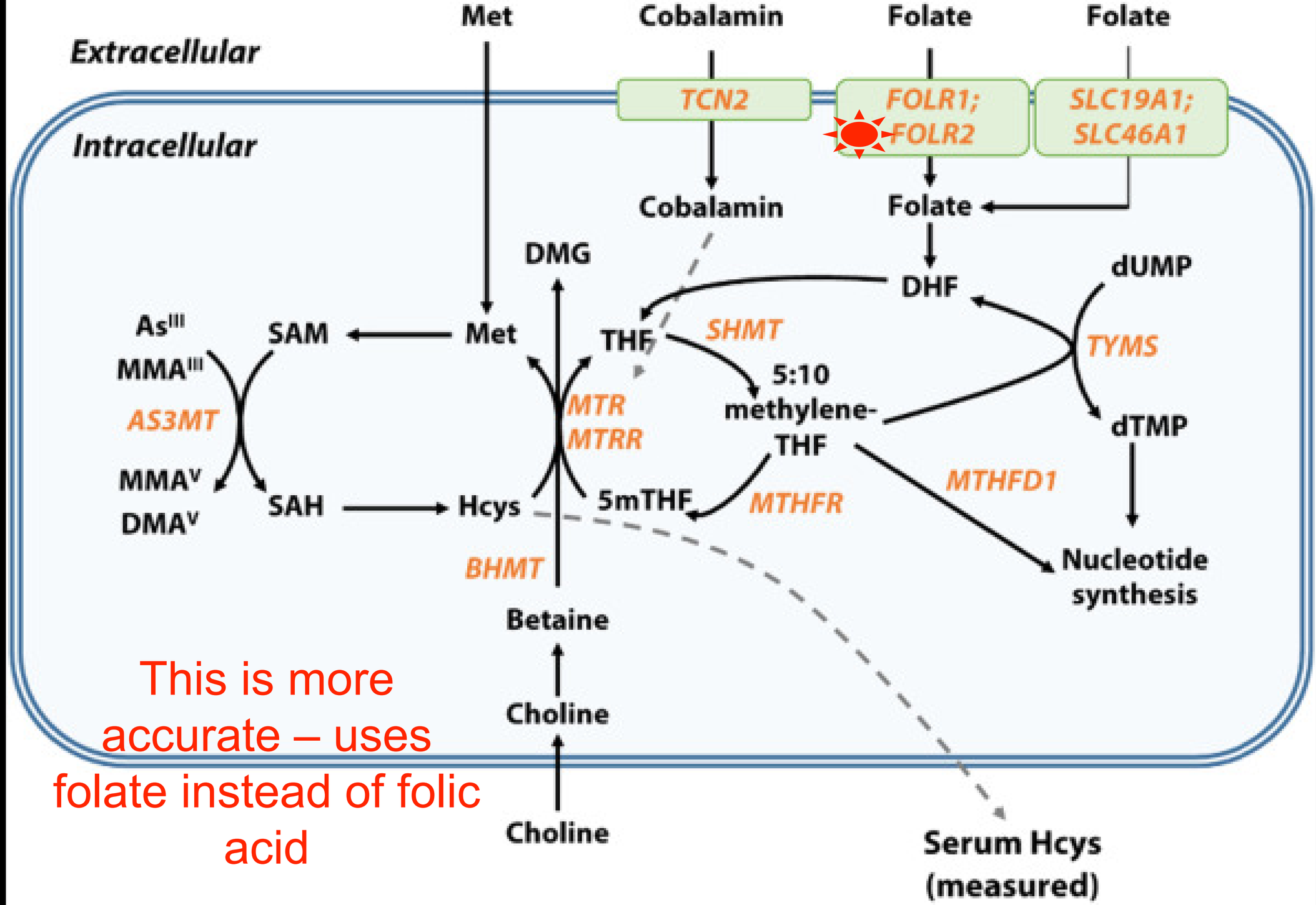
Gene ID: 2350, updated on 23-Nov-2018

Summary

FOLR2

Official Symbol	FOLR2 provided by HGNC
Official Full Name	folate receptor beta provided by HGNC
Primary source	HGNC:HGNC:3793
See related	Ensembl:ENSG00000165457 MIM:136425; Vega:OTTHUMG00000150394
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	FBP; FR-P3; FR-BETA; BETA-HFR; FBP/PL-1
Summary	The protein encoded by this gene is a member of the folate receptor (FOLR) family, and these genes exist in a cluster on chromosome 11. Members of this gene family have a high affinity for folic acid and for several reduced folic acid derivatives, and they mediate delivery of 5-methyltetrahydrofolate to the interior of cells. This protein has a 68% and 79% sequence homology with the FOLR1 and FOLR3 proteins, respectively. Although this protein was originally thought to be specific to placenta, it can also exist in other tissues, and it may play a role in the transport of methotrexate in synovial macrophages in rheumatoid arthritis patients. Multiple transcript variants that encode the same protein have been found for this gene. [provided by RefSeq, Jul 2008]


folic acid
FOLR3
FOLR2
FOLR1
receptor-mediated endocytosis
DHFR
dUMP
pyrimidine synthesis
DHF
MTHFR
TYMS
dTMP
5-Methyl THF
THF
5,10 Methylene THF
10-Formyl THF
MS
purine synthesis
Methionine
DHF
Homocysteine
SAM
SAH
MT
CH3X
X
methylation of DNA, RNA, histones and other proteins


Met
Cobalamin
Folate
Folate
Extracellular
Intracellular
TCN2
FOLR1;
FOLR2
SLC19A1;
SLC46A1
Cobalamin
Folate
DMG
dUMP
DHF
As^III
MMA^III
AS3MT
MMA^V
DMA^V
SAM
Met
THF
SHMT
TYMS
5:10
methylene-
THF
dTMP
MTR
MTRR
SAH
Hcys
5mTHF
MTHFR
MTHFD1
BHMT
Nucleotide
synthesis
Betaine
Choline
Choline
Serum Hcys
(measured)
This is more accurate – uses folate instead of folic acid

Summaries for FOLR2 Gene

Entrez Gene Summary for FOLR2 Gene

The protein encoded by this gene is a member of the folate receptor (FOLR) family, and these genes exist in a cluster on chromosome 11. Members of this gene family have a high affinity for folic acid and for several reduced folic acid derivatives, and they mediate delivery of 5-methyltetrahydrofolate to the interior of cells. This protein has a 68% and 79% sequence homology with the FOLR1 and FOLR3 proteins, respectively. Although this protein was originally thought to be specific to placenta, it can also exist in other tissues, and it may play a role in the transport of methotrexate in synovial macrophages in rheumatoid arthritis patients. Multiple transcript variants that encode the same protein have been found for this gene. [provided by RefSeq, Jul 2008]

GeneCards Summary for FOLR2 Gene

FOLR2 (Folate Receptor Beta) is a Protein Coding gene. Diseases associated with FOLR2 include Neural Tube Defects and Rheumatoid Arthritis. Among its related pathways are Metabolism and Metabolism of proteins. Gene Ontology (GO) annotations related to this gene include *folic acid binding* and *folic acid transmembrane transporter activity*. An important paralog of this gene is FOLR3.

UniProtKB/Swiss-Prot for FOLR2 Gene FOLR2_HUMAN,P14207

Binds to folate and reduced folic acid derivatives and mediates delivery of 5-methyltetrahydrofolate and folate analogs into the interior of cells. Has high affinity for folate and folic acid analogs at neutral pH. Exposure to slightly acidic pH after receptor endocytosis triggers a conformation change that strongly reduces its affinity for folates and mediates their release.

GeneCards Summary for **FOLR2** Gene. **FOLR2** (Folate Receptor Beta) is a Protein Coding gene. Diseases associated with **FOLR2** include Neural Tube Defects and **Rheumatoid Arthritis**.

FOLR2 Gene - GeneCards | FOLR2 Protein | FOLR2 Antibody

https://www.genecards.org/cgi-bin/carddisp.pl?gene=FOLR2&keywords=POR

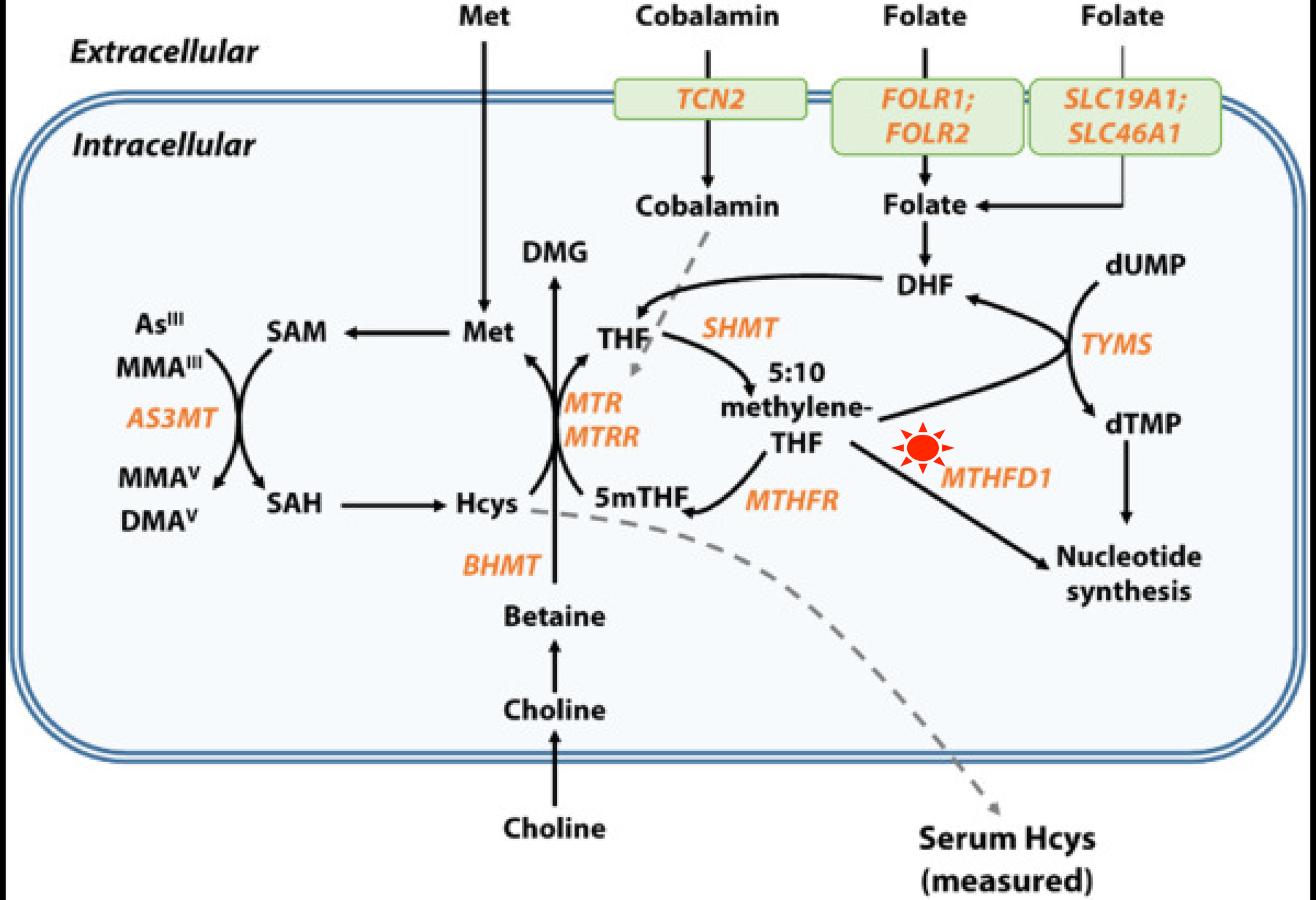
MTHFD1

Entrez Gene Summary for MTHFD1 Gene

This gene encodes a protein that possesses three distinct enzymatic activities, 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methenyltetrahydrofolate cyclohydrolase and 10-formyltetrahydrofolate synthetase. Each of these activities catalyzes one of three sequential reactions in the interconversion of 1-carbon derivatives of tetrahydrofolate, which are substrates for methionine, thymidylate, and de novo purine syntheses. The trifunctional enzymatic activities are conferred by two major domains, an aminoterminal portion containing the dehydrogenase and cyclohydrolase activities and a larger synthetase domain. [provided by RefSeq, Jul 2008]

GeneCards Summary for MTHFD1 Gene

MTHFD1 (Methylenetetrahydrofolate Dehydrogenase, Cyclohydrolase And Formyltetrahydrofolate Synthetase 1) is a Protein Coding gene. Diseases associated with MTHFD1 include Neural Tube Defects, Folate-Sensitive and Combined Immunodeficiency And Megaloblastic Anemia With Or Without Hyperhomocysteinemia. Among its related pathways are histidine degradation and Metabolism. Gene Ontology (GO) annotations related to this gene include *formate-tetrahydrofolate ligase activity* and *methylenetetrahydrofolate dehydrogenase (NADP+) activity*. An important paralog of this gene is MTHFD1L.


Met
Cobalamin
Folate
Folate
Extracellular
Intracellular
TCN2
FOLR1;
FOLR2
SLC19A1;
SLC46A1
Cobalamin
Folate
DMG
DHF
dUMP
As^III
MMA^III
AS3MT
MMA^V
DMA^V
SAM
Met
THF
SHMT
TYMS
5:10
methylene-
THF
dTMP
MTR
MTRR
MTHFD1
SAH
Hcys
5mTHF
MTHFR
Nucleotide
synthesis
BHMT
Betaine
Choline
Choline
Serum Hcys
(measured)

rs1076991

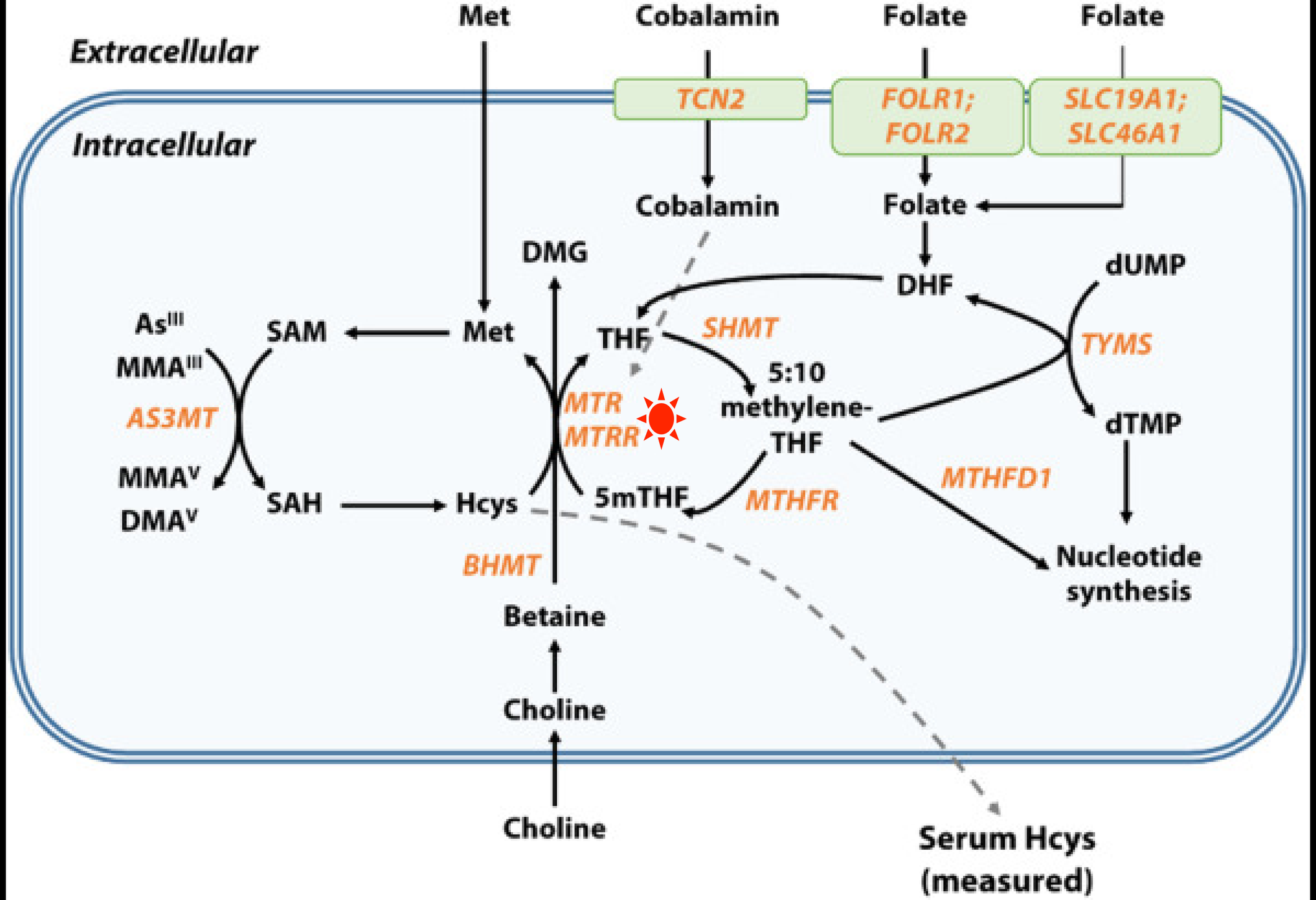
MTHFD1

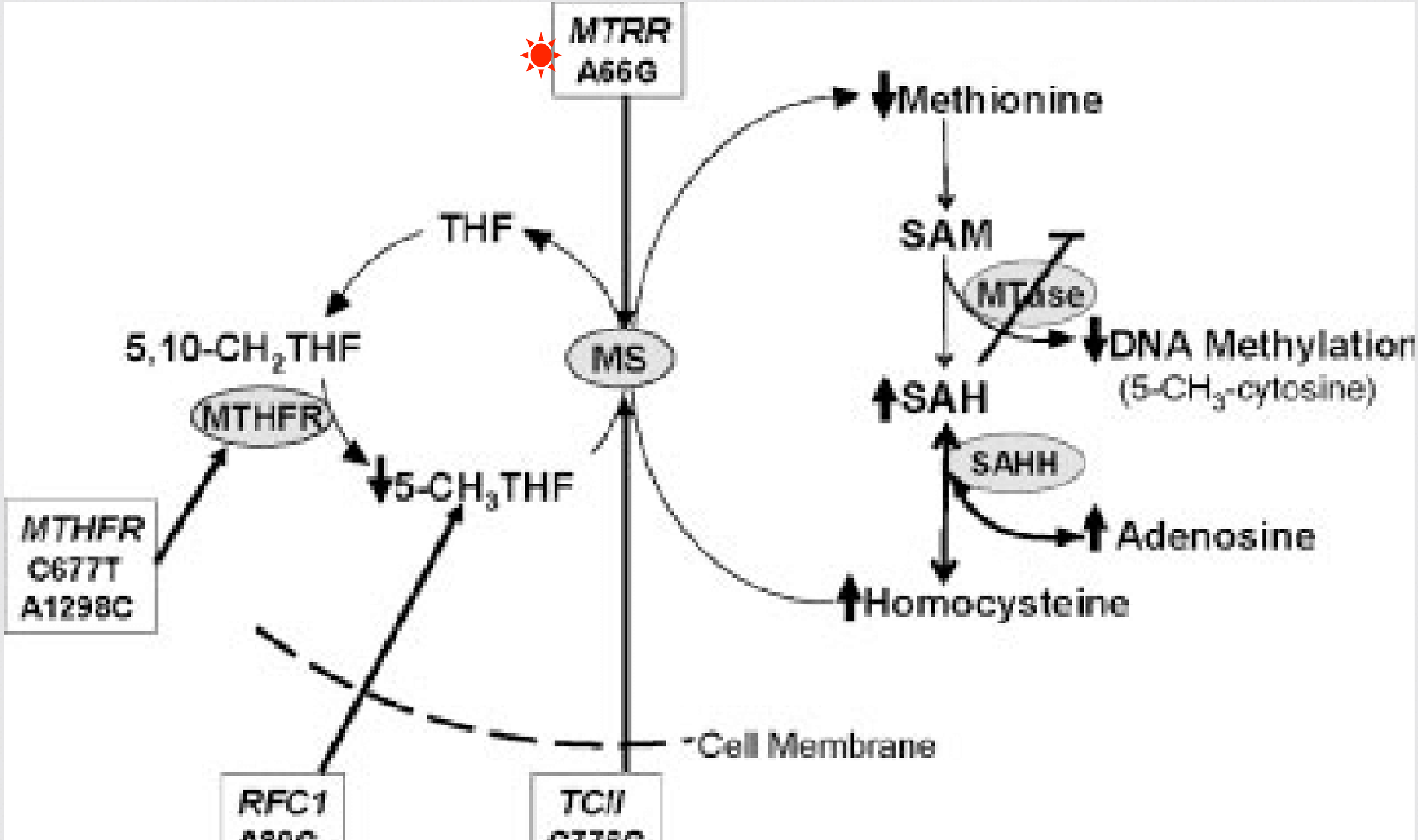
[PMID 19130090] rs1076991 C > T exerts a significant effect on promoter activity in vitro and along with rs2236225 G > A influences embryonic development.

[PMID 19064578] No association of single nucleotide polymorphisms in one-carbon metabolism genes with prostate cancer risk.

[PMID 19808787] Genetics of human neural tube defects.

[PMID 23940529] Roles of genetic polymorphisms in the folate pathway in childhood acute lymphoblastic leukemia evaluated by bayesian relevance and effect size analysis


Met
Cobalamin
Folate
Folate
Extracellular
Intracellular
TCN2
FOLR1;
FOLR2
SLC19A1;
SLC46A1
Cobalamin
Folate
DMG
dUMP
DHF
As^III
MMA^III
AS3MT
MMA^V
DMA^V
SAM
Met
THF
SHMT
TYMS
5:10
methylene-
THF
dTMP
MTR
MTRR
SAH
Hcys
5mTHF
MTHFR
MTHFD1
BHMT
Nucleotide
synthesis
Betaine
Choline
Choline
Serum Hcys
(measured)


MTRR
A66G
Methionine
THF
SAM
MTase
DNA Methylation
(5-CH3-cytosine)
5,10-CH2THF
MS
MTHFR
SAH
5-CH3THF
SAHH
MTHFR
C677T
A1298C
Adenosine
Homocysteine
Cell Membrane
RFC1
TCII

MTRR

5-Methyltetrahydrofolate-Homocysteine Methyltransferase Reductase (MTRR) is an enzyme which interacts with methionine synthase, to ensure the continued production of the essential amino acid methionine, and is encoded for by the MTRR gene [1].

Methionine is an essential amino acid and is required for numerous processes throughout the body. A major source of methionine is the enzyme methionine synthase which converts homocysteine into methionine, using 5-methlytetrahydrofolate (MTHF) produced by methylenetetrahydrofolate reductase (MTHFR) as a methyl donor [2].

The activity of methionine synthase requires vitamin B12 as a co-factor, however over time this becomes inactivated. MTRR breaks the association between methionine synthase and inactive vitamin B12, allowing a new functional vitamin B12 molecule to bind, ensuring continuing production of methionine [3].

So the job of MTRR is to remove the used up B12 from the METHIONINE SYNTHASE and replace with a fresh B12.

MTRR A66G

is carried by about half the population. It seems that combinations of MTRR polymorphisms with MTHFR or other methylation cycle issues may be more of a concern than just carrying the single MTRR variant.

- A 2011 study showed an increased risk for colorectal cancer (OR = 1.39) for those with rs1801394 GG. [ref]
- A 2014 study showed an increased risk for metabolic syndrome for those with the A66G polymorphisms and MTHFR C677T. [ref]
- A 2014 meta-analysis showed an increased risk for congenital heart disease associated with A66G polymorphism. [ref]

CONSIDERATIONS & THERAPY

Treat with MTHFR Support and possibly MTHFR base support product– we did and he loved the way he felt (ended up on 4/day total. Plus lost 30 lbs.

This is one SNP that women, if pregnant, should absolutely receive a MTHFR prenatal (there are a few available).

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	
rs4680	COMT V158M	+/-	B2 (Riboflavin), Methyl Donors Taurine, Choline, Trimethylglycine (TMG), Dimethylglycine (DMG), Inositol, L-Methionine	
rs6323	MAO-A	+/NA		
rs1799836	MAO-B	-/NA		
rs769407	GAD1	+/-	Prescription Amantadine, Ketamine, Glycine, N-Acetyl-Cysteine (NAC), Beta Phenyl GABA, Zinc, Magnesium, Oxaloacetate, Elderberry, L-Theanine, Melatonin	
rs3828275	GAD1	-/-		

Monoamine oxidase A, also known as **MAO-A**, is an enzyme that in humans is encoded by the **MAOA** gene. This gene is one of two neighboring gene family members that encode mitochondrial enzymes which catalyze the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin.

Monoamine oxidase A - Wikipedia

https://en.wikipedia.org/wiki/Monoamine_oxidase_A

Monoamine Oxidase A

MAOA is an X-linked gene encoding MAOA, a mitochondrial enzyme that metabolizes monoamine neurotransmitters including NE, DA and serotonin.

From: Emery and Rimoin's Principles and Practice of Medical Genetics, 2013

X-linked means it comes from MOM's DNA – X chromosome.

MAO-B

Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation

Rose McDermott, Dustin Tingley, Jonathan Cowden, Giovanni Frazzetto, and Dominic D. P. Johnson

PNAS February 17, 2009 106 (7) 2118-2123; https://doi.org/10.1073/pnas.0808376106

MAO-A

Dopamine problems are implicated in ADHD, Alzheimer's, Parkinson's, depression, bipolar disorders, binge eating, addiction, gambling, and schizophrenia. Having too much **dopamine** in the wrong place can make you psychotic. ... Therefore **high** amounts of **dopamine** can **cause** euphoria, aggression and intense sexual feelings.

May 13, 2011

Dopamine Primer | Psychology Today

https://www.psychologytoday.com/us/blog/evolutionary-psychiatry/.../dopamine-primer

MAO-A

Dopamine and addiction

Cocaine and amphetamines inhibit the re-uptake of dopamine. Cocaine is a dopamine transporter blocker that competitively inhibits dopamine uptake to increase the presence of dopamine.

Amphetamine increases the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines are similar in structure to dopamine, and so can enter the presynaptic neuron via its dopamine transporters. By entering, amphetamines force dopamine molecules out of their storage vesicles. By increasing presence of dopamine both these lead to increased pleasurable feelings and addiction.

MAO-A

Dopamine levels and psychosis

Abnormally high dopaminergic transmission has been linked to psychosis and schizophrenia. Both the typical and the atypical antipsychotics work largely by inhibiting dopamine at the receptor level.

MAO-A

https://bebrainfit.com/too-much-serotonin/

kmarks | Webmail | Clinician | Inbox | Brother HL2270D... | AMC K-Reports | Basecamp | Office Em

Symptoms of Too Much Serotonin: Mild to Serious

A high level of serotonin leads to excessive nerve cell activity which can cause a wide range of symptoms, from mild to severe. (1)

According to Datis Kharrazian, PhD, DHSc, author of *Why Isn't My Brain Working?*, mild symptoms of too much serotonin include:

- shyness
- feeling "not good enough"
- desiring, yet fearing, social interactions
- nervousness
- being easily upset by criticism
- lack of motivation (2)

MAO-A

https://bebrainfit.com/too-much-serotonin/

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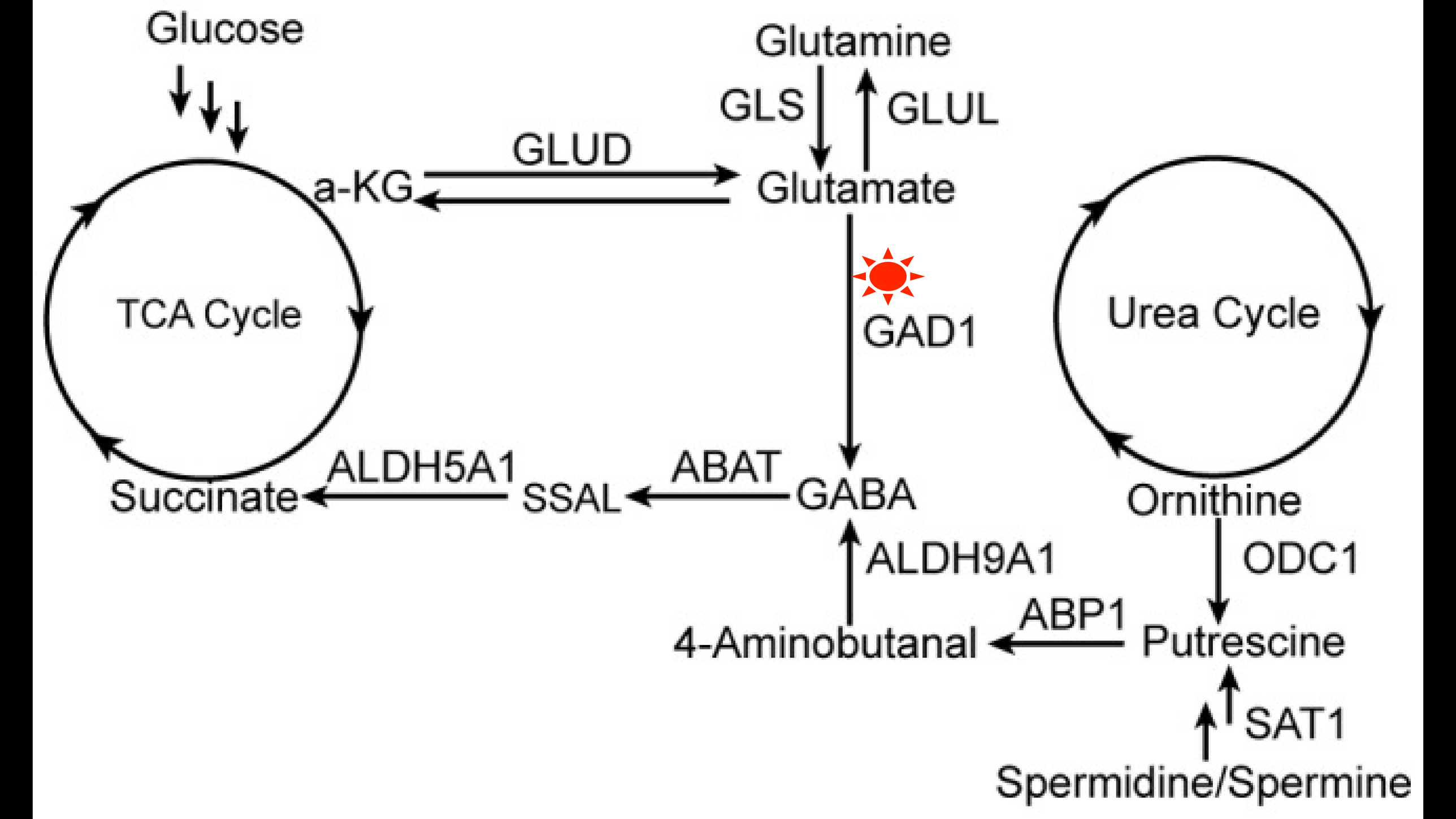
More serious symptoms of too much serotonin include: (3, 4)

- feeling agitated or restless
- mental confusion or disorientation
- headache
- dizziness
- increased heart rate or blood pressure
- dilated pupils
- goose bumps, sweating, or shivering
- diarrhea, nausea, or vomiting
- tremors or twitchy muscles

When serotonin levels get dangerously high, it is referred to as *serotonin syndrome* or serotonin toxicity.

It can be quite serious, even life-threatening.


Glucose
Glutamine
GLS
GLUL
GLUD
a-KG
Glutamate
TCA Cycle
GAD1
Urea Cycle
ALDH5A1
ABAT
Succinate
SSAL
GABA
Ornithine
ALDH9A1
ODC1
ABP1
4-Aminobutanal
Putrescine
SAT1
Spermidine/Spermine

GAD1 glutamate decarboxylase 1 [*Homo sapiens* (human)]

Gene ID: 2571, updated on 22-Nov-2018

Summary

Official Symbol	GAD1 provided by HGNC
Official Full Name	glutamate decarboxylase 1 provided by HGNC
Primary source	HGNC:HGNC:4092
See related	Ensembl:ENSG00000128683 MIM:605363; Vega:OTTHUMG00000044175
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	GAD; SCP; CPSQ1
Summary	This gene encodes one of several forms of glutamic acid decarboxylase, identified as a major autoantigen in insulin-dependent diabetes. The enzyme encoded is responsible for catalyzing the production of gamma-aminobutyric acid from L-glutamic acid. A pathogenic role for this enzyme has been identified in the human pancreas since it has been identified as an autoantigen and an autoreactive T cell target in insulin-dependent diabetes. This gene may also play a role in the stiff man syndrome. Deficiency in this enzyme has been shown to lead to pyridoxine dependency with seizures. Alternative splicing of this gene results in two products, the predominant 67-kD form and a less-frequent 25-kD form. [provided by RefSeq, Jul 2008]

Makes GABA

GAD1

Whilst GABA molecules are inhibitory neurotransmitters, glutamate is an excitatory neurotransmitter, so the balance of GABA to glutamate is thought to be key in regulating sleep [2].

GAD1 is only expressed in the brain as GABA molecules cannot pass the blood-brain barrier (they cannot leave the brain). However, the amino acid glutamate, which is converted by GAD1 into GABA molecules, can pass the blood-brain barrier. For this reason, supplementation with GABA is not recommended as it will not reach the brain where it is required, and simply be passed out the body [3].

There are two SNPs within GAD1 that are associated with poor outcomes, although a mechanism for either has not been described. The ‘C’ allele of G638+315C and the ‘A’ allele of C170814316A are both associated with depression, early awakenings and fatigue.

Trapping Channel Block of NMDA-Activated Responses By Amantadine and Memantine

THOMAS A. BLANPIED,[1] FAYE A. BOECKMAN,[2] ELIAS AIZENMAN,[2] AND JON W. JOHNSON[1]
[1]*Department of Neuroscience, University of Pittsburgh, 15260 and* [2]*Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261*

Blanpied, Thomas A., Faye Boeckman, Elias Aizenman, and Jon W. Johnson. Trapping channel block of NMDA-activated responses by amantadine and memantine. *J. Neurophysiol.* 77: 309–323, 1997. We investigated the mechanisms by which the antiparkinsonian and neuroprotective agents amantadine and memantine inhibit responses to *N*-methyl-D-aspartic acid (NMDA). Whole cell recordings were performed using cultured rat cortical neurons or Chinese hamster ovary (CHO) cells expressing NMDA receptors. Both amantadine and memantine blocked NMDA-activated channels by binding to a site at which they could be trapped after channel closure and agonist unbinding. For neuronal receptors, the IC_{50}s of amantadine and memantine at −67 mV were 39 and 1.4 μM, respectively. When memantine and agonists were washed off after steady-state block, one-sixth of the blocked channels released rather than trapped the blocker; memantine exhibited ''partial trapping.'' Thus memantine appears to have a lesser tendency to be trapped than do phencyclidine or (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[1,d]cyclihepten-5,10-imine (MK-801). We next investigated mechanisms that might underlie partial trapping. Memantine blocked and could be trapped by recombinant NMDA receptors composed of NR1 and either NR2A or NR2B subunits. In these receptors, as in the native receptors

synaptic transmission and plasticity. However, PCP and ketamine, which also block this channel (MacDonald et al. 1991), have severe and deleterious behavioral effects in humans (Krystal et al. 1994; Luby et al. 1959), probably due to their interaction with the NMDA receptor (Javitt and Zukin 1991). Finally, memantine as well blocks the NMDA-activated channel (Bormann 1989; Chen et al. 1992), but is currently used in the treatment of Parkinson's disease (Fischer et al. 1977), dementia (Ditzler 1991), and several movement-related disorders (e.g., Weller and Kornhuber 1991). During therapeutic use, the memantine concentrations found in cerebrospinal fluid suggest that its primary site of action is the NMDA receptor (Kornhuber and Quack 1995), and yet it appears to induce fewer and less profound effects on perception or consciousness (Ditzler 1991) than PCP or ketamine. The reasons for the surprisingly diverse behavioral effects of blockers of the NMDA-activated channel are not known. It is plausible that this variation arises in part from a diversity of mechanisms by which the channel

U.S. Pharmacist
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PUBLISHED MAY 18, 2011

PAIN MANAGEMENT

The Emerging Role of NMDA Antagonists in Pain Management

Journal of Neural Transmission / General Section JNT
February 1993, Volume 92, Issue 1, pp 57–65 | Cite as

Amantadine and the glutamate hypothesis of schizophrenia Experiences in the treatment of neuroleptic malignant syndrome

Authors | Authors and affiliations

J. Kornhuber, M. Weller

CONSIDERATIONS & THERAPY

COMT Hetero: Adenosyl Hydroxy B12 – he will probably love this. Star with liquid drops. Increase, if he desires, to capsules. Watch for overmethylation.

COMT: Chelated Magnesium 250mg as a cofactor once or twice a day.

COMT: Give Lithium Orotate 5mg once or twice a day to slow down dopamine and epinephrine.

GAD1: Give Amantadine 100mg/day then twice a day to reduce pain sensitivity, bring calmness and block glutamine from the MDNA receptor. Note: 100mg or 200mg/day may be optimal.

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result
rs1051266	SLC19A1	+/+	Methyltetrahydrofolate (5-MTHF)
rs4147730	NDUFS3	-/-	CoQ 10, PQQ, L-Carnitine, Ornithine, Magnesium, NADH, Calcium
rs809359	NDUFS7	-/-	
rs1051806	NDUFS8	+/-	
rs11648723	UQCRC2	-/-	
rs4850	UQCRC2	-/-	
rs8042694	COX5A	+/-	
rs4626565	COX6C	-/-	
rs1244414	ATP5C1	-/-	

SLC19A1

From Wikipedia, the free encyclopedia

Solute carrier family 19 (folate transporter), member 1, also known as **SLC19A1** or **RFC1**, is a protein which in humans is encoded by the *SLC19A1* gene.[5]

Contents [hide]

Function [edit]

Transport of folate compounds into mammalian cells can occur via receptor-mediated (see folate receptor 1) or carrier-mediated mechanisms. A functional coordination between these 2 mechanisms has been proposed to be the method of folate uptake in certain cell types. Methotrexate (MTX) is an antifolate chemotherapeutic agent that is actively transported by the carrier-mediated uptake system. RFC1 plays a role in maintaining intracellular concentrations of folate.[6]

Clinical significance [edit]

Individuals carrying a specific polymorphism of SLC19A1 (c.80GG) have lower levels of folate.[7] Other studies have also shown that individuals carrying the c.80AA polymorphism who are treated with methotrexate have higher levels of this anti-folate chemotherapeutic agent. Personalized dosing of the drug depending on the patient's genotype may therefore be required.

SLC19A1 Gene (Protein Coding)

Solute Carrier Family 19 Member 1

GCID: GC21M045493

GIFtS: 52

Genes Participants

Undiagnosed Diseases Network

Jump to section: Aliases | Disorders | Domains | Drugs | Expression | Function | Genomics | Localization | Orthologs | Paralogs | Pathways | Products | Proteins | Publications | Sources | Summaries | Transcripts | Variants

Aliases for SLC19A1 Gene

Aliases for SLC19A1 Gene

- Solute Carrier Family 19 Member 1 [2 3 4 5]
- Solute Carrier Family 19 (Folate Transporter), Member 1 [2 3]
- Reduced Folate Carrier Protein [3 4]
- Placental Folate Transporter [3 4]
- Intestinal Folate Carrier 1 [3 4]
- Reduced Folate Carrier 1 [2 3]
- Folate Transporter 1 [2 3]
- IFC-1 [3 4]
- FOLT [3 4]
- RFC1 [3 4]
- RFC [3 4]
- FLOT1 [4]
- CHMD [3]
- IFC1 [3]
- REFC [3]

Summaries for SLC19A1 Gene

Entrez Gene Summary for SLC19A1 Gene

The membrane protein encoded by this gene is a transporter of folate and is involved in the regulation of intracellular concentrations of folate. Three transcript variants encoding different isoforms have been found for this gene.[provided by RefSeq, Mar 2011]

GeneCards Summary for SLC19A1 Gene

SLC19A1 (Solute Carrier Family 19 Member 1) is a Protein Coding gene. Diseases associated with SLC19A1 include Placental Choriocarcinoma and Methotrexate Toxicity Or Dose Selection. Among its related pathways are Metabolism and Folate Metabolism. Gene Ontology (GO) annotations related to this gene include *oxidoreductase activity* and *folic acid transmembrane transporter activity*. An important paralog of this gene is SLC19A3.

UniProtKB/Swiss-Prot for SLC19A1 Gene S19A1_HUMAN,P41440

Transporter for the intake of folate. Uptake of folate in human placental choriocarcinoma cells occurs by a novel mechanism called potocytosis which functionally couples three components, namely the folate receptor, the folate transporter, and a V-type H(+)-pump.

Gene Wiki entry for SLC19A1 Gene

PharmGKB "VIP" Summary for SLC19A1 Gene

Additional gene information for SLC19A1 Gene

IMPROVED!

HGNC(10937) Entrez Gene(6573) Ensembl(ENSG00000173638) OMIM(600424) UniProtKB(P41440)

Monarch Initiative
Search for SLC19A1 at DataMed
Search for SLC19A1 at HumanCyc

No data available for CIViC summary , Tocris Summary , fRNAdb sequence ontologies and piRNA Summary for SLC19A1 Gene

CONSIDERATIONS & THERAPY

SLC19A1: Give extra folate or folinic acid (may work better).

NDUFS7/COX5A: Try some CoQ10 (ubiquinol) 100-200mg/day. BioPQQ 20mg per day too.

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result
rs1021737	CTH	+/-	N-Acetyl Cysteine (NAC), Glutathione
rs819147	AHCY	-/-	
rs1056806	GSTM1	-/-	Glutathione
rs7483	GSTM3	+/-	
rs1138272	GSTP A114V	+/-	
rs1695	GSTP1 I105V	+/-	
rs1208	NAT2	-/-	Silymarin, Alpha Lipoic Acid (ALA), P-5-P, Catechins
rs4880	SOD2	+/+	High Dose Antioxidants, Curcumin, Sulforaphane, Vitamin C

- GSTM1, GSTM3, GSTP, when present, all decrease the body’s ability to reduce glutathione. Use a patented, validated, absorbable, reduced glutathione daily with this patient.

rs4880

SOD2

The rs4880(T) allele, part of the codon for amino acid valine at codon 16 of the antioxidant protein from the mitochrondrial superoxide dismutase 2 SOD2 gene, is the most common in most populations studied. The rs4880(C) allele gives rise to an alanine at this position is it also known as Val16Ala manganese superoxide dismutase, or A16V.

There appears to be some conflict in the literature over the effect of this SNP. Having a valine at codon 16 is said to reduce enzyme activity [PMID 15864132], and thus lead to increased oxidative stress, yet in at least one study of the actual enzyme levels measured in people, SOD2 activity was 33% higher in (C;T) or (T;T) individuals compared to (C;C) individuals [PMID 16538174]. Regardless of how this resolves, several phenotypic associations have been reported for this SNP, including:

- A 10 fold higher risk for heart disease in hereditary hemochromatosis patients with rs4880(T;T) genotypes compared to similar patients with rs4880(C;T) or rs4880(C;C) genotypes. [PMID 15591282]
- An increased risk of malignant pleural mesothelioma (MPM) was found in individuals with rs4880(C;C) (OR = 3.07, CI: 1.55-6.05) genotypes. Odds ratios for developing mesothelioma were even higher for patients lacking obvious exposure to asbestos fibers. [PMID 17290392]
- Among prostate cancer patients with a rs4880(T;T) genotype, but not the (C;C) genotype, higher iron intake level was associated with a 2.3-fold increase in risk for aggressive forms of the cancer (OR=2.3, CI: 1.0-4.9). [PMID 18296681]
- rs4880(C;T) prostate cancer patients being treated by radiation therapy are more likely (8% compared to 0%, p=0.02) to exhibit a significant increase in grade 2 late rectal bleeding after irradiation than (C;C) or (T;T) patients, based on a study of 135 patients. The odds for this are worse if the patient also has the rs861539(C;T) genotype (14% vs 1%, p=0.002).[PMID 18582155]
- A study of non-Hispanic Caucasians with various types of brain tumors concluded that there was an increased risk of acoustic neuroma (odds ratio 2.0, CI: 1.1-2.7) associated with the alanine-encoding rs4880(C) allele.[PMID 18682580]
- rs4880(C) carriers with breast cancer and being treated with cyclophosphamide had worse survival rates (i.e. didn't benefit as much), based on a 2009 study of 248 US and 340 Norwegian patients.[PMID 19509150]

About Superoxide Dismutase 2 (SOD2)

Superoxide dismutases are enzymes that transform the superoxide (O_2^-) radical into either ordinary oxygen (O_2) or hydrogen peroxide (H_2O_2).

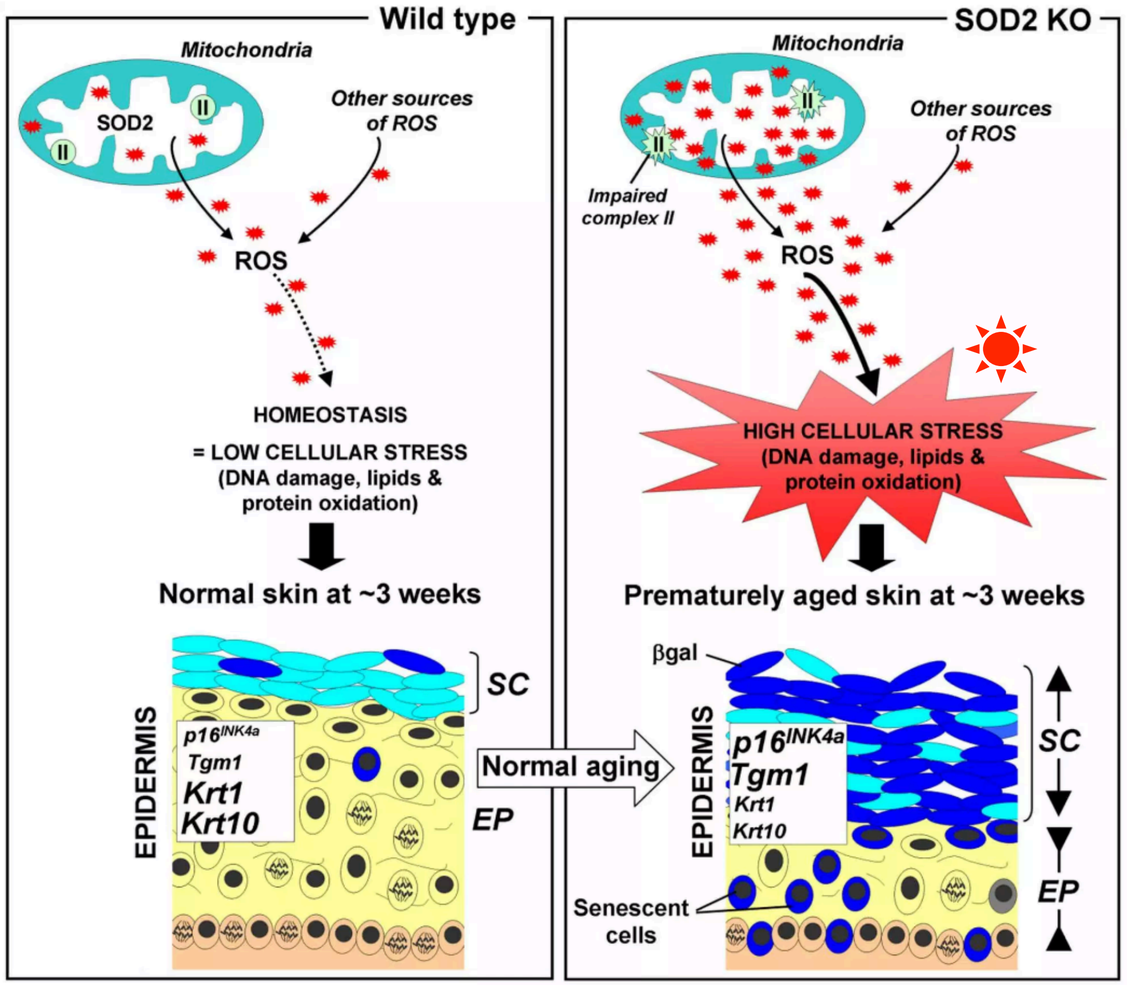
Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, causes many types of cell damage. Hydrogen peroxide is also damaging, but less so, and is degraded by other enzymes such as catalase. Thus, SOD is an important antioxidant defense in nearly all living cells exposed to oxygen.

This protein plays a protective role against oxidative stress, ionizing radiation, and inflammatory cytokines.

There are three forms of SOD: SOD1, SOD2, and SOD3.

SOD1 is located in the cellular fluid, SOD2 in the mitochondria, and SOD3 outside the cell.

Superoxide is one of the main reactive oxygen species in the cell. As a consequence, SOD serves a key antioxidant role.



SOD2 too would benefit from glutathione.

http://archive.impactaging.com/papers/v4/n2/full/100433.html

Superoxide has a few very positive functions in the body: clearing infections, cellular communication, creating new mitochondria and destroying tumors.

However, superoxide is damaging, and every chronic disease has too much oxidative stress as a contributory cause.

IL5

Aliases for IL5 Gene

- Interleukin 5 [2 3 5]
- Eosinophil Differentiation Factor [2 3 4]
- T-Cell Replacing Factor [2 3 4]
- Colony-Stimulating Factor, Eosinophil [2 3]
- B-Cell Differentiation Factor I [3 4]
- Interleukin-5 [2 3]
- IL-5 [3 4]
- TRF [3 4]
- Interleukin 5 (Colony-Stimulating Factor, Eosinophil) [2]
- B Cell Differentiation Factor I [2]
- EDF [3]

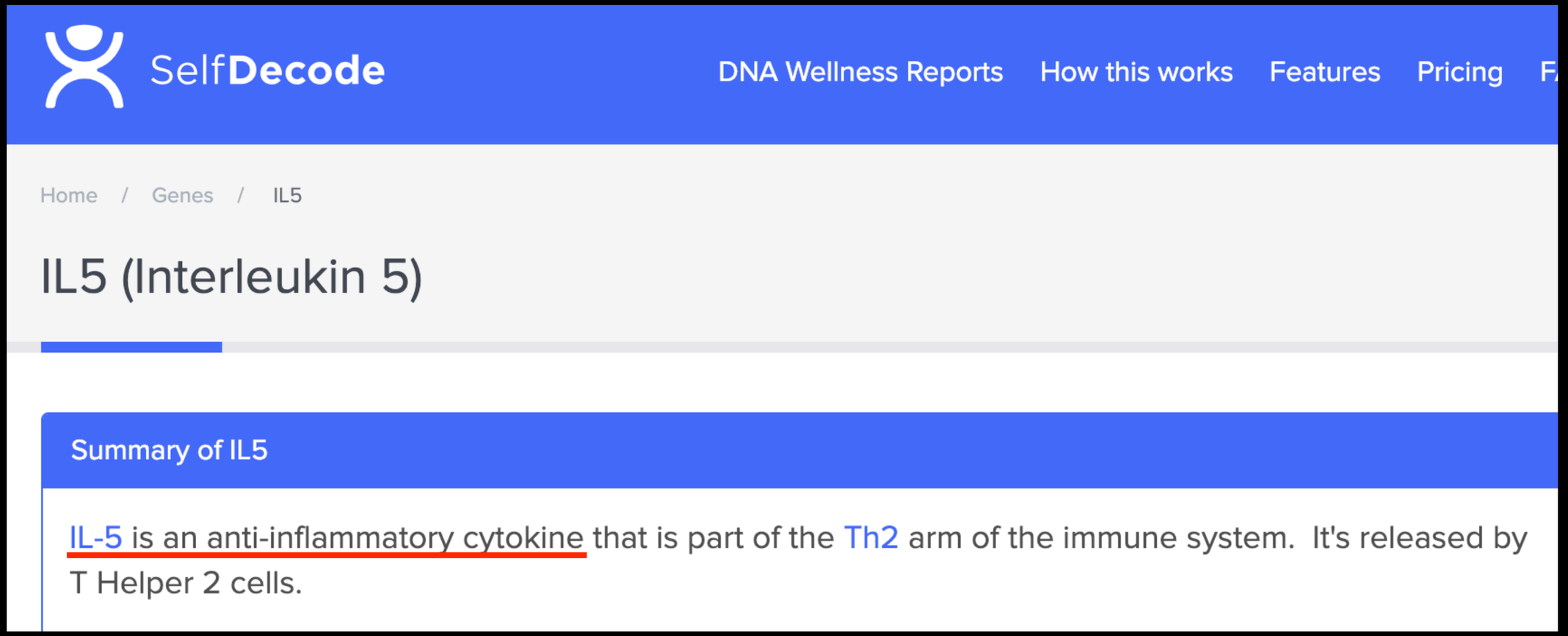
External Ids for IL5 Gene

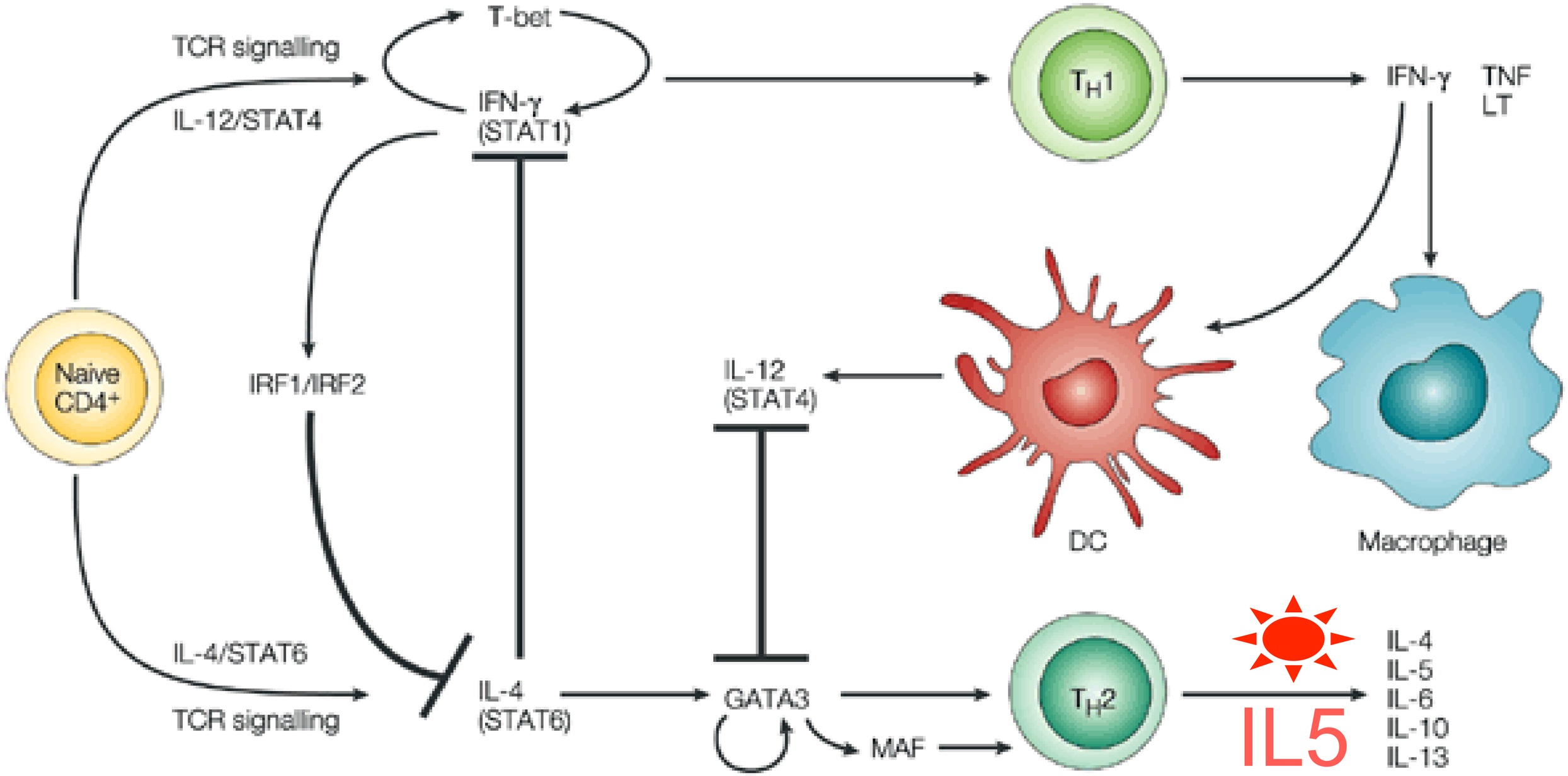
HGNC: 6016 Entrez Gene: 3567 Ensembl: ENSG00000113525 OMIM: 147850 UniProtKB: P05113

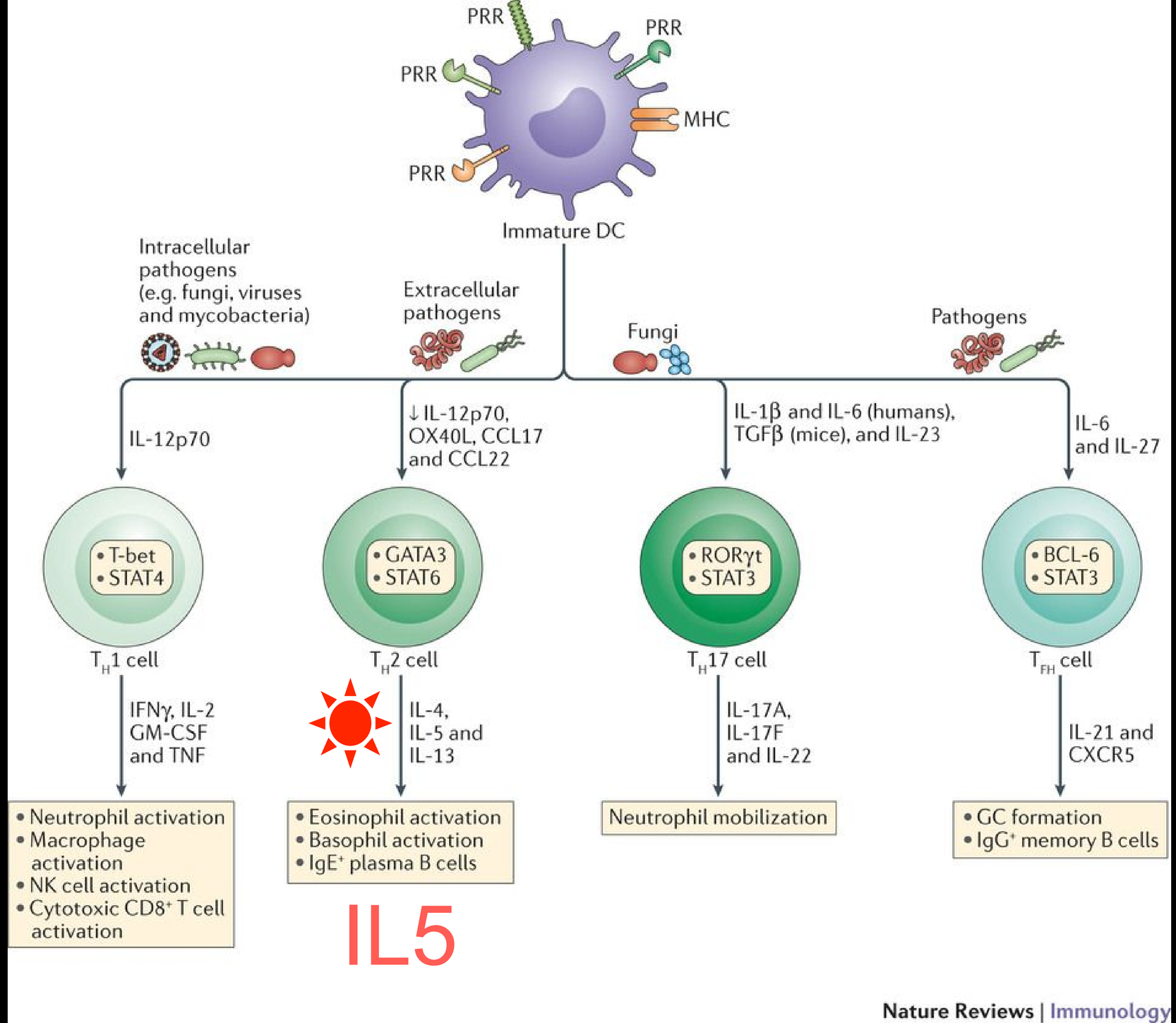
Previous GeneCards Identifiers for IL5 Gene

GC05M131399, GC05M132324, GC05M131907, GC05M131953, GC05M131905, GC05M127069, GC05M131881

IL5 -- > Error of this gene causes painful underlying lifelong inflammation




T-bet
TCR signalling
IL-12/STAT4
IFN-γ
(STAT1)
T_H1
IFN-γ
TNF
LT
Naive
CD4+
IRF1/IRF2
IL-12
(STAT4)
DC
Macrophage
IL-4/STAT6
TCR signalling
IL-4
(STAT6)
GATA3
MAF
T_H2
IL5
IL-4
IL-5
IL-6
IL-10
IL-13


PRR
PRR
PRR
PRR
MHC
Immature DC
Intracellular pathogens (e.g. fungi, viruses and mycobacteria)
Extracellular pathogens
Fungi
Pathogens
IL-12p70
↓IL-12p70, OX40L, CCL17 and CCL22
IL-1β and IL-6 (humans), TGFβ (mice), and IL-23
IL-6 and IL-27
• T-bet • STAT4
• GATA3 • STAT6
• RORγt • STAT3
• BCL-6 • STAT3
T_H1 cell
T_H2 cell
T_H17 cell
T_{FH} cell
IFNγ, IL-2 GM-CSF and TNF
IL-4, IL-5 and IL-13
IL-17A, IL-17F and IL-22
IL-21 and CXCR5
• Neutrophil activation • Macrophage activation • NK cell activation • Cytotoxic CD8⁺ T cell activation
• Eosinophil activation • Basophil activation • IgE⁺ plasma B cells
Neutrophil mobilization
• GC formation • IgG⁺ memory B cells
IL5
Nature Reviews | Immunology

IL5

Entrez Gene Summary for IL5 Gene

This gene encodes a cytokine that acts as a growth and differentiation factor for both B cells and eosinophils. The encoded cytokine plays a major role in the regulation of eosinophil formation, maturation, recruitment and survival. The increased production of this cytokine may be related to pathogenesis of eosinophil-dependent inflammatory diseases. This cytokine functions by binding to its receptor, which is a heterodimer, whose beta subunit is shared with the receptors for interleukine 3 (IL3) and colony stimulating factor 2 (CSF2/GM-CSF). This gene is located on chromosome 5 within a cytokine gene cluster which includes interleukin 4 (IL4), interleukin 13 (IL13), and CSF2 . This gene, IL4, and IL13 may be regulated coordinately by long-range regulatory elements spread over 120 kilobases on chromosome 5q31. [provided by RefSeq, Jul 2013]

GeneCards Summary for IL5 Gene

IL5 (Interleukin 5) is a Protein Coding gene. Diseases associated with IL5 include Pulmonary Eosinophilia and Chronic Eosinophilic Pneumonia. Among its related pathways are Akt Signaling and T cell receptor signaling pathway. Gene Ontology (GO) annotations related to this gene include *cytokine activity* and *interleukin-5 receptor binding*.

UniProtKB/Swiss-Prot for IL5 Gene IL5_HUMAN,P05113

Factor that induces terminal differentiation of late-developing B-cells to immunoglobulin secreting cells.

Tocris Summary for IL5 Gene

Cytokines are proteinaceous signaling compounds that are major mediators of the immune response. They control many different cellular functions including proliferation, differentiation and cell survival/apoptosis but are also involved in several pathophysiological processes.

Med Microbiol Immunol. 2000 Nov;189(2):67-74.

IL-5 is essential for vaccine-induced protection and for resolution of primary infection in murine filariasis.

Martin C[1], Al-Qaoud KM, Ungeheuer MN, Paehle K, Vuong PN, Bain O, Fleischer B, Hoerauf A.

Author information

IL5

Abstract

The pathways conferring immunity to human filariases are not well known, in part because human-pathogenic filariae do not complete a full life cycle in laboratory mice. We have used the only fully permissive infection of mice with filariae, i.e., infection of BALB/c mice with the rodent filarial nematode Litomosoides sigmodontis. Our previous results showed that worm development is inversely correlated with Th2 cytokine production and eosinophilia. The scope of the present study was to directly elucidate the role of interleukin-5 (IL-5) and eosinophils in controlling the development of L. sigmodonitis after vaccination and in primary infection. BALB/c mice immunized with irradiated third-stage larvae (L3) were confirmed to have elevated IL-5 levels as well as high subcutaneous eosinophilia and to attack and reduce incoming larvae within the first 2 days, resulting in 70% reduction of worm load. Treatment of vaccinated mice with anti-IL-5 antibody (TRFK-5) suppressed both blood and tissue eosinophilia and completely abolished protection. This demonstrates, for the first time in a fully permissive filarial infection, that IL-5 is essential for protection induced by irradiated L3 larvae. In contrast, in primary-infected mice, anti-IL-5 treatment did not modify filarial infection within the 1st month, most likely because during primary infection IL-5-dependent mechanisms such as subcutaneous eosinophilia are induced too late to disturb worm establishment. However, there is a role for IL-5 late in primary infection where neutrophil-dependent worm encapsulation is also under the control of IL-5.

PMID: 11138639

CONSIDERATIONS

IL-5: Warn of inflammatory reactions to vaccinations.

EVERYTHING: May also warrant life compounded low dose naltrexone (LDN) for pain and inflammation. Start at 0.5mg in the AM and slowly titrate up to 3mg in AM only (not at night).

And fish oil (omega-3, 2500mg a day of DHA and EPA).

C3 Curcuminoids (validated) too.

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result
rs1867277	FOXE1	+/+	Iodine, Selenium, Increased Risk of Hypothyroidism
rs4343	ACE	+/+	Increased risk of salt retention and hypertension
rs1800440	CYP1B1	+/-	Increased Levels of 4-hydroxy Estrogen, Endometriosis and Osteoporosis
rs6025	F5	-/-	
rs3211719	F10	+/-	

rs1867277 FOXE1

rs1867277, also known as -283G>A, is a SNP upstream of the FOXE1 gene.

Based on ~1,000 thyroid cancer patients (and an equal number of controls), a per allele odds ratio of 1.49 (CI: 1.30-1.70, p=5.9x10e-9) was found for the rs1867277(A) allele. This allele is thought to be a causal variant.[PMID 19730683]

[PMID 22282540] Thyroid cancer susceptibility polymorphisms: confirmation of loci on chromosomes 9q22 and 14q13, validation of a recessive 8q24 locus and failure to replicate a locus on 5q24

[PMID 22493691] Novel associations for hypothyroidism include known autoimmune risk loci.

[PMID 22736773] Association of FOXE1 polyalanine repeat region with papillary thyroid cancer.

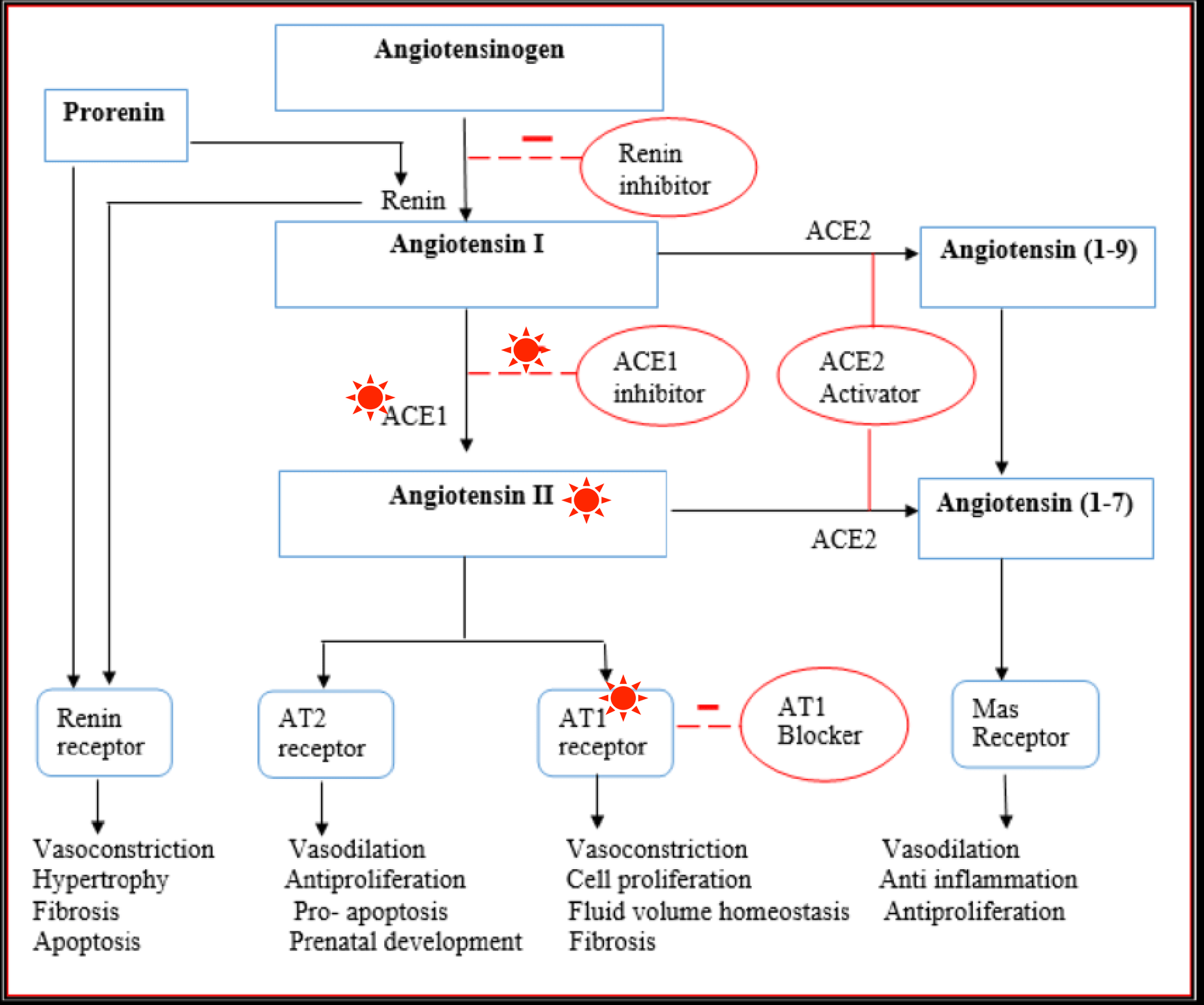
[PMID 22882326] FOXE1 polymorphisms are associated with familial and sporadic nonmedullary thyroid cancer susceptibility.

[PMID 23327367] Patterns of FOXE1 expression in papillary thyroid carcinoma by immunohistochemistry.

The Variant rs1867277 in *FOXE1* Gene Confers Thyroid Cancer Susceptibility through the Recruitment of USF1/USF2 Transcription Factors

Iñigo Landa, Sergio Ruiz-Llorente, Cristina Montero-Conde, Lucía Inglada-Pérez, Francesca Schiavi, Susanna Leskelä, Guillermo Pita, Roger Milne, Javier Maravall, Ignacio Ramos, Víctor Andía, Paloma Rodríguez-Poyo, Antonino Jara-Albarrán, [...], Mercedes Robledo [view all]

Published: September 4, 2009 • https://doi.org/10.1371/journal.pgen.1000637



So without ACE1 you get more Angiotensin II at the AT1 Receptor and higher vasoconstriction so higher BP.

rs4343

ACE

See ACE for a more complete description of the history of the ACI insertion/deletion (I/D) allele and various associations reported over the years.

Perhaps the best documented correlation of a linked SNP to the presence or absence of the Alu insertion represented by the I/D ACE polymorphism is rs4343. More specifically: the rs4343(A) allele is associated with the ACE-I (insertion) allele, and the rs4343(G) allele is associated with the ACE-D allele.[PMID 18057531]

Another SNP in linkage disequilibrium with the ACE I/D polymorphism is rs4341.[PMID 18622756],[PMID 19291311]

[PMID 19108684] A haplotype of rs4311, rs4343, rs699 increases risk of diabetic nephropathy 4x.

[PMID 19956428] Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes

[PMID 20639399] Association between angiotensin converting enzyme G2350A polymorphism and hypertension risk: a meta-analysis

ACE and ACE2: a tale of two enzymes FREE

Lawrence S. Zisman ✉

European Heart Journal, Volume 26, Issue 4, 1 February 2005, Pages 322–324, https://doi.org/10.1093/eurheartj/ehi043
Published: 24 January 2005

READ For More Info

This editorial refers to 'Myocardial infarction increases ACE2 expression in rat and humans'† by Burrell *et al.*, on page 369

The cardiac renin–angiotensin–aldosterone system (RAAS) is an endocrine cascade, which results in the conversion of the inactive pro-hormone angiotensin I (Ang I) to the active peptide hormone Ang II, and may also function as an autocrine/paracrine system to modulate cardiac function and growth. Renin, the initial enzyme of this cascade, cleaves the amino terminus of the pre-pro-hormone angiotensinogen, thereby releasing the decapeptide pro-hormone Ang I. Angiotensin-converting enzyme (ACE) removes two additional amino acids to yield the active octapeptide hormone Ang II. Ang II, acting through the AT1 receptor, is a potent vasoconstrictor and stimulates cardiac growth.

CONSIDERATIONS

Homozygous FOXE1: Increased risk for thyroid cancer (WARN THEM) and risk of hypothyroidism. Treat with iodine and 3X/wk selenium 200mcg (can become toxic).

Check annual FT4 and FT3.

Due to Homozygous ACE: Watch for high BP and use other than ACE1 inhibitor. Check BP and HgbA1C every 6 months.

Warn of increased risk of diabetic neuropathy.

They should warn their cardiologist.

OVERALL CONSIDERATIONS & THERAPIES

C677T: MTHFR Support + MTHFR Support Plus: 4-5 TOTAL per day.

FOLR2, MTHFD1, MTRR A66G: Though MTHFR Support contains a lot of 5-MTHF, consider treating, if necessary, with extra 5-MTHF.

COMT: Chelated Magnesium 250mg as a cofactor once or twice a day.

COMT: Give Lithium Orotate 5mg once or twice a day to slow down dopamine and epinephrine.

GAD1: Give prescription Amantadine 100mg a day or twice a day to bring calmness.

OVERALL CONSIDERATIONS & THERAPIES

SLC19A1: Give extra folate or folinic acid.

GSTM1/3/GSTP, SOD2: Treat with VALIDATED ABSORBABLE REDUCED Glutathione – lots of it to helps scavenge the superoxide free radicals – and Vitamin C and focus on natural antioxidants.

SOD2: Use glutathione.

IL-5: Warn of inflammatory reactions to vaccinations and treat with LDN up to 3mg in AM (start low go slow).

FOXE1: Selenium 200 mcg every other day. Check thyroid annually.

ACE: Check BP and HgbA1C every 6 months. No diabetes allowed.

THANKS FOR LISTENING!

Good luck!

THE END

Dan Purser MD

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