Methylation, Hormones, & Genetics

With

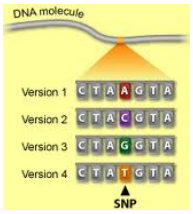
Michalene Casey

Medical Disclaimer: The information in this presentation is not intended to replace a one-on-one relationship with a qualified health care professional and is not intended as medical advice. It is intended as a sharing of knowledge and information from the research and experience of *Michalene Casey*, **MichaleneCasey.com**, and the experts who have contributed. We encourage you to make your own health care decisions based upon your research and in partnership with a qualified health care professional.

The Draw of Genetics

- ✓ I've always been intrigued with the idea of being able to glimpse the blueprint of why I am the way I am
- ✓ Perhaps this is the Soul longing for Reconnection to Self?
  - ➢ *To Thine Own Self Be True*
- ✓ I'd heard about Epigenetics and was further intrigued
- ✓ Then a 23andMe test - $99 for my genetics? You betcha!
- ✓ My personal genome, or a portion, now accessible
- ✓ Took my 23andMe results and dove in head 1st to this rapidly evolving, complex area
- ✓ SO much to learn beyond our Genetic Map being inherited from our parents

SNPs
Single Nucleotide Polymorphisms



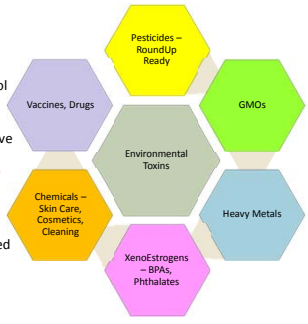
- ✓ 3 billion base pairs of nucleotides
- ✓ **Single base pair** can get added, deleted, or substituted
- ✓ **SNP**s are base pair *variations* (polymorphisms) which occur in 1% >= in the population
- ✓ Most lead to no observable differences
- ✓ Many lead to normal variations
- ✓ Others contribute to **disease or nutrient imbalances**

Importance of
Diet & Nutrigenomics

- ✓ Food is *more than just energy.*
- ✓ We now know that Diet & Lifestyle can have *profound* effects on our health and can even ***be healing.***
- ✓ Experts say 5% of genetic expression is truly tied to our genes. The ***remaining 95% is within your control*** via diet, lifestyle, and environment.
- ✓ **Nutrigenomics** examines how foods and food constituents affect gene expression.
- ✓ The influence of genetic variation on nutrition
- ✓ The correlation between SNPs and a nutrient's absorption, metabolism, elimination or biological effects

Environmental Toxins

Since 1976, when President Ford signed the Toxic Substances Control Act into law, chemical manufacturers have registered for use more than ***80,000 chemicals***. ***More than 15,000 chemicals*** have been manufactured or imported in medium-to-high amounts ***over the past 25 years***.
Ken Cook, Environmental Working Group



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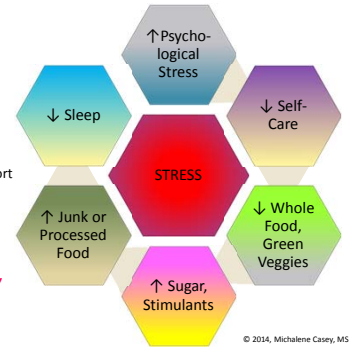
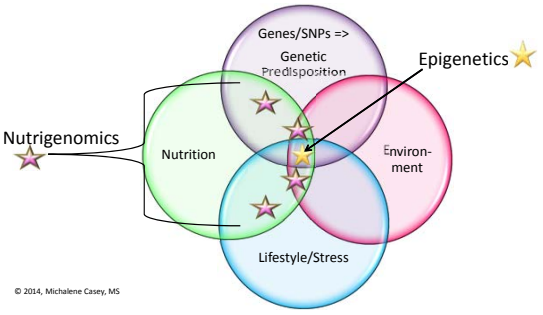
In ***April 2010***, the President's Cancer Panel concluded that "to a disturbing extent, ***babies are being born pre-polluted***." It declared that the number of cancers caused by toxic chemicals is "grossly underestimated" and warned that Americans face "***grievous harm***" from largely ***unregulated chemicals that contaminate air, water and food*** *(President's Cancer Panel 2010).*

Lifestyle Choices & Stress

- ***#1 Issue*** for most Westerners
- Digital Leashes
- Go, go, go!
- Not saying NO!
- Putting others 1st
- Not getting support
- Lack of time in nature
- Lack of time, period!
- Leads to poor choices ***internally and externally***



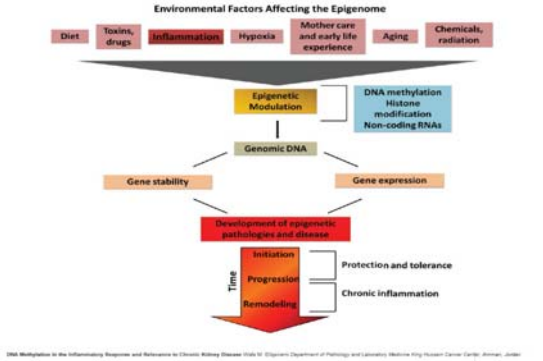
Influences on Genetic Expression



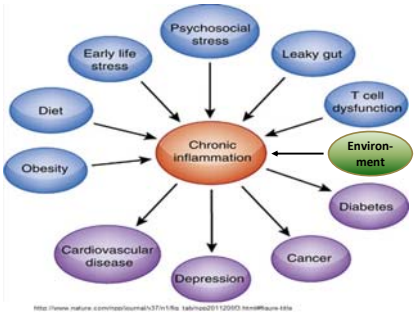
Epigenetics

- ✓ Epigenetics is like a meta-layer over the genes, a conductor of the Genetic Orchestra
- ✓ Epigenetic modifications do not change the sequence of DNA, but *alter the way genes are expressed – silenced or activated*
- ✓ Stem cells get their organ specific functions turned on through Epigenetic processes – *a unique, function specific DNA Library card*
  - ✓ The entire DNA Library is in the cell, but only certain pieces are activated or turned on via Methylation
- ✓ A change in gene expression can result from environmental factors or stressors which go beyond the tipping point – e.g. cancer and tumor suppressor genes

Epigenetic Stress – Environment



Epigenetic Stress – Inflammation



Chronic Inflammation

- ✓ Progressive lack of appropriate nutrients needed for healthy functioning
- ✓ Compensatory processes can no longer keep going – Uncle!
- ✓ Stress altering dynamics between major organs, systems
- ✓ ***Chronic inflammation and oxidative stress*** stop things from working properly
- ✓ We will see it can have a great impact on genes

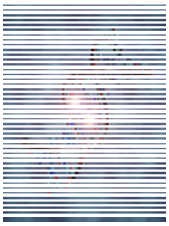
Super Centenarians

- ✓ Studies by Nir Barzilai, MD on *super centenarians* at Albert Einstein Medical College:
  - ✓ "Studies on people over 100 years old showed they were *all* found to harbor most of the *bad* genes we already know about." ***Dr. Jack Kruse***
  - ✓ "**The *bad* genes were *turned off* in these people**. The ultimate arbiter of a long healthy life is the *expression of our genes-whether they are turned on or off*. This is called the ***epigenetic expression of disease***." ***Dr. Jack Kruse***

Methylation

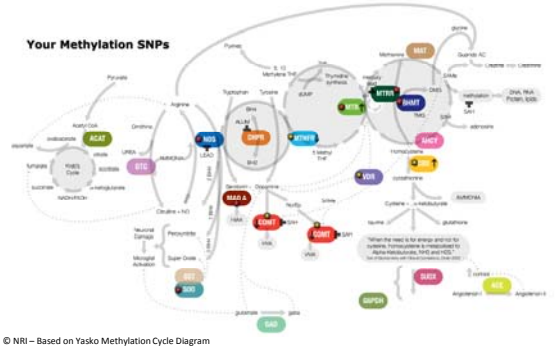
- ✓ **Methylation** is *process* of creating special tags to affect the expression of a gene
- ✓ These tags are called **Methyl groups** – 1 Carbon and 3 Hyrdogens
- ✓ Whether or not a gene is methylated can affect its expression – most often ***silenced***
- ✓ Molecular form (shape) is function-methyl tags change the shape and thus alter expression
- ✓ Methylation is a core Epigenetic process that enables us to be who we are at the most fundamental level – DNA
- ✓ Proper functioning of Methylation facilitates health
- ✓ Poor functioning of Methylation enables illness
- ✓ ***Methylation may very well be one of the most important biological processes in our bodies!***

Usage of the Word Methylation



- ✓ **DNA Methylation** is either the maintenance or change to DNA by adding or removing Methyl groups – usually *silencing* gene expression
- ✓ Sometimes people call the **SAMe/Methionine Cycle** the **Methylation Cycle** because it can affect DNA Methylation and is the major generator of Methyl groups
- ✓ The **Methylation Cycle, Process, Pathways** also refers to a group of processes involved in the Methylation Dance

All About Methylation



© NRI – Based on Yasko Methylation Cycle Diagram

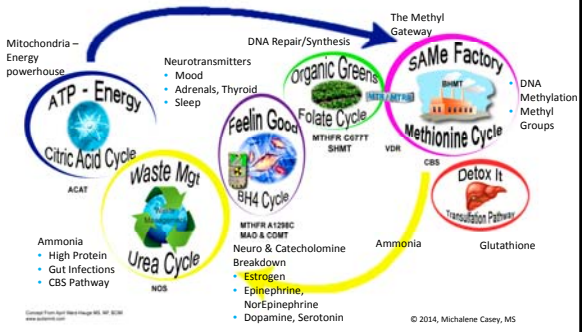
Methylation Functions

- ✓ Turn on and off genes (gene regulation)
- ✓ Process chemicals, endogenous and xenobiotic compounds (biotransformation)
- ✓ Build neurotransmitters (norepinephrine → epinephrine, serotonin → melatonin)
- ✓ Metabolize neurotransmitters (dopamine, epinephrine)
- ✓ Process hormones (estrogen)
- ✓ Build immune cells (T cells, NK cells)
- ✓ DNA and Histone Synthesis (Thymine aka 5-methyluracil)
- ✓ Produce energy (CoQ10, carnitine, creatine, ATP)
- ✓ Produce protective coating on nerves (myelination)
- ✓ Build and maintain cell membranes (phosphatidylcholine)

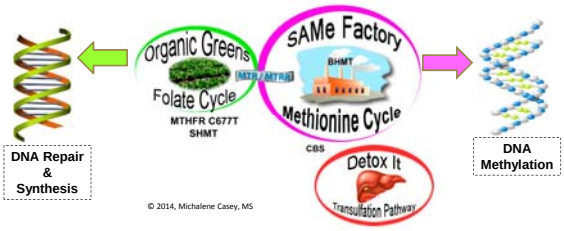
Disrupting Methylation

- ✓ Lack of cofactors/substrate driving methylation forward (zinc, B2 (Riboflavin), magnesium, cysteine, B6 (P5P), methylcobalamin)
- ✓ Medications (antacids, methotrexate, metformin, nitrous oxide)
- ✓ Specific nutrients depleting methyl groups (high dose Niacin)
- ✓ Environmental toxicity, heavy metals, chemicals (acetylaldehyde, arsenic, mercury, high copper)
- ✓ Excessive substrate (feedback inhibition – eg. DMG, SAMe, Methylfolate)
- ✓ Genetic mutations/polymorphisms (MTHFR)
- ✓ Mental state (stress, anxiety, lack of sleep, attitude)

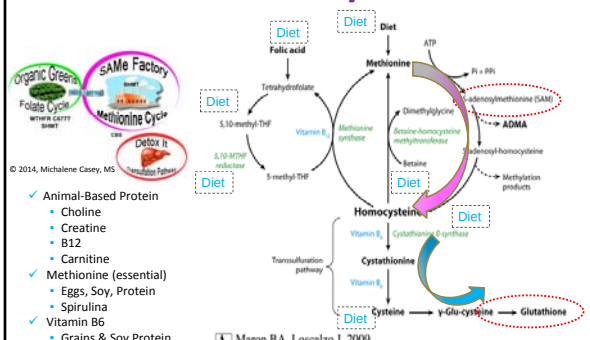
Methylation Players



Methylation & DNA



Diet & Methylation



- ✓ Animal-Based Protein
  - Choline
  - Creatine
  - B12
  - Carnitine
- ✓ Methionine (essential)
  - Eggs, Soy, Protein
  - Spirulina
- ✓ Vitamin B6
  - Grains & Soy Protein
  - Nuts and Seeds

Methylation & Gene Expression

- ✓ SAMe is a key product of the Methionine Cycle and has *over 400 known* methylation reactions
- ✓ 1 key function is the regulation of DNA

The Folate Cycle

Functions:

- Synthesis of nucleic acids (for DNA production/repair and tRNA)
- Drive the Methionine Cycle (SAMe production, DNA Methylation)
- Inter-conversion of amino acids (for neurotransmitter production and detoxification)
- Formation and maturation of RBC, WBC and platelet production

Some MTHFR Problems

- ✓ Excess ***Folic Acid*** may lead to problems such as cancer
- ✓ Increased Homocysteine (HCY) levels
- ✓ Increased risk of cardiovascular disease or thrombosis
- ✓ Insufficient substrate for DNA Repair, Synthesis, or Methylation
- ✓ Increased risk of pregnancy miscarriage
- ✓ Potential Methotrexate intolerance (used in treating RA & cancer) and may require dosage adjustments
- ✓ Neurotransmitter problems
- ✓ ***Folic Acid*** blocks Methylfolate at Blood Brain Barrier
- ✓ Dairy can block folate receptors, especially in Brain (**FOLR1, FOLR2, FOLR3**)

Who is Impacted?

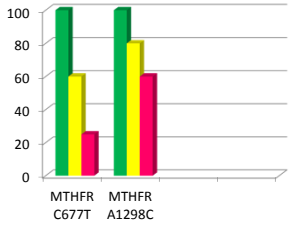
Approximately 45% of the population has 1 copy of the MTHFR C677T.

Approximately 90% of those with chronic disease have 1 copy of the MTHFR C677T.

Dr. Ben Lynch recommends that ***everyone be tested.***

Impact of MTHFR Variants

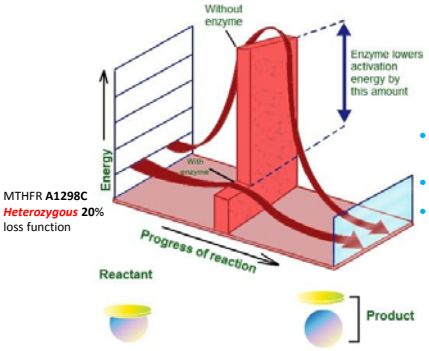
MTHFR SNPs result in ***downregulation-loss of function***



- **MTHFR C677T** *Heterozygous* = approximately **60%** of normal activity
- **MTHFR C677T** *Homozygous* = approximately **25%** of normal activity
- **MTHFR A1298C** *Heterozygous* = approximately **80%** of normal activity
- **MTHFR A1298C** *Homozygous* = approximately **60%** of normal activity
- **MTHFR C677T & A1298C** *Compound Heterozygous* = approximately **60%** of normal activity

Source: http://jmg.highwire.org/content/41/6/454.full.pdf and van der Put, N.M.J. et al., A Second Common Mutation in the Methylenetetrahydrofolate Reductase Gene: An Additional Risk Factor for Neural-Tube Defects, Am. J. Hum. Genet. 1998; 62:1044-1051

Impact of MTHFR Mutations



MTHFR **C677T** ***Homozygous*** **75%** loss function

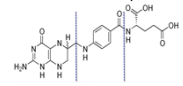
MTHFR **A1298C** ***Heterozygous*** **20%** loss function

- Heterozygous or Homozygous?
- Climb the wall
- Just a small hop

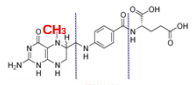
Does Folic Acid = Folate?

- ✓ ***Folic acid does NOT equal Folate***.
- ✓ Folic Acid is only ONE type of Folate.
- ✓ Folic acid is not found in nature, it's synthetic.
- ✓ Folic acid must undergo various transformations prior to utilization.

FOLIC ACID →



METHYLFOLATE →



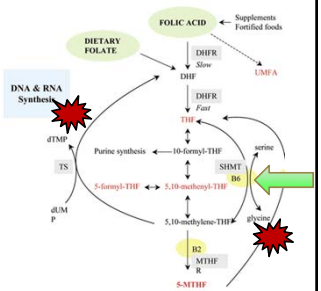
- ✓ **Different types**
  - ✓ Folic acid
  - ✓ Folinic acid (5-FormylTHF)- product of SHMT enzyme within Folate Cycle
  - ✓ Methylfolate (5-MTHF)

The Challenge of Converting Folic Acid or Folate to MTHF

Requires:
- Uncooked Leafy Greens
- Functioning Enzymes
- Available Receptors
- Transport

Vitamins, Minerals and pH:
- B2
- B6
- B12
- Acidic environment (for absorption) – ***Good and sufficient stomach acid***

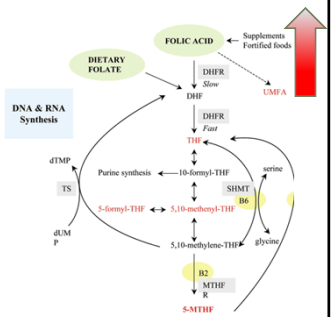
Healthy Gut - absorption
- **SHMT** SNP associated with ***Leaky Gut***
- Impacts DNA Repair/Synthesis
- Impacts Glycine levels => ***Glutathione*** - the body's key anti-oxidant



Source: Herb, Nutrient and Drug Interactions by Stargrove et al

UnMetabolized Folic Acid - UMFA

- ✓ Enzymes reach saturation point – **UMFA** results
- ✓ High UMFA levels have been associated with ***cancer progression***
- ✓ Increased levels may decrease NK cell activity (***risk for cancer***). ***PMID: 16365081***
- ✓ Studies show that Folic Acid is *less effective* than Methylfolate (L-5-MTHF), in reducing HCY
- ✓ ***Take ALL Folic Acid out of your diet***: fortified foods and supplements (including B12 patch)
- ✓ Many combo B12 products contain Folic Acid
- ✓ Methylfolate does NOT increase UMFA levels



http://www.aacc.org/publications/cln/2011/january/Pages/FolateMetabolismFigure.aspx and Herb, Nutrient and Drug Interactions

Food Sources of Folate

EXCELLENT SOURCES

Food	Serving Size	Cals	Amount (mcg)	DV (%)	Nutrient Density	World's Healthiest Foods Rating
Lentils	1 cup cooked	229.7	358.38	89.59	7.0	excellent
Spinach	1 cup cooked	41.4	262.80	65.70	28.6	excellent
Collard Greens	1 cup cooked	49.4	176.70	44.17	16.1	excellent
Turnip Greens	1 cup cooked	28.8	169.92	42.48	26.5	excellent
Beets	1 cup raw	58.5	148.24	37.06	11.4	excellent
Romaine Lettuce	2 cups	16.0	127.84	31.96	36.0	excellent
Mustard Greens	1 cup cooked	21.0	102.20	25.55	21.9	excellent
Asparagus	1 cup raw	26.8	69.68	17.42	11.7	excellent
Cauliflower	1 cup raw	26.8	60.99	15.25	10.3	excellent
Broccoli	1 cup raw	30.9	57.33	14.33	8.3	excellent

Source: www.whfoods.com

Supplemental Forms of Folate

✓ **Quality forms of Methylfolate**
- ✓ L-5-MTHF (L is important to avoid racemic R forms)
- ✓ Quatrefolic (glucosamine form)
- ✓ Metafolin (calcium form)
- ✓ L-Methylfolate
- ✓ (6S)-5-Methylfolate

✓ **Important Methylfolate Issues**
- ✓ Maximum of 1,000 mcg of L-Methylfolate used alone
- ✓ Maximum of 800 mcg of L-Methylfolate usage in a formula
- ✓ ***If no 'L' or (6S) or Quatrefolic or Metafolin is used on the label, avoid it!***

Source: http://mthfr.net/l-methylfolate-methylfolate-5-mthf/2012/04/05/

MTHFR & Neurotransmitters

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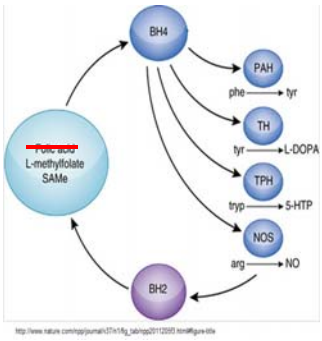
- ✓ L-Methylfolate and SAMe provide the substrate for **BH4** to Build neurotransmitters
- ✓ Key amino acids and cofactors are needed as well
- ✓ *BH4 Cycle* one of primary functions is to build neurotransmitters
- ✓ Removal of ammonia is a priority and when levels are high less **BH4** is available for neurotransmitters
- ✓ Imbalances amongst excitatory and calming neurotransmitters may result as well as mood disorders

BH4 Cycle & Neurotransmitters

Deficiencies and Conditions
- **Depression** => *Serotonin*
- **Insomnia** => *Melatonin*
- **Anxiety** => *Dopamine*
- **Erectile Dysfunction** => *Nitric Oxide*
- **Thrombosis** => *Nitric Oxide*
- **Thyroid Disorders** => *Tyrosine*
- **Adrenal issues** => *Tyrosine*

Many Studies

Must have sufficient amino acids and cofactors to produce neurotransmitters
- *Dopamine* (Ascorbic Acid) => Norepinephrine
- *5-HTP* (P5P) => Serotonin

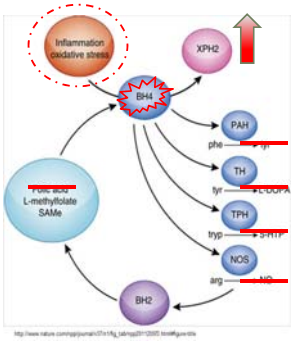


BH4 Cycle Problems

Big problem
- **Inflammation and oxidative stress** – must address this!
- Supplementation with amino acids may help bypass BH4 deficiency
- 5-HTP, Tyrosine, Melatonin
- Heavy Metals – Aluminum blocks **BH4**
- Bacterial infections retain Aluminum

Ammonia processing takes priority
- Excess protein from diet
- Bacterial infection in gut
- **CBS** (Transsulfuration Pathway) upregulation may produce ammonia

↑ NO Can potentially be a problem, inhibiting *The Methyl Gateway*



The Methyl Gateway – MTR/MTRR

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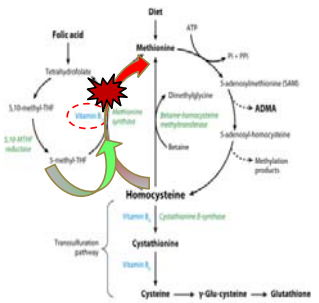
DNA Repair & Synthesis

DNA Methylation

A KEY gateway enzyme combo
- **MTR** and **MTRR** work together to recycle Homocysteine (HCY) back into Methionine in order to produce SAMe: the ***Major*** Methyl Donor
- Utilizes Methylfolate and B12
- **MTR** (with zinc) transfers the Methyl group from Methyl B12 to HCY to become Methionine
- **MTRR** (with B2/FAD - Flavin Adenine Dinucleotide) remethylates cobalamin with Methylfolate, and Folate goes back into Folate Cycle
- Several factors can block this enzyme activity, including SNPs for **MTR/MTRR**

Methyl Trapping

Methyl trapping occurs when
- Insufficient B12 to recycle HCY to Methionine
- Methylfolate gets *trapped*
- Requires combination of L-5-MTHF and appropriate cobalamin (B12)
- Sublingual forms suggested for those with digestive disorders or issues with Intrinsic Factor (B12)



Maron BA, Loscalzo J. 2009. Annu. Rev. Med. 60:39-54

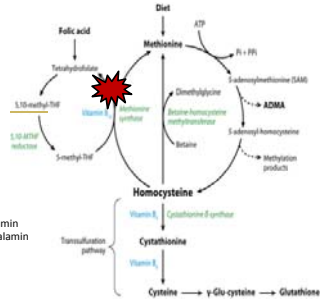
MTR/MTRR Inhibition

MTR/MTRR Inhibition by:
Acetylaldehyde **(CYP2E1)**
- Metabolite of ethanol metabolism
- Released from Candida → **Leaky Gut**
- Also from Alcohol
- Nutrient deficiencies Zn, B2, B12, B9

Solution:
- Limit alcohol / sugar ingestion
- Treat candida overgrowth, Leaky Gut
- Support detox symptoms

MTR/MTRR Inhibition by:
- Oxidative Stress → **Inflammation** → ↑Cortisol
- Heavy Metals – Mercury, Lead, Aluminum
- ↑ NO preventing regeneration of Methylcobalamin
- Nitrous oxide produces oxidation, depletes cobalamin

Solution:
- ↓ Oxidative stress
- ↓ NO levels – Hydroxylcobalamin, Niacin
- Avoid use of Nitrous Oxide
- Support Methylation and chelation



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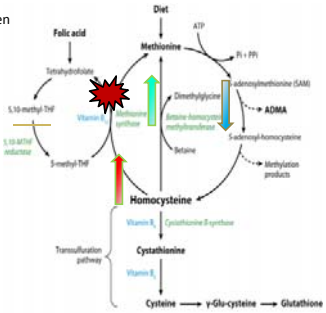
http://mthfr.net/methylation-inhibited-by-candidas-toxin/2012/09/09/

BHMT – The Shortcut

- The **BHMT** Shortcut compensates when **MTR/MTRR** is inhibited
- **MTR/MTRR** affects most cells
- **BHMT** upregulates (**liver/kidney**)
- 'Burn' through Betaine and Choline, especially under ***stress***
- Homocysteine may ↑

Over time:
- SAM production ↓
- ↑ HCY
- Methyltransferases slow:
  - ↓ Creatine
  - ↓ Phosphatidylcholine
  - ↓ Glycine
  - ↓ Sarcosine
  - ↓ Carnitine
  - ↓ CoQ10
- ↑Cell Membrane Damage
- ROS Levels ↑



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Homocysteine Routes

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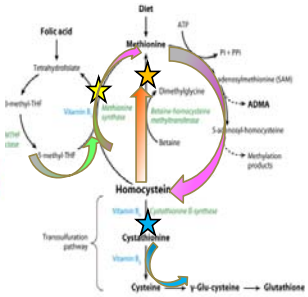
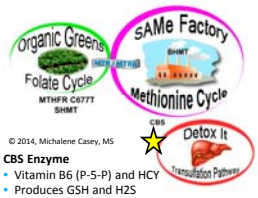


Three Possible Routes:
- **MTR/MTRR** - *The Long Way*
  - ✓ (B12 and MTHF)
- **BHMT** – *The Shortcut*
  - ✓ (TMG and Zn)
- **CBS** – *The Elimination Route*
  - ✓ (B6)

Maron BA, Loscalzo J. 2009. Annu. Rev. Med. 60:39-54

CBS Enzyme & Transsulfuration



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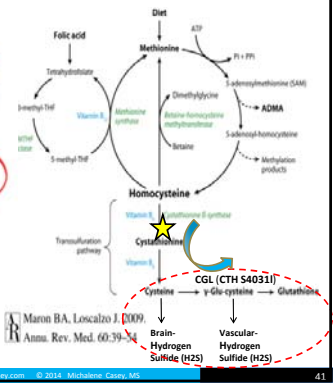
CBS Enzyme
- Vitamin B6 (P-5-P) and HCY
- Produces GSH and H2S

Slowed by:
- ↓ P-5-P and ↓ HCY
- ↓ Oxidative Stress
- ↑ GSH (reduced)
- ↑ NO

Upregulated by:
- P-5-P
- ↑ Oxidative Stress
- ↓ GSH (reduced)

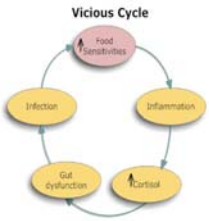


Maron BA, Loscalzo J. 2009. Annu. Rev. Med. 60:39-54

The Gut & The Environment

- ✓ The gut is the 1st barrier to many things entering from the environment
- ✓ The junctions between the villi and the brush border of the gut lining are designed to only let appropriate things through, like a "Police Line", and immune surveillance is high
- ✓ Optimal Vitamin D levels are linked to tighter junctions
- ✓ Vitamin D plays a huge role in immune surveillance of our GI tracts, activating T regulator cells
- ✓ Food allergens, additives, pesticides, drugs, alcohol, heavy metals can lead to ***Dsybiosis***
- ✓ Bacterial and fungal overgrowth, parasites, infections can lead to ***Leaky Gut***, made worse by antibiotics, anti-inflammatory drugs, alcohol

The Gut, Inflammation, Cortisol



- ✓ Dysbiosis → ↓Thyroid conversion in the gut (~20%)
- ✓ ↑Cortisol → ↑Insulin → ↑IL-6
- ✓ Beta-glucuronidase unconjugates Estrogens into metabolites to be recirculated → ↑Estrogen
- ✓ ↑Estrogen and ↑Cortisol → ↑Demand on COMT for breakdown
- ✓ ↓Magnesium, zinc → ↓COMT
- ✓ Magnesium, zinc and CoQ10 all major cofactors in the stress response and used up quickly by Leaky gut → Many are already deficient → ↑ Adrenal stress

Gluten & Dairy Sensitivity

"Although wheat is not technically genetically modified, **gluten has been dramatically deaminated and hybridized** over time which ***creates inflammation in everyone***, not just Celiacs. So we now have a new wheat which can trigger immune reactions, especially in your nervous system." ***Suzy Cohen***

"A new study shows a **significant portion** of the US population not only reacts to gluten and dairy but also that this reaction causes the immune system to destroy brain and nervous tissue in a scenario called ***neurological autoimmunity*** (as evidenced by positive tissue antibodies)." ***Dr. Datis Kharrazian***

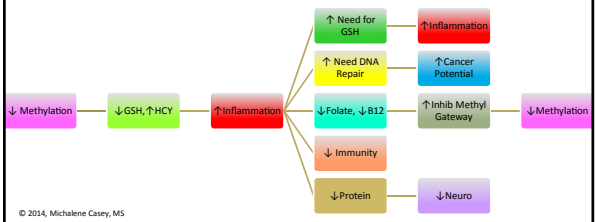
- One of the first studies to show a connection between gluten and neurological autoimmunity in a random population of ***healthy*** subjects.
  - 400 people – ***no known pathologies***
  - ***Significant correlation*** between gluten and neurological autoimmunity
  - Majority of neurological reactions due to **molecular mimicry**
- Evaluated the **entire wheat protein** for immune reactivity, not just the alpha gliadin portion
- Neurological autoimmunity can cause a diverse array of symptoms and disorders, which can be as ***mild as brain fog*** or as debilitating as multiple sclerosis or Parkinson's disease.

***Source*: The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities, Nutrients, 2014, Vojdani, A., Kharrazian, D.** http://www.mdpi.com/2072-6643/6/1/15

Autoimmunity

- ✓ Gluten and Cross-Reactive Foods are a significant contributor to Leaky Gut
- ✓ Immune complexes are formed as a result of the leakage
- ✓ Antibodies are generated in response to the food antigens
- ✓ Molecular Mimicry → Autoimmunity
- ✓ Early research in Ovarian Cancer shows high association with Gluten Intolerance and Autoimmunity ***Dr. Jeanne Drisko***
- ✓ Brain, Ovarian, and Lung Cancers have been associated with Gluten Intolerance, not simply Celiac Disease
  - ✓ Grade/Severity of malignancy in Glioblastoma associated with the degree of Gluten Intolerance
- ✓ 90% of hypothyroidism cases in the United States are caused by Hashimoto's disease, an autoimmune disease.
  - ✓ "These patients universally have defective Vitamin D Receptors (VDR) receptors." ***Dr. Jack Kruse***
- ✓ "Studies have shown that a significant number of patients with autoimmune diseases have several VDR SNPs." ***Dr. Jack Kruse***

Methylation & Leaky Gut - 1



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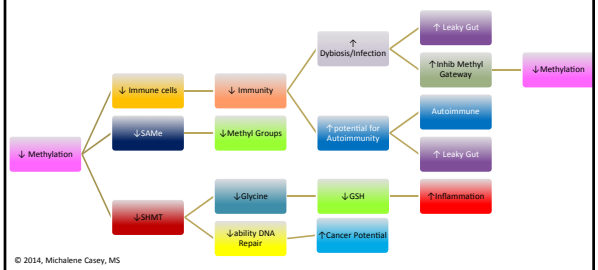
Methylation & Leaky Gut - 2



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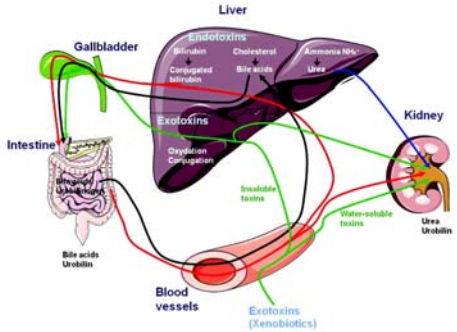
Liver – Detox Gateway

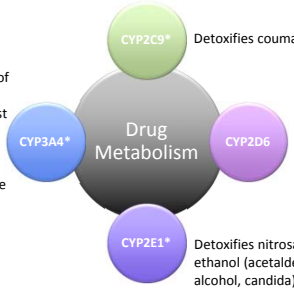


CYP450 Enzyme Down Regulation & Gut Disruption

- ✓ Glyphosate residue in sugar, corn, soy and wheat; major components of the Western Diet.
- ✓ "We have found ***clear evidence*** that glyphosate ***disrupts gut bacteria and suppresses the CYP enzyme class***."
- ✓ "Glyphosate's demonstrated toxicity to *Enterococcus spp*. leads to an ***imbalance in the gut favoring overgrowth of the toxic Clostridium species***.!!"

Source: "Glyphosate's Suppression of Cytochrome P450 Enzymes and Amino Acid Biosynthesis by the Gut Microbiome: Pathways to Modern Diseases", Entropy, April 2013, www.mdpi.com/journal/entropy

Drug Metabolism – CYP 450 SNPs



Detoxifies coumadin

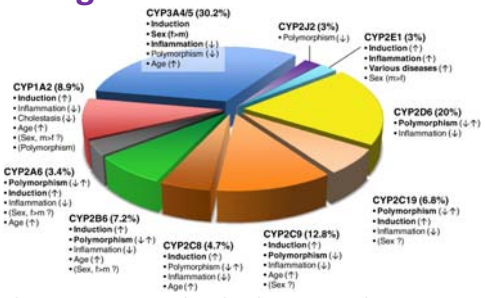
Detoxifies over 50% of all prescription medications and most steroid hormones (cortisol, estrogen, testosterone, etc.) and organophosphate insecticides (e.g. parathion)

Detoxifies ~20% of all prescription drugs including tricyclics, MAOIs, SSRIs, opiates, anti-arrhythmics, beta-blockers, Cimetidine, etc.

Detoxifies nitrosamines and ethanol (acetaldehyde - alcohol, candida)

See SNPedia.com for Drug list for CYP450 SNPs, also www.GeneMedRx.com

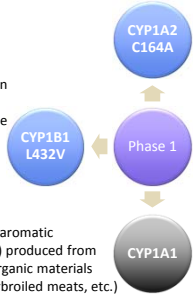
Drug Metabolism – CYP 450



Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability. A total of 248 drug metabolism pathways with known CYP involvement (chemicals and endogenous substrates excluded) were analyzed. Each metabolic pathway was only counted once for the major contributing CYP isoform. Important variability factors are indicated by bold type with possible directions of influence indicated (↑, increased activity; ↓, decreased activity; ↑↓, increased and decreased activity). Factors of controversial significance are shown in parentheses.

***Source**: Zanger, U., Schwab, M., "Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation", Pharmacology & Therapeutics, 2013*

Hormone Metabolism CYP 450 SNPs



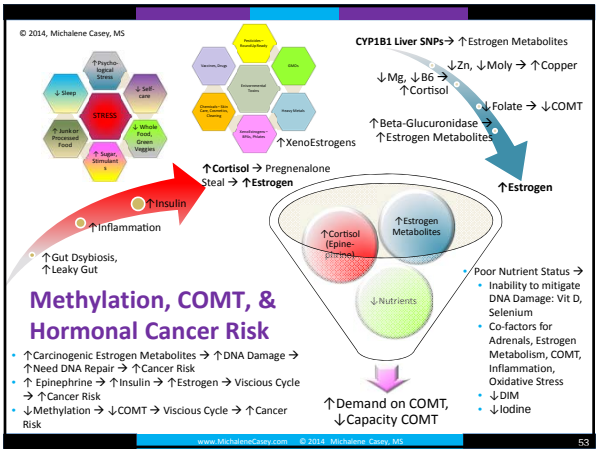
Caffeine and Estrogen metabolism, breast, ovarian, and prostate cancers

Caffeine and Estrogen metabolism, breast, ovarian , and prostate cancers*

Caffeine and Estrogen metabolism, breast, ovarian, and prostate cancers*

Detoxifies polycyclic aromatic hydrocarbons (PAHS) produced from the combustion of organic materials (exhaust fumes, charbroiled meats, etc.)

*Upregulator - involved in the 4-hydroxylation of estrogen. ***See connection to COMT for additional processing of hormone metabolites!***



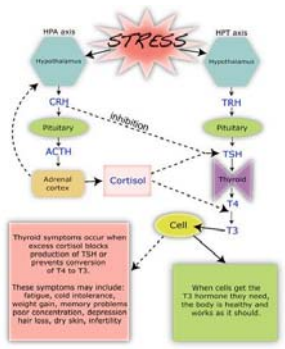
Methylation, COMT, & Hormonal Cancer Risk

- ↑Carcinogenic Estrogen Metabolites → ↑DNA Damage → ↑Need DNA Repair → ↑Cancer Risk
- ↑ Epinephrine → ↑Insulin → ↑Estrogen → Viscious Cycle → ↑Cancer Risk
- ↓Methylation → ↓COMT → Viscious Cycle → ↑Cancer Risk

Thyroid & MTHFR

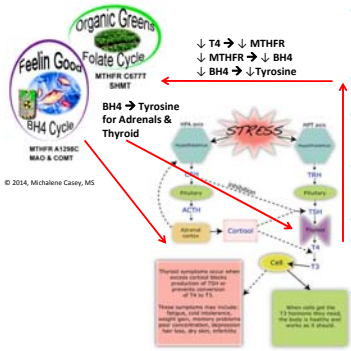
- ✓ Adequate dietary intake of iodine or supplemental sources of iodine are needed to generate T4.
- ✓ B2 is needed to convert iodine and tyrosine to thyroid hormone (T4).
- ✓ Other nutrients such as selenium, iron, zinc, B12, magnesium, D3 are needed for a healthy thyroid.
- ✓ Gluten intolerance may contribute to Thyroid Peroxidase (TPO) anti-bodies in Hashimoto's (**CTL4**).
- ✓ Vitamin A deficiency (**BCMO1**) and ↑HCY (which can result from **MTHFR**) can contribute to Thyroid receptor resistance.
- ✓ All of these factors can contribute to Hypothyroid conditions.

Adrenals & Thyroid



- ✓ Blood sugar imbalances can negatively impact both Thyroid status and Adrenal health.
- ✓ Excess cortisol damages thyroid receptors and causes thyroid resistance.
- ✓ Excess cortisol decreases T4 to T3 conversion.
- ✓ Excess cortisol increases blood sugar and insulin, which decreases thyroid function.

Thyroid/Adrenals, MTHFR, BH4



- ✓ Thyroid hormone (thyroxine) regulates the enzymatic conversion of Riboflavin (B2) to its active coenzyme forms, such as **FAD** (Flavin Adenine Dinucleotide).
- ✓ **FAD** helps stabilize mutant forms of **MTHFR C677T**.
- ✓ If you are Hypothyroid, you may have lower levels of thyroxine in your system.
- ✓ Inadequate Thyroxine levels or B2 deficiency can result in ↓**FAD** levels → ↓ **MTHFR**.
- ✓ ↓ **MTHFR** → ↓ **BH4** → ↓Tyrosine
- ✓ ↓Tyrosine → ↓Functioning of Thyroid & Adrenals as both depend on Tyrosine.
- ✓ You need to balance **MTHFR** (methylation), **BH4** (Neurotransmitters), adrenals and all thyroid hormones.

Take Aways - Diet & Lifestyle

- ✓ Diet and Lifestyle have a ***significant*** impact on your health and well being. **Start with the Basics.**
- ✓ Healing the gut and any infections is key.
- ✓ Get rid of gluten, cross-reactive foods, and allergens.
- ✓ Regardless of your diet orientation, eat plenty of organic veggies, especially greens and foods rich in natural Folate.
- ✓ ***Reduce Inflammation and oxidative stress***. This is an underlying cause in virtually every health problem and greatly affects the proper functioning of your genes, with or without SNPs!
- ✓ Balance your blood sugar.
- ✓ ***Reduce stress and*** find ways to improve how you react to it.
- ✓ Get plenty of sleep.
- ✓ ***Consistency*** over time will support or impede your healing.

Take Aways – The Big Picture

- ✓ The ***symptoms*** of a Health Challenge need to be ***addressed***, as well as ***Resolving the Root Cause*** (i.e. Anti-inflammatories AND removing the root cause of inflammation).
- ✓ **All of the genetic and epigenetic interactions are more complicated than they appear.** This is leading edge stuff and evolving quickly, so learning and understanding will increase over time.
- ✓ **Caution:** There is a natural tendency for ***Empowered Health Go-Getters*** to just Dive In! Proceed slowly and incrementally. Educate yourself, listen to your body, and consider getting help from someone familiar with this area.
- ✓ Working with Methylation is ***very Individualized***. One protocol does **NOT** fit all.
- ✓ It **IS** possible to work around some of these genetic variations and heal. It takes time and patience.
- ✓ The ultimate arbiter of a long healthy life is the *expression of our genes-whether they are turned on or off*. This is called the ***epigenetic expression of disease***." ***Dr. Jack Kruse***
- ✓ You have a tremendous power to Heal, to transform YOUR Epigenetics. Your genes are NOT your Destiny! Daily habits add up. Choose wisely.

Thank You!