Methylation Diet

Masters Series Webinar

With Guest Speakers
Kara Fitzgerald & Romilly Hodges

BioIndividual Nutrition Institute

Julie Matthews, Certified Nutrition Consultant

Julie Matthews is not a physician. She does not diagnose or treat disease. This information and her statements are not intended to replace a one-on-one relationship with a qualified health-care professional, and is not intended to provide medical advice. For medical advice, always seek a physician. This information is intended for educational purposes only, and is solely as a sharing of knowledge and information based upon the experience and research of Julie Matthews/Nourishing Hope.

About Julie Matthews

Julie Matthews is a Certified Nutrition Consultant and global thought leader in the field of bioindividual nutrition and specialized diets for complex chronic conditions. She has a special focus in autism, ADHD and related disorders and has authored the award-winning book, *Nourishing Hope for Autism*. **BioIndividual Nutrition FOUNDATIONS** Training and the **Nourishing Hope for KIDS** Training are written and created by Julie Matthews based on her 14 years of nutrition research and practice.

Julie has educated physicians and professionals at trainings for ARI/DAN!, IMMH, MAPS, and the MINDD Forum in Australia. There is great need for a body of professionals with advanced understanding and capability for nourishing hope in each person, which is why she has launched this comprehensive training for clinicians.

NourishingHope
Nutrition for Autism, ADHD, and Healthy Children

Julie's courses and writings are backed by an evidence-based approach. She is the Co-Founder and Director of Clinical Research for the BioIndividual Nutrition Institute, and Founder of Nourishing Hope. She is a writer, speaker, and clinician with a nutrition practice in San Francisco, CA.

Making Diet and Nutrition Recommendations

Clinical Application

Underlying Factors in Autism That Apply to Many Disorders

Underlying Factors

- Inflammation
- Mitochondrial dysfunction
- Poor detoxification
- Poor methylation
- Poor sulfation
- Poor digestion
- Microbiome imbalance

Disorders

- Autism and ADHD
- Asthma
- Anxiety
- Alzheimer's
- Autoimmune disorders
- Digestive disorders
- Parkinson's
- Multiple sclerosis

BioIndividuality

Need to Consider:

- Gene expression
- Biochemical imbalances
- Nutrient deficiencies
- Health conditions
- Environmental stressors
- Microbiome

No "one-size-fits-all" Diet

- Diet that helps one person, doesn't help another
- Diet that helps one, can even be harmful for another
- One diet does not always meet all needs
- Diets may need to be customized and have certain foods/principles removed (or added)
- Multiple diets may need to be combined into one

Goal: BioIndividual Nutrition®

A food and nutrition strategy
(special diets and supplementation)
based on the **individual needs**
of each person

Food is Medicine

but there is **NO** "one-size-fits-all" Diet

Individuals have **SPECIFIC DIETARY NEEDS**,
based on their **Unique Biochemistry, Health History, and Genetics**

Customizing Diet and Nutrition is Essential

Goal: BioIndividual Nutrition Plan

- Determine a diet direction
  - What foods to avoid and which to include
  - What diets to combine
  - Rules to break or add
- Proper supplementation
  - Based on individual need

BioIndividual Nutrition Institute

BioIndividual Nutrition Training

- Led by Julie Matthews
- Two courses
  - Foundational
    - 12 Modules
    - 28 hours of recorded sessions
    - Handouts and research references
  - Additional Training/Certification in Autism, ADHD, and Kids' Nutrition
    - 7 Modules and 16 hours
- Website Directory
- Clinical Charts and Tools
  - Food/Symptom Charts
  - Client 1-page diet handouts
  - Client questionnaires

BioIndividual Nutrition® Institute

Empowering Health Practitioners with the Science
& Clinical Application of Personalized Diet and Nutrition

http://BioIndividualNutrition.com

Contact us with questions:
Info@BioIndividualNutrition.com
415-235-2960

The Methylation Diet and Lifestyle

Supporting Healthy Methylation and Gene Expression

Kara Fitzgerald ND and Romilly Hodges MS CNS

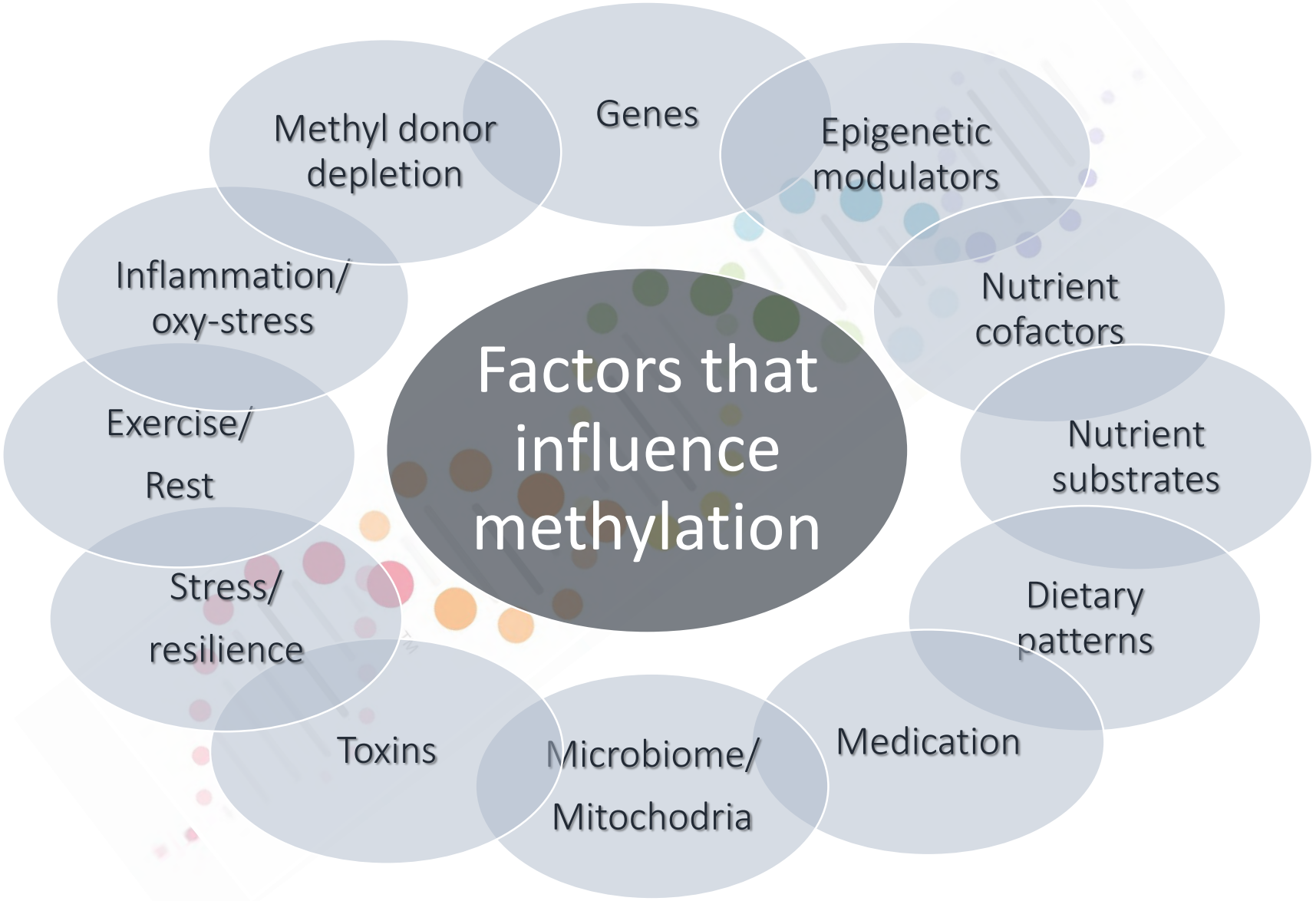
08/16/16

We will cover some of the fundamental principles of the Methylation Diet and Lifestyle in this webinar, but for full information, please see the eBook at www.drkarafitzgerald.com/practitioners/eBook.
Use the following code for a 10% discount: BNI10

The best way to stay up-to-date with our latest methylation content is through our **monthly newsletters.** Go to www.drkarafitzgerald.com to get on the newsletter list.

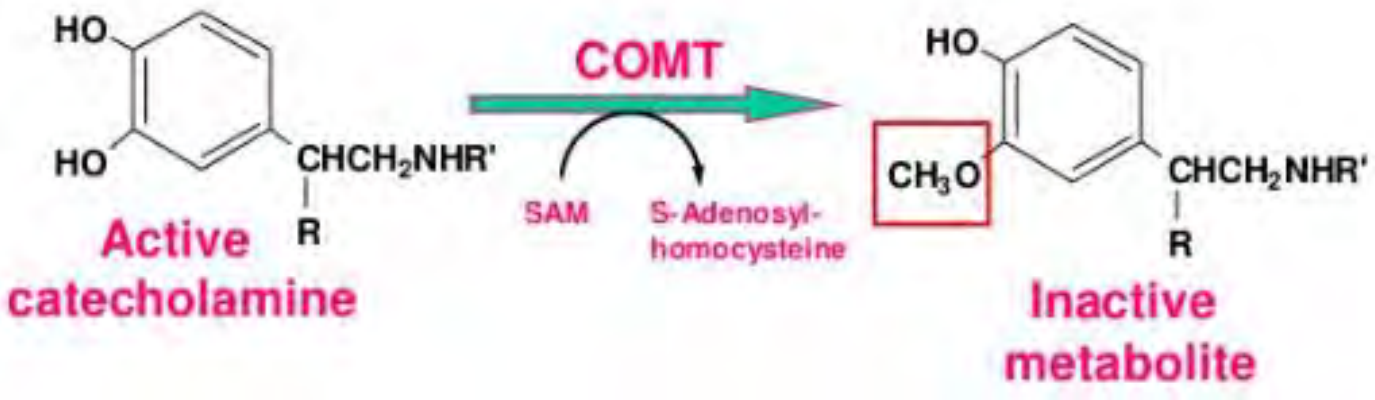
What You Will Learn

- The History behind the methylation diet & lifestyle program
- Leaps and limitations in current research
- Our clinic's approach to supporting homeodynamic methylation balance considers
  - Dietary patterns
  - Inflammation/oxidative stress
  - Gut microbiome
  - Mitochondrial fitness
  - Environmental toxins & detoxification
  - Methyl donor drain
  - Stress management & resilience
  - Sleep
  - Physical exercise


Factors that influence methylation
Genes
Methyl donor depletion
Epigenetic modulators
Inflammation/ oxy-stress
Nutrient cofactors
Exercise/ Rest
Nutrient substrates
Stress/ resilience
Dietary patterns
Toxins
Microbiome/ Mitochodria
Medication

Methylation Activity in the Body

- “One-carbon metabolism” = transfer or formation of methyl (CH3) groups
- E.g. MTHFR, COMT, DNMT
- Often uses SAMe as methyl donor

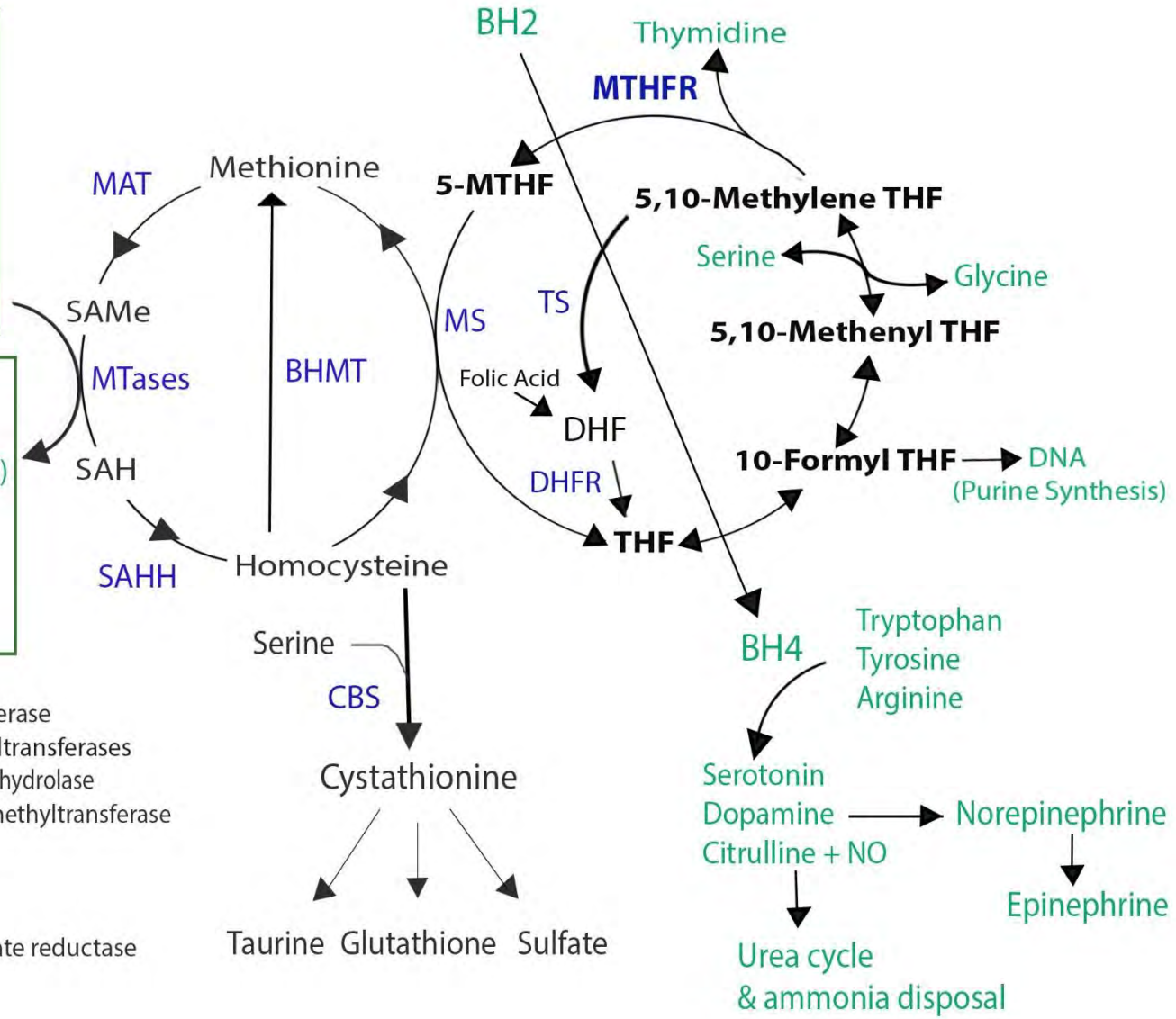


What Do We Use Methylation For?

- **Cell division (DNA, RNA synthesis)**
- **Epigenetic regulation of gene expression**
- Early CNS development (neural tube defects)
- Immune cell differentiation
- Neurotransmitter biosynthesis and metabolism (dopamine, norepinephrine, epinephrine, acetylcholine)
- Histamine clearance
- Detoxification and hormone biotransformation
- Cellular energy metabolism
- Phospholipid synthesis
- Myelination of peripheral nerves

DNA
RNA
Norepinephrine
Dopamine
Estrogen
Histamine
Arginine
Phosphatidylethanolamine

Methylated Metabolites
include but not limted to:
5-methylcytosine (DNA/RNA)
Epinephrine
Creatine
Phosphatidyl choline
and degredation products



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
DHF - Dihydrofolate
THF - Tetrahydrofolate
BH2 - Dihydropterin
BH4 - Tetrahydrobiopterin

Genetic Methylation

- Highly regulated- some epigenetic marks very stable
- **Methylation at CpG sites by DNMT enzymes (associated with gene repression)**
- Histone methylation (can induce or inhibit expression)
- RNA methylation
- Mitochondrial DNA methylation (miDNMT)
- Demethylation (active and passive)

http://www.sigmaaldrich.com/technical-documents/articles/biofiles/introduction-to-dna-methylation.html

DNA Methylation and Fetal Programming

- Metastable epialleles
  - Significant inter-individual differences
  - Passed down to offspring during critical periods of fetal development
  - Preserved across multiple generations
  - Highly sensitive to environmental influences

Waterland et al., *Genesis*, vol. 44, no. 9, pp. 401–6, Sep. 2006.

Barres et al., *Am. J. Clin. Nutr.*, vol. 93, no. 4, p. 897S–900, Apr. 2011.

Dolinoy et al., *Pediatr. Res.*, vol. 61, no. 5 Pt 2, p. 30R–37R, 2007.

DNA Methylation at Other Life Stages

Outside fetal programming windows, DNA methylation is required to preserve epigenetic imprints during cell division

Human Studies

- 6-100 μmol/L homocysteine significantly, inversely correlated with DNA hypomethylation in humans[1]
- Induced folate deficiency worsened hyperhomocysteinemia[1]
- Folate treatment (15mg/d 5-mTHF x 8 weeks) decreased plasma homocysteine and increased DNA methylation[1]

[1]Ingrosso et al. *Lancet*, vol. 361, no. 9370, pp.1693-1699

The Clinical Problem - Methylation Deficits

Associated conditions:

ADD/ADHD, addiction, allergies, Alzheimer's Disease, anxiety, asthma, atherosclerosis, autism spectrum disorder, behavioral changes, bipolar disorder, cancers, chemical sensitivity, chronic fatigue, cleft palate, diabetes, dementia, depression, Downs syndrome, essential hypertension, fertility issues, fibromyalgia, insomnia, multiple sclerosis, neuropathy, Parkinson's Disease, schizophrenia, and thyroid disease.

Metabolic Imbalance Associated with Methylation Dysregulation and Oxidative Damage in Children with Autism

Stepan Melnyk · George J. Fuchs · Eldon Schulz · Maya Lopez · Stephen G. Kahler · Jill J. Fussell · Jayne Bellando · Oleksandra Pavliv · Shannon Rose · Lisa Seidel · David W. Gaylor · S. Jill James

Published online: 26 April 2011

Abstract Oxidative stress and abnormal DNA methylation have been implicated in the pathophysiology of autism. We investigated the dynamics of an integrated metabolic pathway essential for cellular antioxidant and methylation capacity in 68 children with autism, 54 age-

The metabolic pathology of autism is relatively unexplored even though metabolic imbalance is implicated in the pathogenesis of multiple other neurobehavioral disorders (Frankenburg 2007; Gysin et al. 2007; Small et al. 2000; Smythies et al. 1997). An abnormal accumulation or deficit

athway can provide

d/or environmental

. Further, the identi-

lite imbalance can

to restore metabolic

toms of autism. We

es in the highly-reg-

of folate-dependent

en and the impact of

DNA hypomethyla-

tion and protein/DNA oxidative damage in these children. Because these pathways regulate the distribution of precur-

stressors may modulate genetic predisposition to autism.

Oxidative protein/DNA damage and DNA hypomethylation (epigenetic alteration) were found in autistic children but not paired siblings or controls.

These data indicate that the deficit in antioxidant and methylation capacity is specific for autism and may promote cellular damage and altered epigenetic gene expression. Further, these results suggest a plausible mechanism by which pro-oxidant environmental stressors may modulate genetic predisposition to autism.

The Clinical Problem - Methylation Deficits

- Nutrient deficiencies e.g. folate/folic acid, B12
  - Inadequate intake, malabsorption and poor utilization
  - Move away from processed foods/vegan diet – folate/B12 deficiencies can occur
- Competition for methyl donors
  - Catecholamine turnover (high stress states)
  - Medications e.g. L-Dopa
  - Excess histamine
  - Detoxification
  - Nutrient metabolism
- Continued…

The Clinical Problem - Methylation Deficits

Continued from previous slide…

- Methylation Inhibitors
  - Alcohol
  - SAH - Potent competitive inhibitor of SAMe-dependent methyltransferases, including DNMTs
- Genotype
  - SNPs e.g. MTHFR. C677T homozygous 70-75% loss of enzyme activity, heterozygous 33-35% loss. Compound heterozygotes C677T and A1298C up to 52% loss.
- Aging

The Clinical Problem – Folic Acid

- Potential Risks of synthetic folic acid (FA)
  - Unmetabolized FA (UMFA)
    - Potential genotoxicity
  - DHF (intermediate of DHFR enzyme)
    - Inhibits thymidylate synthase
    - Inhibits MTHF (‘pseudo MTHFR deficiency’)
  - General risks (mechanisms unknown)
    - Increased risk for allergic disease and IBD in offspring to mothers with high folic acid intake
    - Impaired Natural Killer cell activity
    - Insulin resistance in offspring at 6 years
    - Embryonic loss and growth delay
    - Diabetic comorbidity (cardiovascular and cerebrovascular), with high RBC folate primarily driven by FA

Folic acid enforces DNA methylation-mediated transcriptional silencing of *PTEN*, *APC* and *RARbeta2* tumour suppressor genes in breast cancer

Katarzyna Lubecka-Pietruszewska [a,*,1], Agnieszka Kaufman-Szymczyk [a,1], Barbara Stefanska [b], Krystyna Fabianowska-Majewska [a]

[a] *Department of Biomedical Chemistry, Medical University of Lodz, 6/8 Mazowiecka Street, 92-215 Lodz, Poland*
[b] *Department of Pharmacology and Therapeutics, McGill University, 3655 Sir William Osler Promenade, Montreal, QC, Canada H3G 1Y6*

ARTICLE INFO

Article history:
Received 12 November 2012
Available online 3 December 2012

Keywords:

ABSTRACT

Folate, one of the most studied dietary compounds, has recently become the main topic of debates on food fortification. Although low folate levels may be associated with increased risk of cancer development, simultaneously several reports indicate a detrimental effects mediated by high folate concentrations. Using the methylation sensitive restriction analysis (MSRA) and *real-time* RT-PCR we tested the effect of folic acid on DNA promoter methylation and expression of *PTEN*, *APC* and *RARbeta2* tumour suppressor genes in breast cancer cell lines with different invasive capacity. The ... of oncogenic intracellular signaling pathways. The ...olic acid lead to a dose-dependent down-regulation ...he increased DNA methylation detected within their ... in non-invasive MCF-7 cells where we also observed ...st folate concentration used. Our findings show that ...acid supplementation since it may lead to cancer progression.

The results show that the increasing concentrations of folic acid lead to a dose dependent down-regulation of tumour suppressor genes which may be linked to the increased DNA methylation detected within their promoter regions

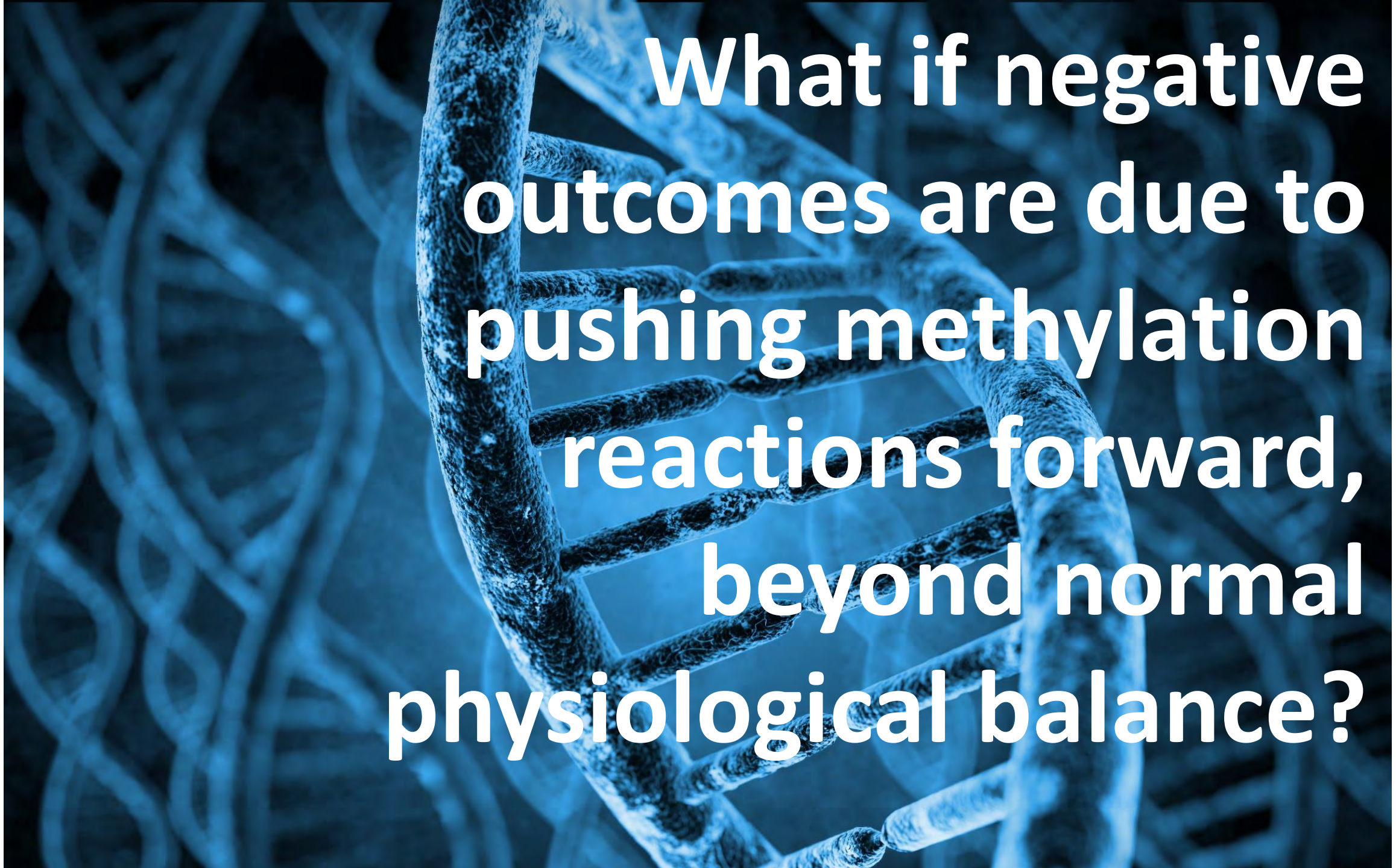
30% up-regulation of DNMT1 expression at the highest folate concentration used (MCF-7 cells)

Methylated B vitamins – the Solution?

- 5mTHF and methylcobalamin (B12) widely used in functional medicine
- Avoids issues of folic acid
- Bypasses MTHFR enzyme deficits

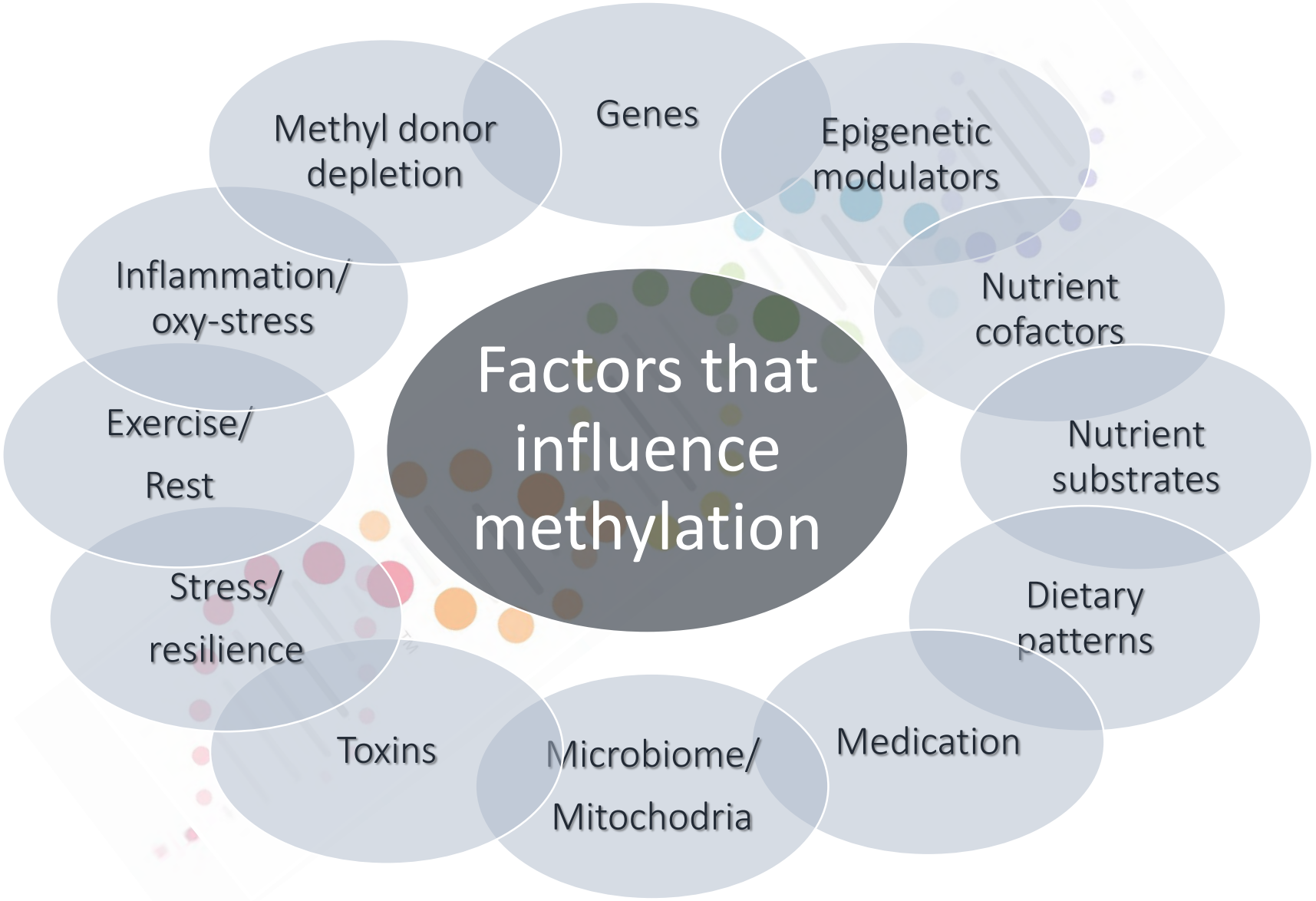
But we don't really understand the long term safety

No long term studies done with high dose 5mTHF or methyl-B12


What if negative outcomes are due to pushing methylation reactions forward, beyond normal physiological balance?

Supporting Methylation Through Diet and Lifestyle

- A safer, more nuanced way to support the homeodynamic balance of methylation activity?
- How we use dietary and lifestyle support in clinical practice:
  - Alongside cautious/cyclical folate and methylation nutrient supplementation to enhance efficacy
  - As an alternative intervention for individuals who do not tolerate methyl donor supplementation
  - As a stand-alone intervention
  - Integrated with other needed non-methylation interventions


Factors that influence methylation
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Methyl donor depletion
Epigenetic modulators
Inflammation/ oxy-stress
Nutrient cofactors
Exercise/ Rest
Nutrient substrates
Stress/ resilience
Dietary patterns
Toxins
Microbiome/ Mitochodria
Medication

"It's fashionable now to use large doses of methylating agents. But in various studies looking at Prozac [and other antidepressants as compared] to using very high doses of methyl folate in depression, you have to realize that we have no idea what that is doing to the function of all the other genes. So if you need to use it for someone who has, say a mood disorder, use it, but follow the indices and use it for as short a period as possible.

…There are places for these things, but don't overdo it. Don't overdo it."

Robert Hedaya, MD, DLFAPA. Clinical Professor of Psychiatry, Georgetown University School of Medicine. Faculty, Institute of Functional Medicine

http://pro.psychcentral.com/l-methylfolate-for-depression-the-real-deal/004087.html#

Excess folate/B12 and autism: a possible connection

- Recent release of preliminary findings from Johns Hopkins study
- 1,391 mother-child pairs in Boston Birth Cohort
- Highest maternal levels of B12 (>600 pmol/L) and, separately, folate (59 nmol/L) associated with increased risk of ASD. **Risk was 17-fold greater when both combined.**
- No risk difference based on MTHFR genotype or homocysteine

April 2016. FASEB. Vol. 30 no. 1. S 151.6**. [No full text available]**

Prenatal Vitamins, One-carbon Metabolism Gene Variants, and Risk for Autism

Rebecca J. Schmidt,[a,b] *Robin L. Hansen,*[b,c] *Jaana Hartiala,*[d] *Hooman Allayee,*[d] *Linda C. Schmidt,*[e] *Daniel J. Tancredi,*[c,f] *Flora Tassone,*[b,e] *and Irva Hertz-Picciotto*[a,b]

Background: Causes of autism are unknown. Associations with maternal nutritional factors and their interactions with gene variants have not been reported.

Methods: Northern California families were enrolled from 2003 to 2009 in the CHARGE (CHildhood Autism Risks from Genetics and Environment) population-based case-control study. Children aged 24–60 months were evaluated and confirmed to have autism (n = 288), autism spectrum disorder (n = 141), or typical development (n = 278) at the University of California–Davis Medical Investigation of Neurodevelopmental Disorders Institute using standardized clinical assessments. We calculated adjusted odds ratios (ORs) for

taking prenatal vitamins periconceptionally (4.5 [1.4–14.6]; 2.6 [1.2–5.4]; and 7.2 [2.3–22.4], respectively). Greater risk was also observed for children whose mothers had other one-carbon metabolism pathway gene variants and reported no prenatal vitamin intake.

Conclusions: Periconceptional use of prenatal vitamins may reduce the risk of having children with autism, especially for genetically susceptible mothers and children. Replication and mechanistic investigations are warranted.

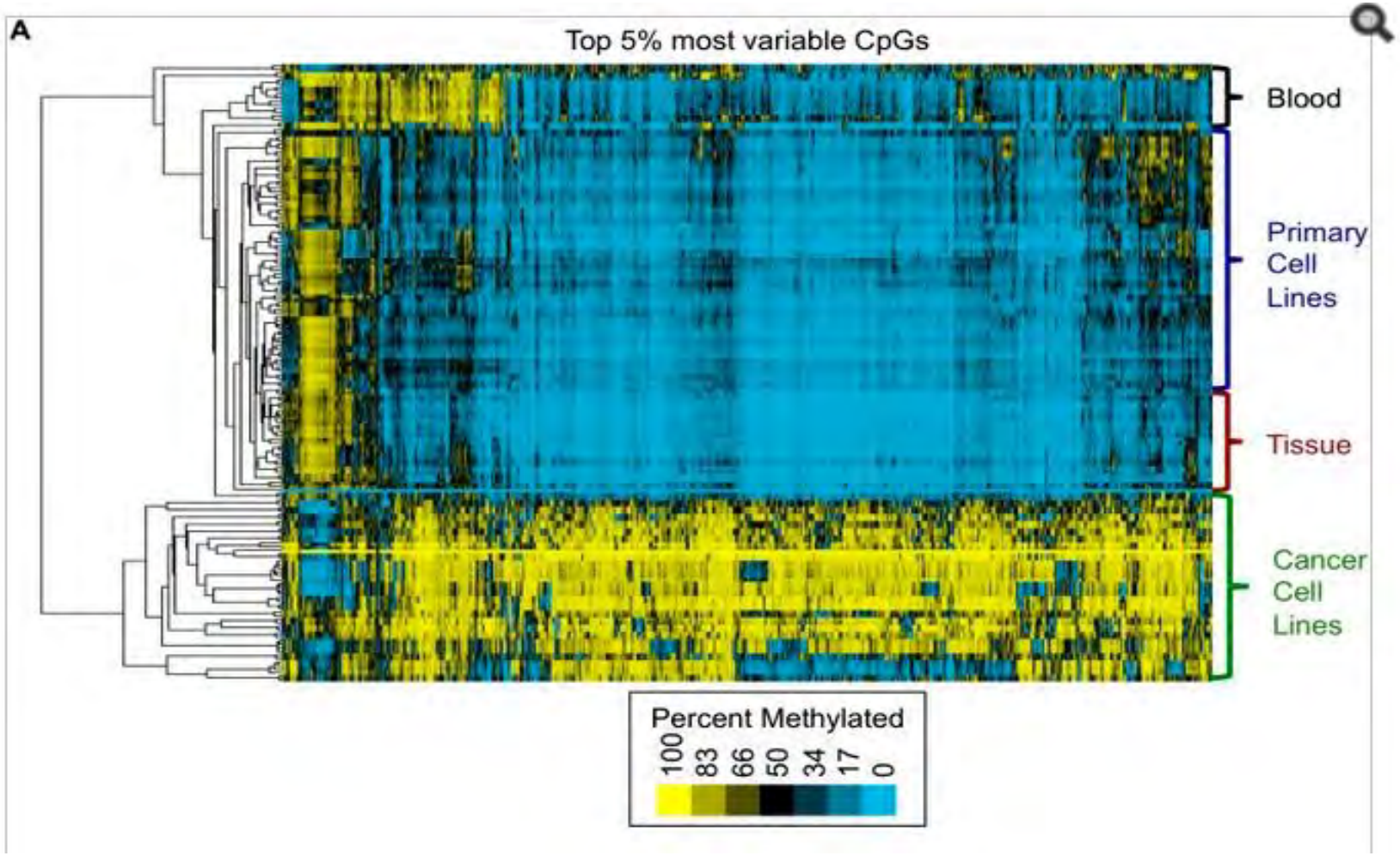
(*Epidemiology* 2011;22: 476–485)

It is known that the MTHFR C677T polymorphism is associated with an increased risk of autism spectrum disorder (odds ratio = 1.42, 95% CI 1.09-1.85), but that this risk can be mitigated by sufficient periconceptional folate or folic acid intake.

But if a maternal MTHFR C677T polymorphism is combined with a CBS polymorphism, a lack of prenatal supplementation with B vitamins and a fetal COMT polymorphism, the odds ratio for autism spectrum disorder rises dramatically to 7.2 (CI = 2.3–22.4; P=0.05).

ɔmental disorder defined by the
ɔcial reciprocity, abnormal com-
interests or repetitive behavior,
3 years of age. Prevalence of
approximately 1 in 110 children
incidence appears to be rising.[2]
ɔns to autism etiology are widely
nce, inconsistent findings from
n 100% concordance in monozygotic twins suggest a role for multiple interactions between susceptibility genes and environmental factors.[3] A recently

Excessive Methylation Risks



Pooled cancer cell lines from breast, prostate, lung, ovarian, endometrial, liver and pancreatic cancer cells, as well as neuroblastoma and leukemias.

K. E. Varley, et al., "Dynamic DNA methylation across diverse human cell lines and tissues.," Genome Res., vol. 23, no. 3, pp. 555–67, Mar. 2013.

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

JAMA. 2007 Jun 6;297(21):2351-9.

Folic acid for the prevention of colorectal adenomas: a randomized clinic

Cole BF[1], Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, CA, Snover DC, Church TR, Alle LA, Pe
Rees JR, Marcon N, Saibil F, U

Author information

Abstract

CONTEXT: Laboratory and e oplas
intestine.

OBJECTIVE: To assess the s color

1mg/d FA for colorectal cancer prevention failed to reduce recurrence risk.
Risk for recurrent colorectal adenoma and noncolorectal cancers, especially prostate cancer, increased.

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

Nutr Rev. 2006 Oct;64(10 Pt 1):468-75.

Does a high folate intake increase the risk of breast cancer?

Kim YI[1].

Author information

Abstract

Although not uniformly consistent, epide
intake and blood measurements of folat
Ovarian (PLCO) Cancer Screening trial h
intake on breast cancer risk. In this study, the risk of developing breast cancer was significantly inc
women reporting supplemental folic acid intake > or = 400 microg/d compared with those reporting
intake. Furthermore, although food folate intake was not significantly related to breast cancer risk,
mainly from folic acid supplementation, significantly increased breast cancer risk by 32%. The data

Supplement >=400mcg/d FA associated with a 20% increase in breast cancer risk compared with no supplement intake

Folate *Status* and Cancer

- Highest tertile of plasma folate associated with highest likelihood of ERbeta(-) breast cancer (OR 2.67, P=0.001, n=612)
- Increased risk specifically when MTHFR C677T combined with high plasma folate levels
- High serum folate associated with progression of benign polyps to colorectal cancer (n=300)

J. Nutr., vol. 140, no. 9, pp. 1661–1668, 2010.

Am. J. Clin. Nutr., vol. 90, no. 5, pp. 1380–9, 2009.

F.-F. Chiang, et al., *Clin. Nutr.*, Nov. 2014.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Folic acid enforces DNA methylation-mediated transcriptional silencing of *PTEN*, *APC* and *RARbeta2* tumour suppressor genes in breast cancer

Katarzyna Lubecka-Pietruszewska [a,*,1], Agnieszka Kaufman-Szymczyk [a,1], Barbara Stefanska [b], Krystyna Fabianowska-Majewska [a]

[a] Department of Biomedical Chemistry, Medical University of Lodz, 6/8 Mazowiecka Street, 92-215 Lodz, Poland
[b] Department of Ph

ARTIC

Article histor
Received 12
Available on

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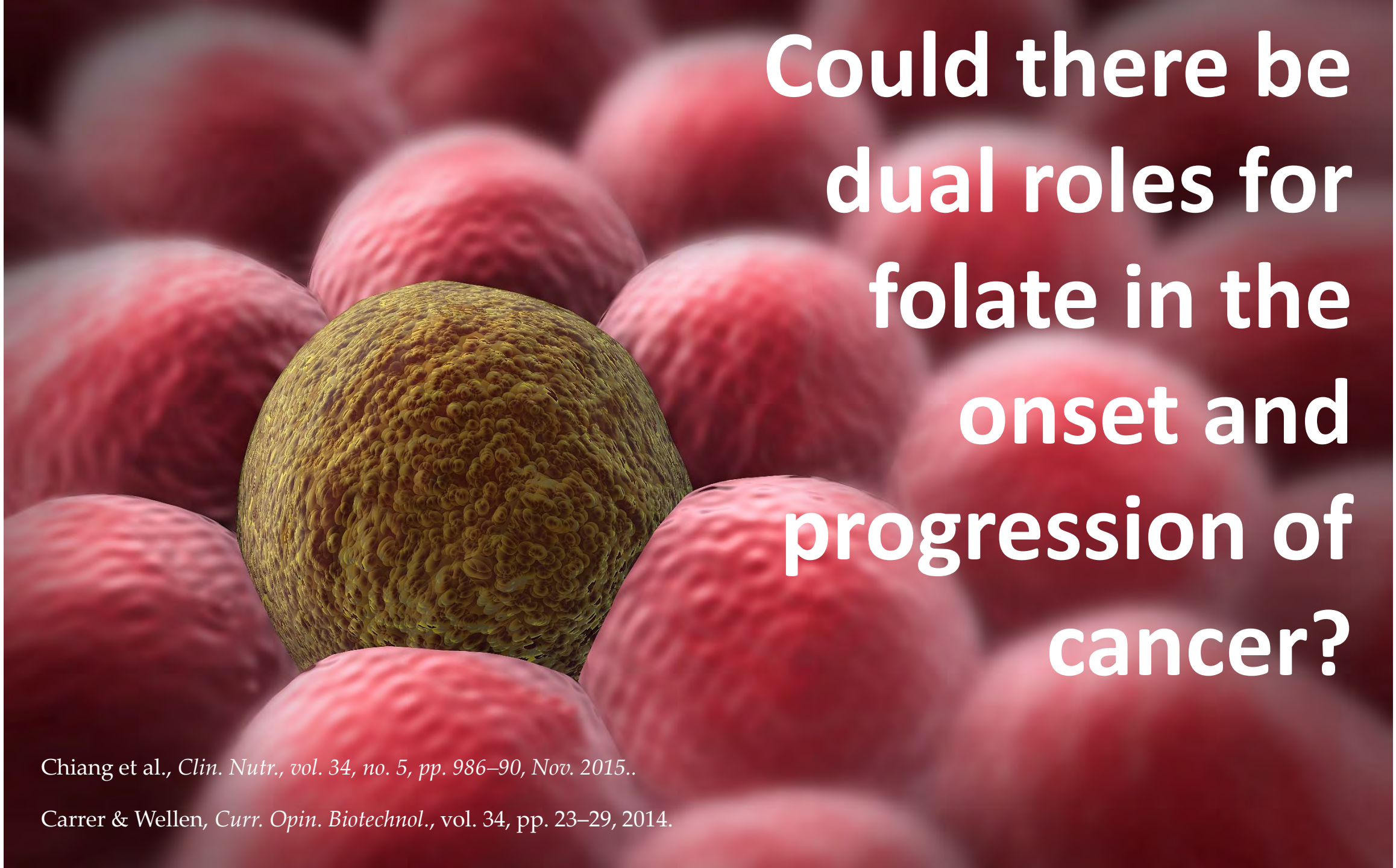
Folic acid
Epigenetic r
DNA methyl
Breast cance

In conclusion, in the present study we demonstrate that folic acid at increasing concentrations impairs transcriptional activities of the tested tumour suppressor genes that is concomitant with increased DNA methylation within their promoters. **The highest folate concentration used in our experiments caused induction of DNMT1 expression.**



Could there be dual roles for folate in the onset and progression of cancer?

Chiang et al., *Clin. Nutr., vol. 34, no. 5, pp. 986–90, Nov. 2015..*

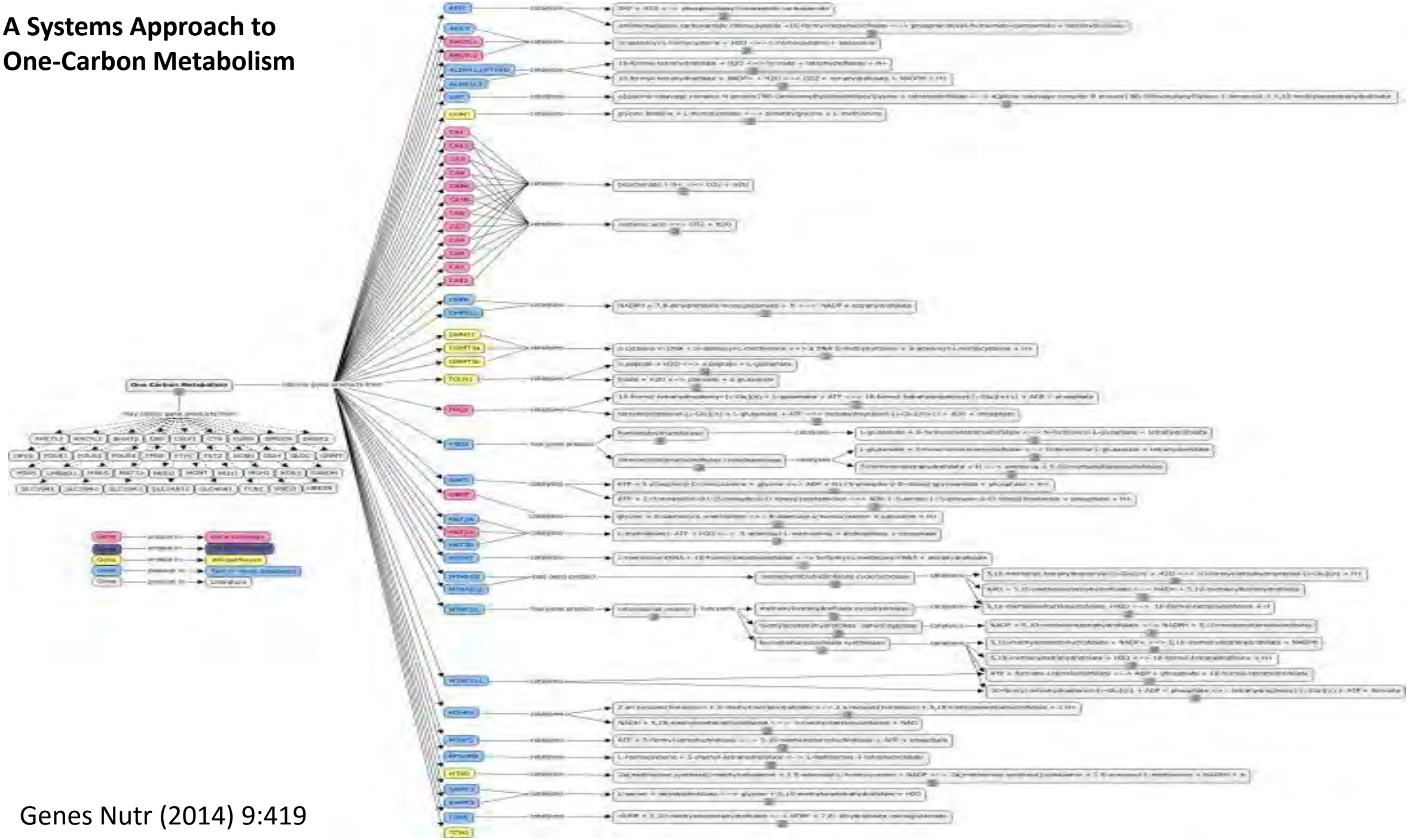
Carrer & Wellen, *Curr. Opin. Biotechnol.*, vol. 34, pp. 23–29, 2014.

Points to Consider - Genetics

- Overwhelming majority of SNP effects are not quantifiable
- Overall effects of SNP combinations are not well understood
- Not just MTHFR, but other gene polymorphisms, including: AHCY, BHMT, CBS, COMT, MAO, MAT1A, MTR, MTRR.

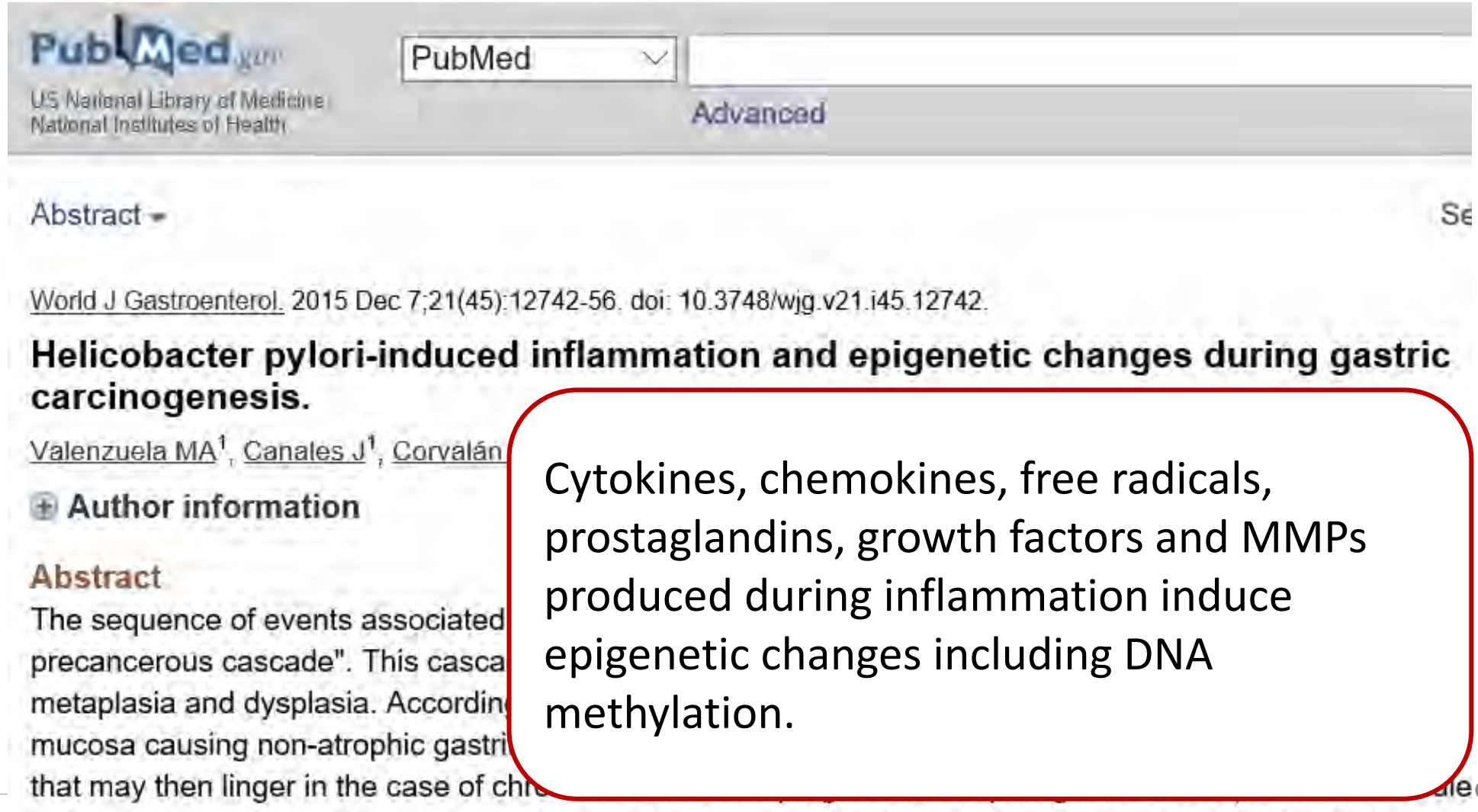
rs1643659	DHFR A20965G	C	TT	-/-
rs1677693	DHFR C19483A	T	GG	-/-
rs1650697	DHFR/MSH T-473A	A	AA	+/+
rs479405	DMGDH G67591T	C	AC	+/-
rs532964	DMGDH T835C	A	AG	+/-
rs2071010	FOLR1 G-20A	A	GG	-/-
rs651933	FOLR2 G-1316A	A	AA	+/+

A Systems Approach to One-Carbon Metabolism



Genes Nutr (2014) 9:419

Points to Consider - Inflammation



Cytokines, chemokines, free radicals, prostaglandins, growth factors and MMPs produced during inflammation induce epigenetic changes including DNA methylation.

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

Pathol Oncol Res. 2015 Jul;21(3):527-34. doi: 10.1007/s12253-015-9913-z. Epub 2015 Mar 5.

The role of the mediators of inflammation in cancer development.

Fernandes JV[1], Cobucci RN, Jatobá CA, Fernandes TA, de Azevedo JW, de Araújo JM.

Author information

Abstract

Epigenetic disorders such as p… translational modifications are … alterations in critical pathways … inflammatory response which c… mechanism activated in response to an injury tissue, of any nature, that involves both innate and ada… responses, through the collective action of a variety of soluble mediators. Many inflammatory signali…

IL-1beta suppresses p53 expression via methylation, creating a more favorable environment for tumorigenesis.

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

Cancer Res. 2005 Jun 1;65(11):4673-82.

Interleukin 6 supports the maintenance of p53 tumor suppressor gene promote methylation.

Hodge DR[1], Peng B, Cherry JC, Hurt EM, Fox SD, Kelley JA, Munroe DJ, Farrar WL.

Author information

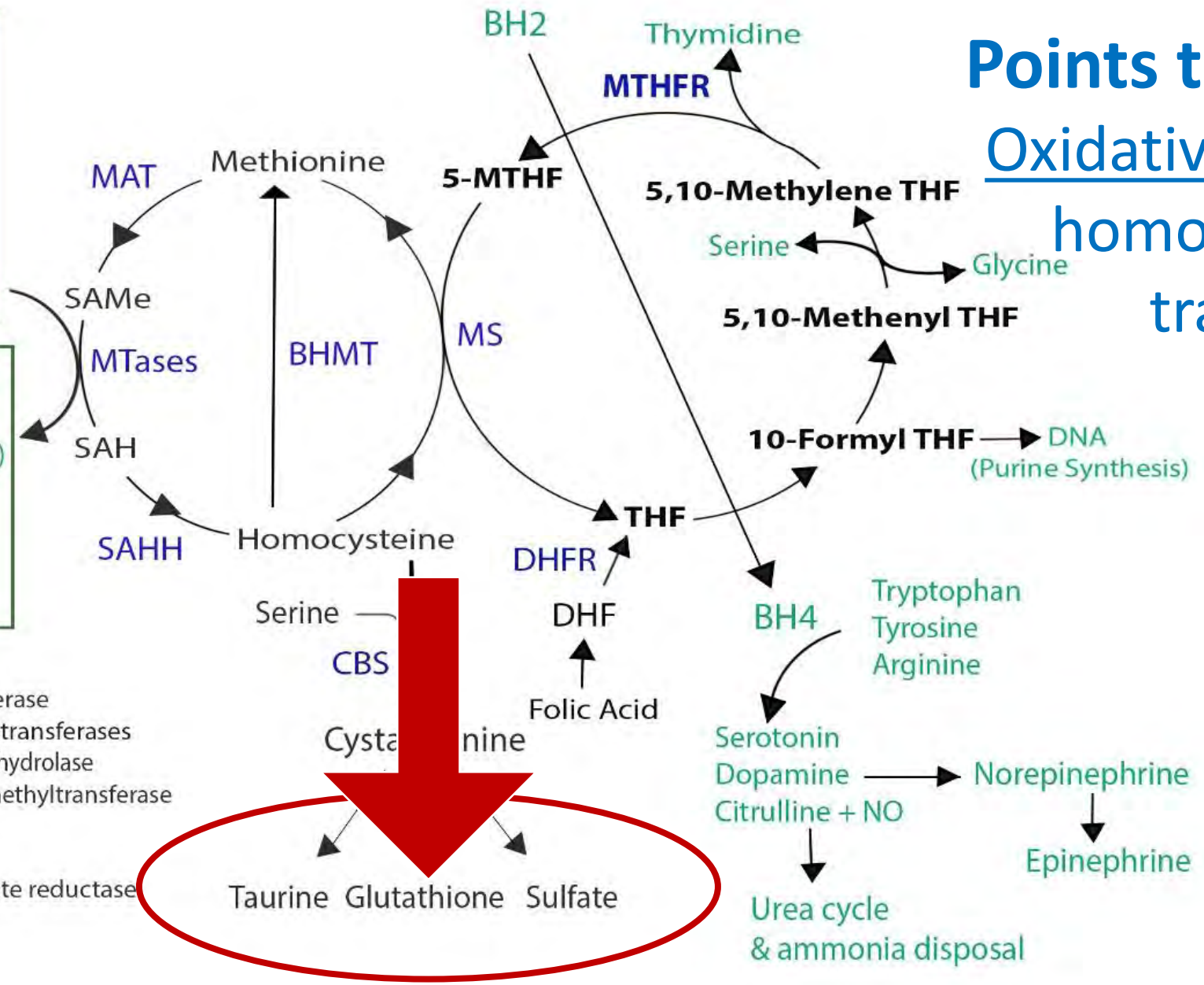
Abstract

A strong association exists between states of chronic inflammation and cancer, and it is believed that me inflammation may be responsible for this phenomenon. Interleukin 6 (IL-6) is an inflammatory cytokine kr a role in the growth and survival of many types of tumors, yet the mechanisms employed by this pleomor cytokine to accomplish this fe be the hypermethylation of Cp

IL-6 regulates activity of DNMTs, microRNAs and histone methyltransferases

DNA
RNA
Norepinephrine
Dopamine
Estrogen
Histamine
Arginine
Phosphatidylethanolamine

Methylated Metabolites
include but not limted to:
5-methylcytosine (DNA/RNA)
Epinephrine
Creatine
Phosphatidyl choline
and degredation products



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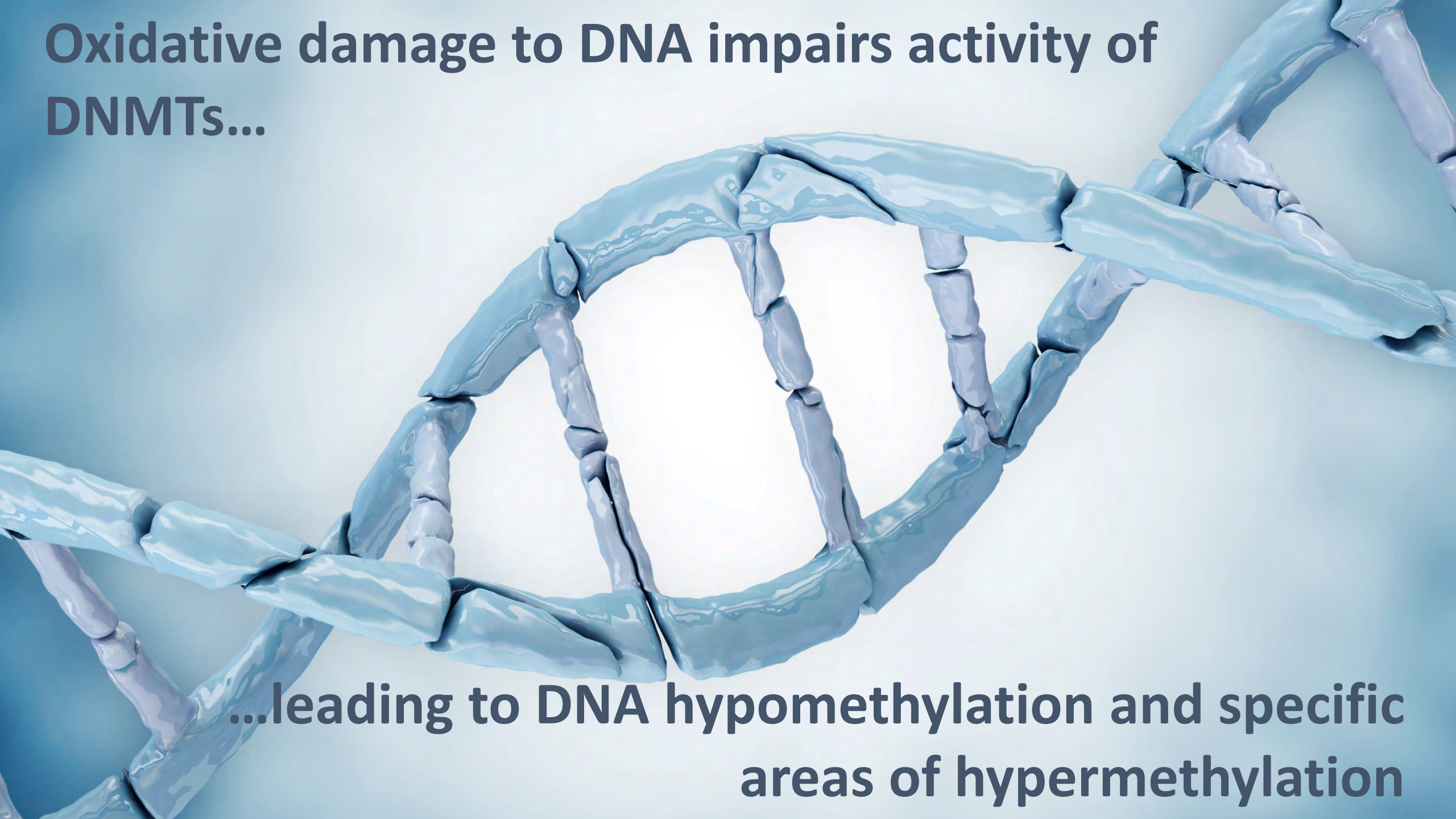
MS - Methionine synthase
DHF - Dihydrofolate
THF - Tetrahydrofolate
BH2 - Dihydropterin
BH4 - Tetrahydrobiopterin

Points to Consider:

Oxidative stress pulls homocysteine into transulfuration pathways

Oxidative damage to DNA impairs activity of DNMTs…



…leading to DNA hypomethylation and specific areas of hypermethylation

Points to Consider – Microbiome

- DNA methylation of intestinal epithelial cells shown to be significantly dysregulated and reduced in germ-free mouse models when compared with conventional controls
- Reestablishing commensal bacterial populations via fecal transplant correlates with significant increases in CpG methylation
- Findings suggest a sophisticated, directive role for microbes in host epigenetic regulation, beyond simple facilitation

Yu et al., *Genome Biol.*, vol. 16, no. 1, p. 211, 2015.

Microbes for Methylation Support

- Folate-producing bacterial species
  - *L. plantarum*
  - *B. bifidum*
  - *B. infantis*
  - *B. breve*
  - *B. longum*
  - *B. adolescentis* – appears to be the highest producer of 5mTHF
  - *B. pseudocatenulatum*

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Abstract

MBio. 2014 Dec 16;5(6). pii: e02113-14. doi: 10.1128/mBio.02113-14.

Gut microbiota as an epigenetic regulator: pilot study based on whole-ger methylation analysis.

Kumar H[1], Lund R[2], Laiho A[2], Lundelin K, Ley RE[3], Isolauri E[4], Salminen S[5].

Author inform

Abstract

The core human g r
To evaluate the pr e
based on their dom q
methylomes revea s
differentially methyla o r
predominantly to cardiovascular disease and specifically to lipid metabolism, obesity, and the infla

Human pilot study: higher levels of bacteroidetes (vs firmicutes) associated with increased promoter methylation of 568 genes, and decreased promoter methylation of 245 genes (P=0.05). The genes affected were associated with **cardiovascular disease, inflammation, metabolic pathways and cancer**

PubMed.gov
US National Library of Medicine
National Institutes of Health

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Abstract

J Ren Nutr. 2005 Jan;15(1):77-80.

Beneficial effects of Bifidobacteria in a gastroresistant seamless capsule on hyperhomocysteinemia in hemodialysis patients.

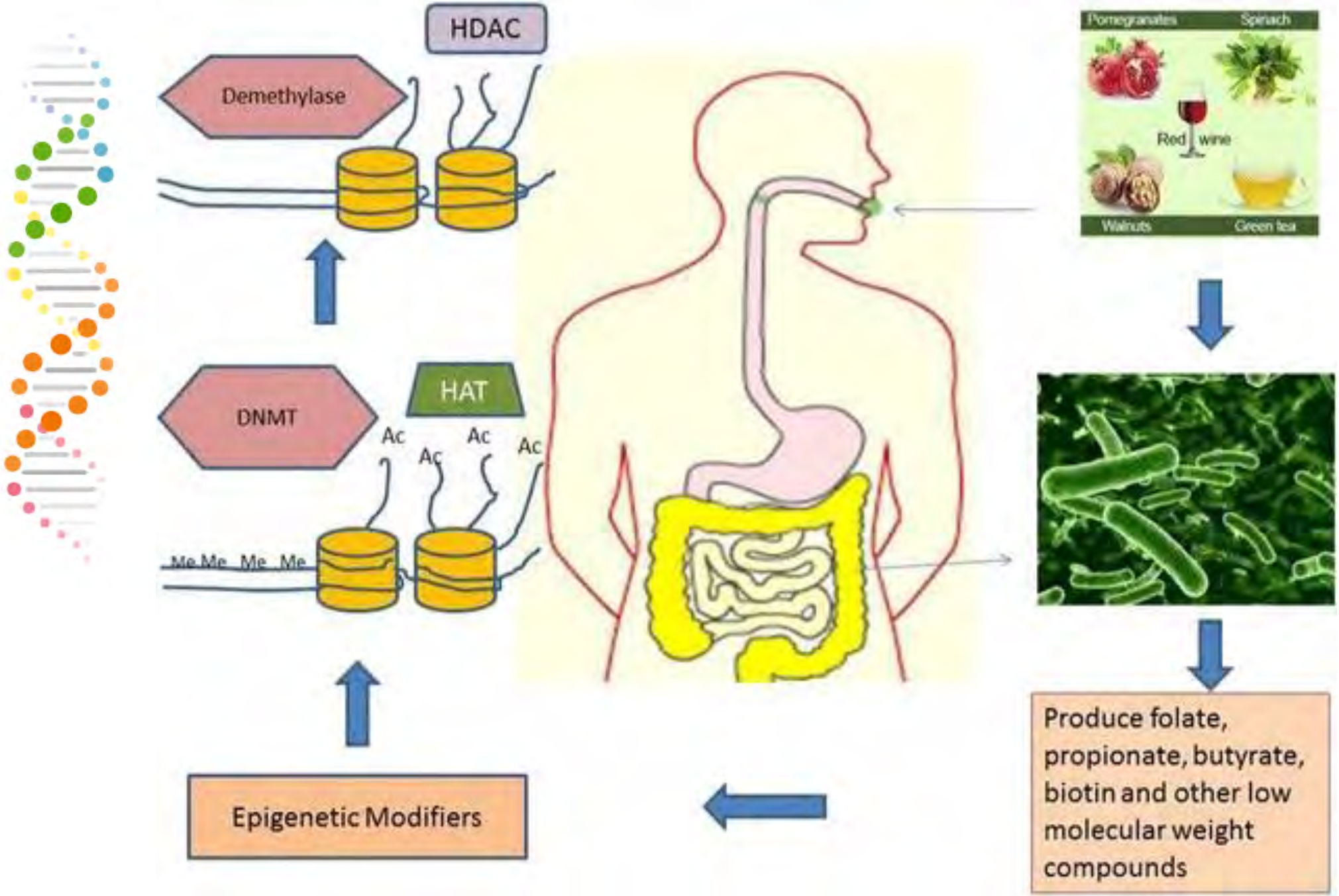
Taki K[1], Takayama F, Niwa T.

Author information

Abstract

Intestinal microflora ... uch as E
coli and a decrease ... drates to
acetic acid and lac ... ectively
the disturbed micro ... ods can
usually survive bec ... tant sear

Administration of ***B. longum*** **to hemodialysis patients** reduced serum homocysteine.
Attributed to increased supply of folate produced by this species in the gut.



Clin Epigenetics. 2015; 7: 112.

Points to Consider: Mitochondrial DNA Methylation

- mtDNMT1 identified recently showing that methylation actively occurs in mitochondria
- Mitochondria also alter nuclear DNA/mtDNA methylation by influencing folate metabolism, leading to SAMe or SAH synthesis
- Epigenetic changes in mitochondrial DNA can be triggered by disease, aging, chronic stress, certain environmental exposures, and medication use.
- “Next generation biomarker for disease”

Mitochondria and Epigenetic Regulation

- Key energy metabolites including SAMe, acetyl-CoA, NAD+ , α-KG, and ATP serve as essential cofactors for epigenetic enzymes that regulate DNA methylation, posttranslational histone modifications, and nucleosome position
- Significant contributors in the epigenomic machinery are formed during energy metabolism in eukaryotic cell mitochondria signifying that any disorder in these processes can lead to a wide variety of diseases associated with epigenetic modifications

Paul et al. Clinical Epigenetics (2015) 7:112

Toxins That Alter DNA Methylation

- Pesticides
- Fertilizer
- Automobile fumes
- Bisphenol A
- Phthalates
- Persistent Organic Pollutants (POPs)
- Jet fuel
- Benzene
- Mold toxins (aflatoxin, fumonisin)
- Arsenic
- Mercury
- Lead
- Cadmium
- Nickel

Detoxification Competes for Methyl Donors

Competition for methyl donors

- Detoxification
- Catecholamine turnover (high stress states)
- Medications e.g. L-Dopa
- Excess histamine
- Nutrient metabolism

High Stress States Deplete Methyl Donors

Competition for methyl donors

- Detoxification
- Catecholamine turnover (high stress states)
- Excess histamine
- Medications e.g. L-Dopa
- Nutrient metabolism

Stress and DNA Methylation

- **Early life stress associated with altered levels of DNA methylation in the glucocorticoid receptor promoter**, and increased expression of the receptor, suggesting that traumatic experiences, perhaps especially during vulnerable periods of development, **might 'prime' an individual for later, hyper-stress responses**[1]
- **Traumatic experiences outside prenatal/perinatal development periods** also appear to alter methylation of the glucocorticoid receptor gene promoter, corresponding with attenuated cortisol responsiveness[2]

[1]Weaver et al., *J. Neurosci.*, vol. 25, no. 47, pp. 11045–11054, 2005.
[2]Tyrka et al., *PLoS One*, vol. 7, no. 1, p. e30148, 2012.

Differential Immune System DNA Methylation and Cytokine Regulation in Post-Traumatic Stress Disorder

Alicia K. Smith,[1] Karen N. Conneely,[2] Varun Kilaru,[1] Kristina B. Mercer,[3] Tamara E. Weiss,[1] Bekh Bradley,[4] Yilang Tang,[2] Charles F. Gillespie,[1] Joseph F. Cubells,[1,2] and Kerry J. Ressler[1,3,5]*

[1]Department of Psychiatry & Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

[2]Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia

[3]Howard Hughes Medical Institute, Maryland

[4]Atlanta VA Medical Center, Decatur, Georgia

[5]Yerkes National Primate Research Center, Atlanta, Georgia

Received 8 March 2011; Accepted 31 May 2011

Together, these results suggest that **psychosocial stress may alter global and gene-specific DNA methylation patterns potentially associated with peripheral immune dysregulation**.

Higher serum IL-2, IL-4 and TNFa all associated with changes to methylation patterns of genes associated with inflammation

How to Cite this Article:
Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley-Davino B, Tang Y, Gillespie CF, Cubells JF, Ressler KJ. 2011. Differential Immune System DNA Methylation and Cytokine Regulation in Post-Traumatic Stress Disorder.
Am J Med Genet Part B 156:700–708.


1.80LT


FUNZUG.COM

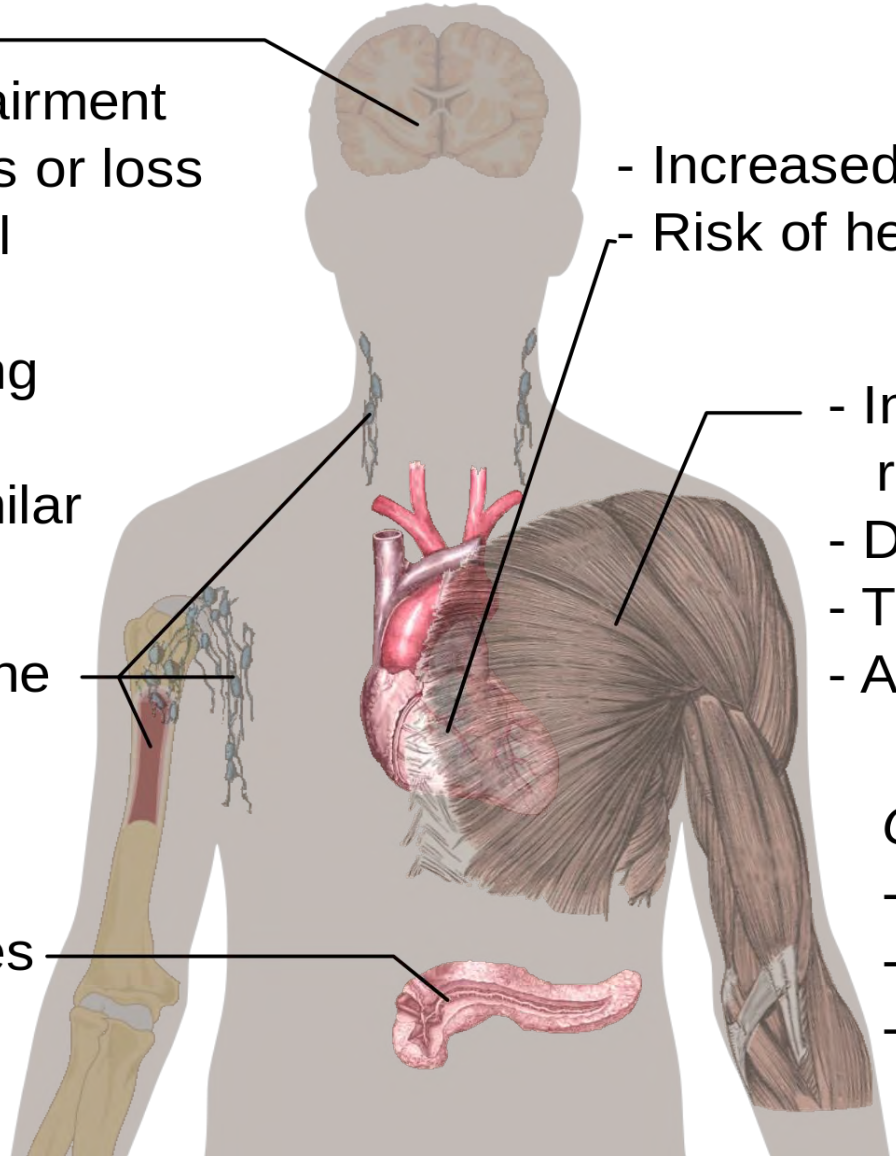
Effects of

Sleep deprivation

- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD

- Impaired immune system

- Risk of diabetes Type 2



- Increased heart rate variability
- Risk of heart disease

- Increased reaction time
- Decreased accuracy
- Tremors
- Aches

Other:
- Growth suppression
- Risk of obesity
- Decreased temperature

Wikipedia.com

ORIGINAL ARTICLE

The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes

R Massart[1,8], M Freyburger[2,3,8], M Suderman[1], J Paquet[3], J El Helou[3], E Belanger-Nelson[3], A Rachalski[3], OC Koumar[3], J Carrier[3,4], M Szyf[1,5,6] and V Mongrain[3,7]

Sleep is critical for normal brain function and mental health. However, the molecular mechanisms mediating the impact of sleep loss on both cognition and the sleep electroencephalogram remain mostly unknown. Acute sleep loss impacts brain gene expression broadly. These data contributed to current hypotheses regarding the role for sleep in metabolism, synaptic plasticity and neuroprotection. These changes in gene expression likely underlie increased sleep intensity following sleep deprivation (SD). Here we tested the hypothesis that epigenetic mechanisms coordinate the gene expression response driven by SD. We found that

We found that acute sleep deprivation altered the cortical genome-wide distribution of two major epigenetic marks: DNA methylation and hydroxymethylation.

DNA methylation differences were enriched in gene pathways involved in neuritogenesis and synaptic plasticity, whereas large changes (>4000 sites) in hydroxymethylation where observed in genes linked to cytoskeleton, signaling and neurotransmission

n and hydroxymethylation. DNA
lasticity, whereas large changes
nd neurotransmission, which
applied to elements previously
xample, *Dlg4*, *Nrxn1* and *Nlgn3*),
gn1 mutant mice display an
does not affect SD-dependent
triggering gene expression
changes in SD. These data reveal that acute SD reprograms the epigenetic landscape, providing a unique molecular route by which sleep can impact brain function and health.

Translational Psychiatry (2014) **4,** e347; doi:10.1038/tp.2013.120; published online 21 January 2014

Unresolved Reactivity Depletes Methyl Donors

Competition for methyl donors

- Detoxification
- Catecholamine turnover (high stress states)
- Excess histamine
- Medications e.g. L-Dopa
- Nutrient metabolism

Medications Can Deplete Methyl Donors

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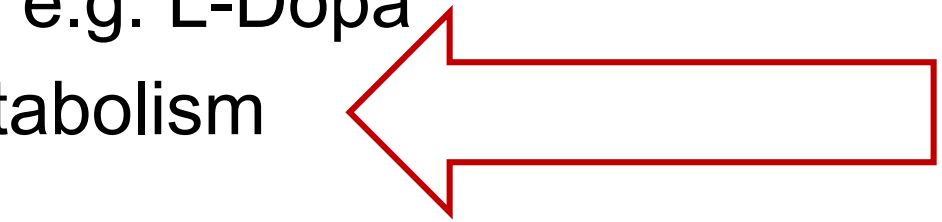
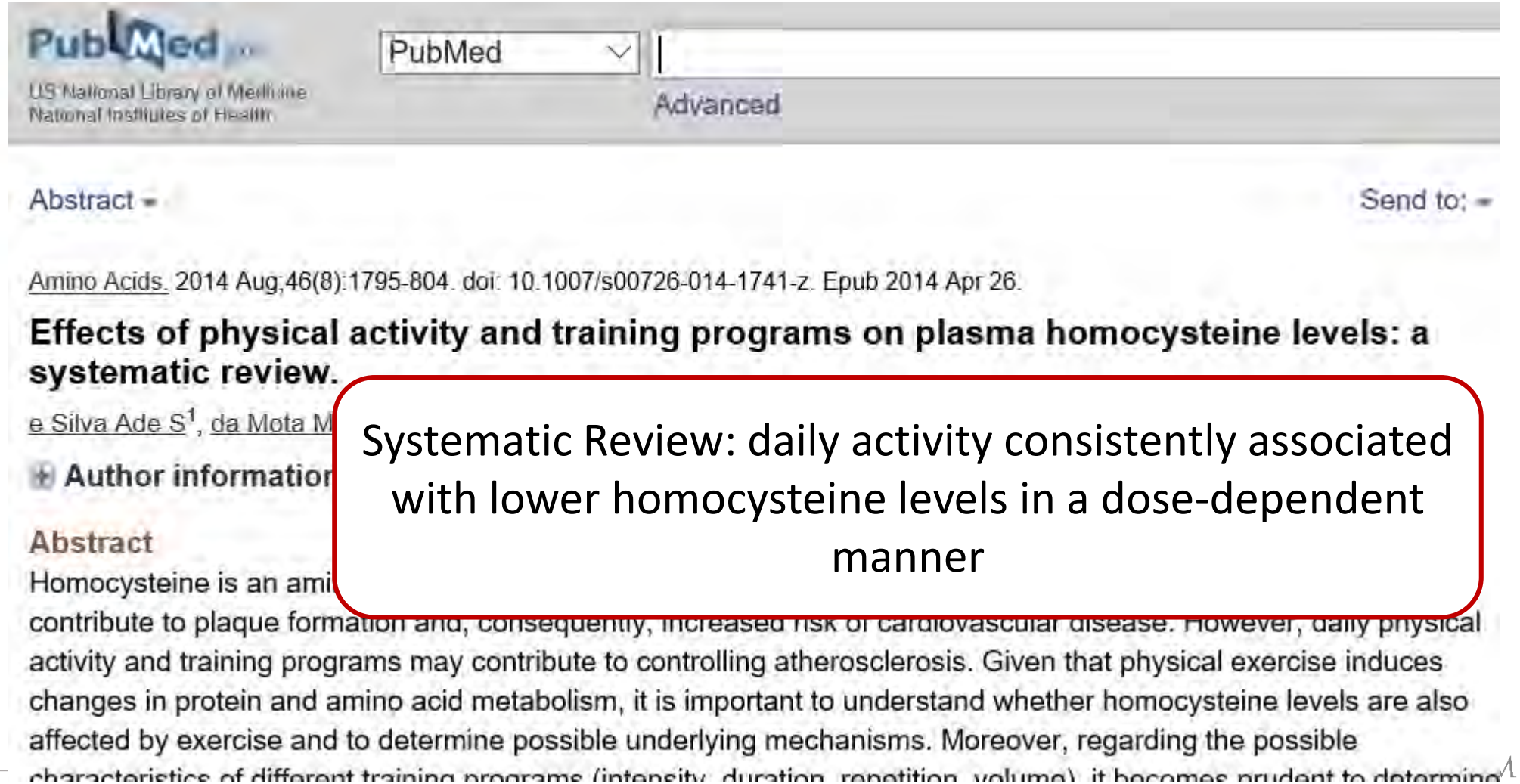


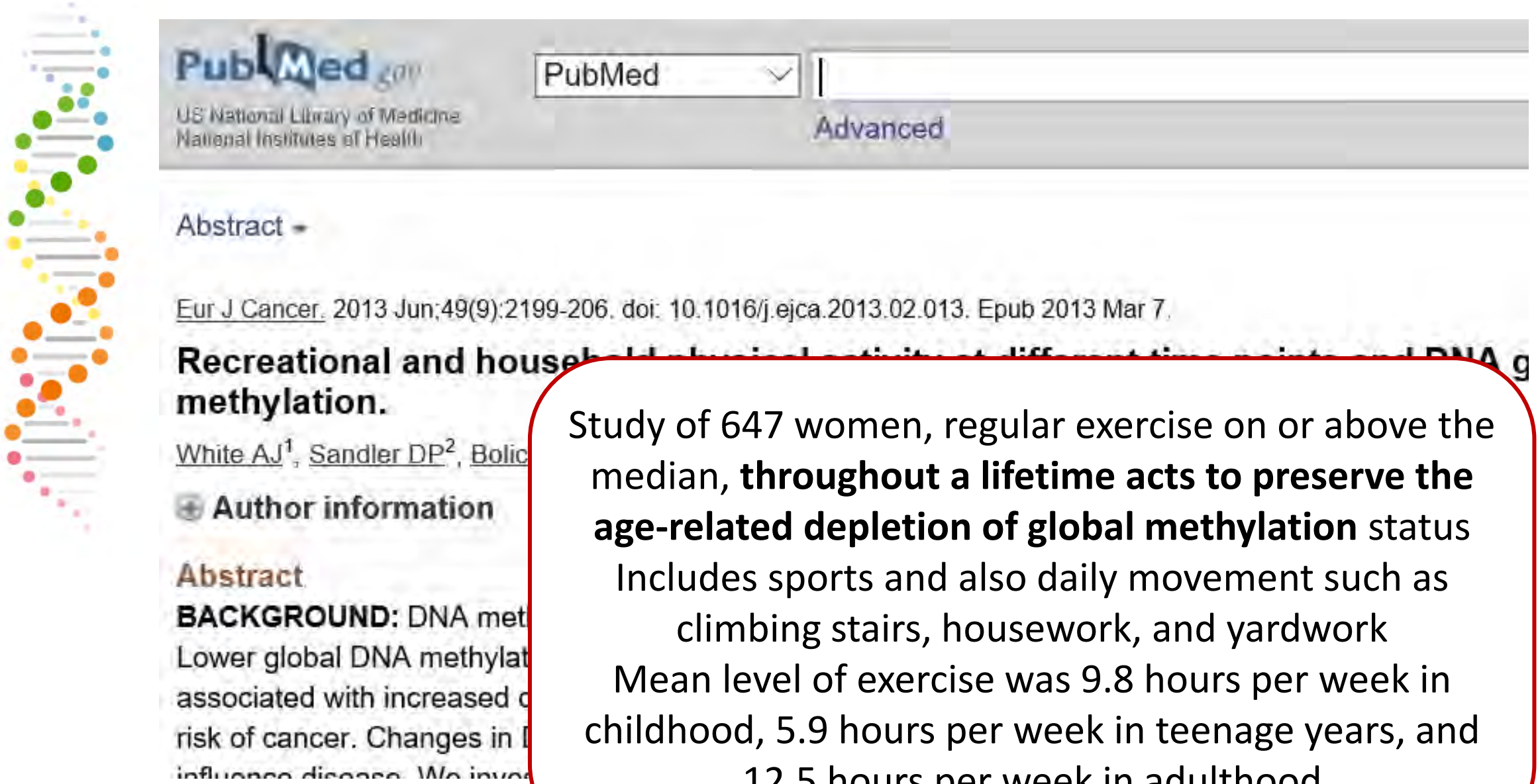
Nutrients that are metabolized via methylation

- Niacin
- Selenium
- Phosphatidylethanolamine

Be mindful with high dose supplementation

Points to Consider - Exercise

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Abstract
Eur J Cancer. 2013 Jun;49(9):2199-206. doi: 10.1016/j.ejca.2013.02.013. Epub 2013 Mar 7.
Recreational and household
methylation.
White AJ[1], Sandler DP[2], Bolic
Author information
Abstract
BACKGROUND: DNA met
Lower global DNA methylat
associated with increased c
risk of cancer. Changes in
Study of 647 women, regular exercise on or above the median, throughout a lifetime acts to preserve the age-related depletion of global methylation status
Includes sports and also daily movement such as climbing stairs, housework, and yardwork
Mean level of exercise was 9.8 hours per week in childhood, 5.9 hours per week in teenage years, and 12.5 hours per week in adulthood

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Abstract

Evid Based Complement Alternat Med. 2012;2012:841810. doi: 10.1155/2012/841810. Epub 2012 Jun 5.

Epigenetic changes in response to tai chi practice: a pilot investigation of DN methylation marks.

Ren H[1], Collins V, Clarke SJ, Han JS, La

Author information

Abstract

Tai chi exercise has been shown to
disease conditions. The biological m
investigated whether tai chi practice
methylation profiles of sixty CpG-din
have been practising tai chi for three

Study of 500 females:

Long-term tai-chi practice(1+ hours per week, 3+ years) associated with slowing of age-related DNA methylation losses, of between 5-70% compared with controls

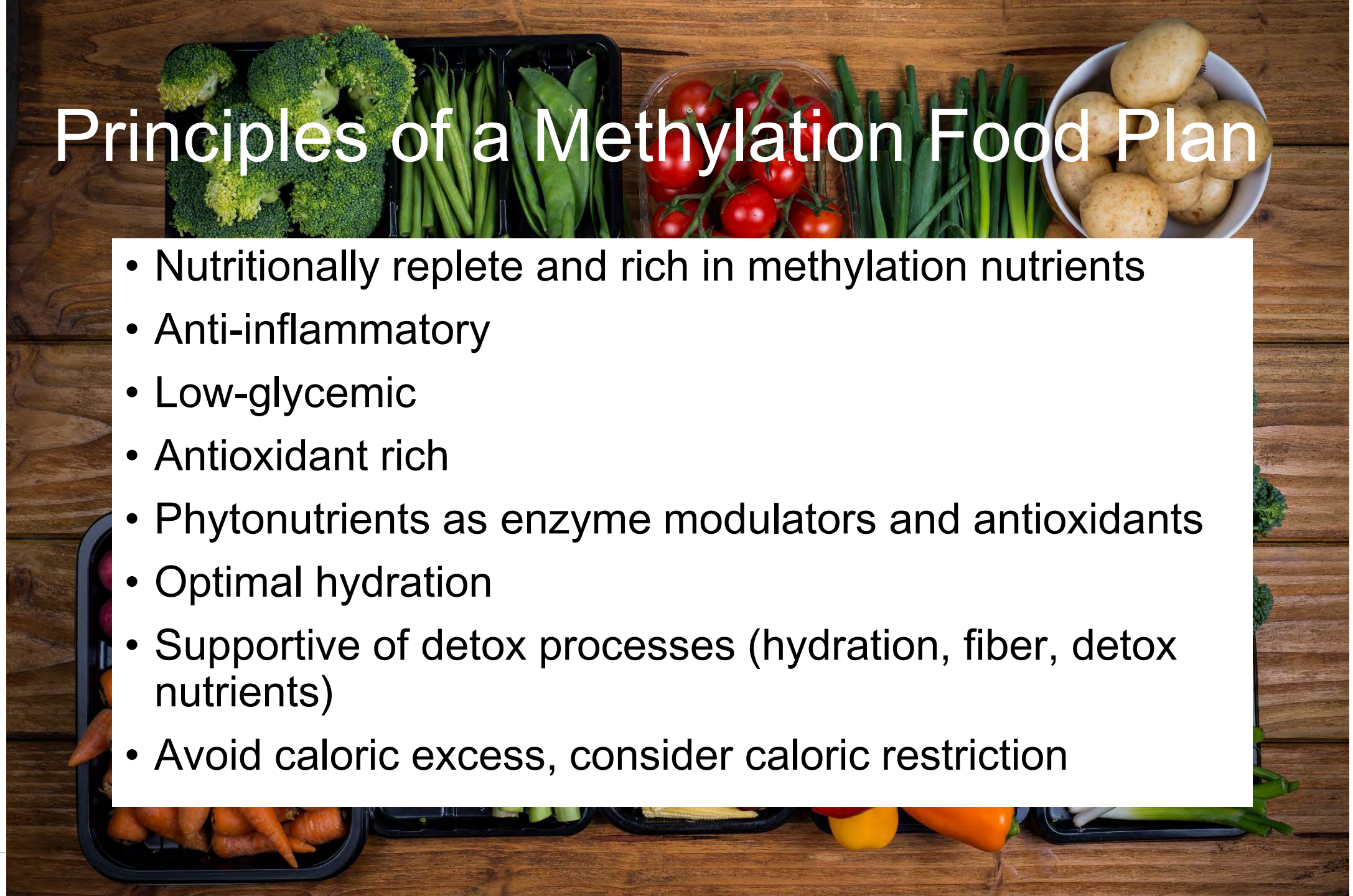
May be particularly beneficial from age 50-55+

Caution with Overtraining, Especially with Low Nutrient Stores

- Acute exercise, especially in untrained individuals with low folate and vitamin B12 status temporarily increases plasma homocysteine
- Endurance exercise can produce circulating IL-6 up to 120 times baseline
- High-intensity, anaerobic exercise can reduce the antioxidant response

Personalized exercise programs that gradually build up tolerance via regular practice or training can yield highest benefits for methylation balance

Principles of a Methylation Food Plan



- Nutritionally replete and rich in methylation nutrients
- Anti-inflammatory
- Low-glycemic
- Antioxidant rich
- Phytonutrients as enzyme modulators and antioxidants
- Optimal hydration
- Supportive of detox processes (hydration, fiber, detox nutrients)
- Avoid caloric excess, consider caloric restriction

Principles of a Methylation Food Plan

- Avoid folic acid-fortified foods
- Avoid/minimize alcohol
- Minimize AGE formation (advanced glycation end products)
- Minimize added sugars
- Avoid foods from animals raised with antibiotics, hormones
- Avoid high-mercury fish including tuna, King mackerel, shark and swordfish
- Avoid plastic food and beverage containers

Methylation Nutrients Through Food

- Cochrane Systematic Review: Food-sourced folate has a protective effect on breast cancer risk[1]
- Higher food folate intake associate with lower risk of sex-hormone receptor-negative breast cancer in premenopausal women[2]
- No known adverse effects from food folate and methylation nutrients, as part of a healthy, balanced diet

[1]Chen et al., *Br. J. Cancer*, vol. 110, no. 9, pp. 2327–38, May 2014.

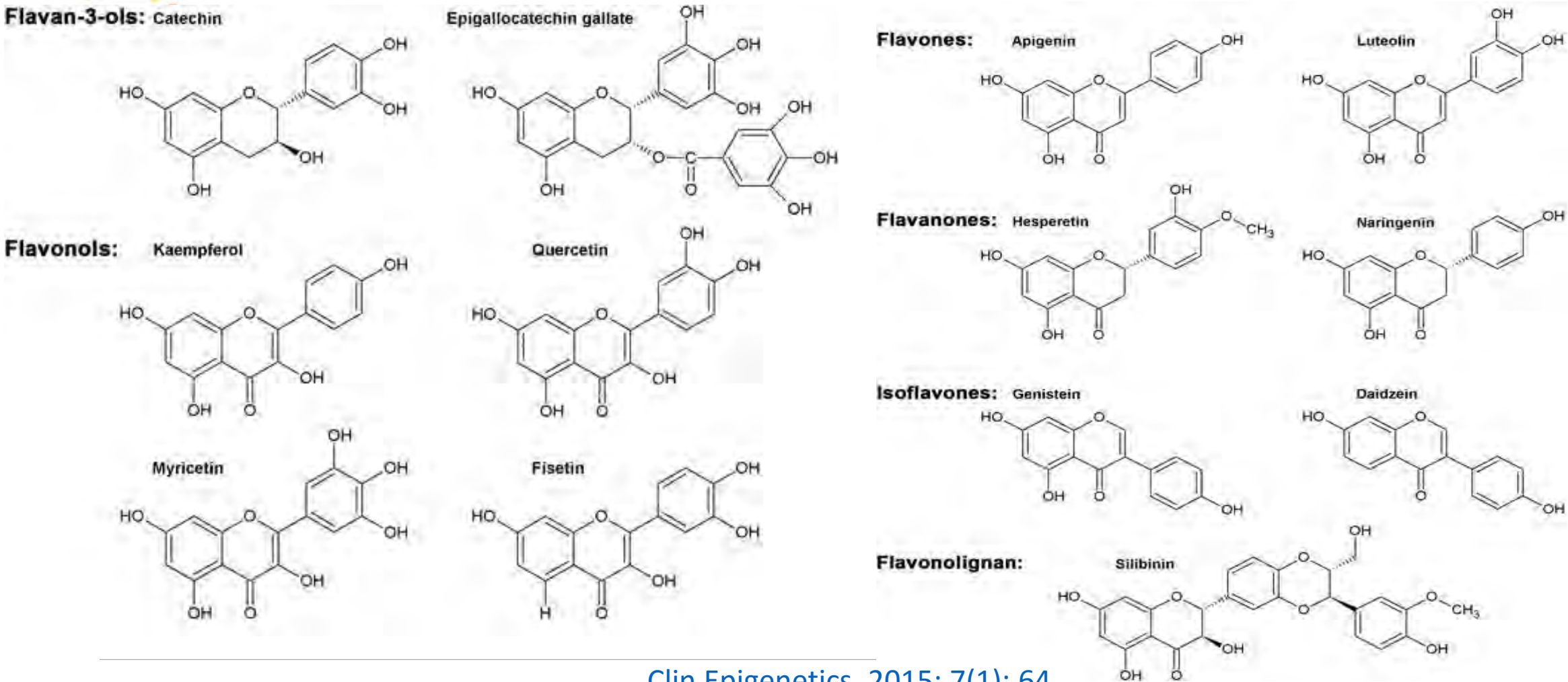
[2]de Batlle et al., *J. Natl. Cancer Inst.*, vol. 107, no. 1, p. 367, Jan. 2015.

Methylation “Adaptogens”

- Phytonutrients such as epigallocatechin and genistein reverse hypermethylation (and silencing) of tumor suppressor genes
- Anthocyanins suppress DNMT1 to reactivate tumor suppressor genes
- D3 and retinoic acid regulate DNMT enzymes
- DNMT regulators: curcumin, ellagic acid, lycopene, quercetin, resveratrol, rosmarinic acid, sulforaphane and more.

Fang et al., 2005; Lu et al., 2006; Stefanska et al., 2012; Szarc vel Szic et al., 2010

Epigenetically Active Flavonoids



Clin Epigenetics. 2015; 7(1): 64.

Intermittent Fasting

Coupled with lower carbohydrate diet, an extended nighttime fast (such as by completing all food intake by 7pm) that stimulates low ketone production may have protective effects on the epigenome and counteracts inflammation.

Kaelin et al., *Cell*, vol. 153, no. 1, pp. 56–69, Mar. 2013.

Lim et al., *PLoS One*, vol. 6, no. 9, p. e24620, Jan. 2011.

Yuom et al., *Nat. Med.*, vol. 21, no. 3, pp. 263–9, Feb. 2015.

Alcohol and Methylation

Alcohol produces unfavorable DNA methylation patterns, may interfere with SAMe activity and impedes folate metabolism including via inhibition of MTR enzymes

Hardy & Tollefsbol, *Epigenomics*, vol. 3, no. 4, pp. 503–18, Aug. 2011.

Yuom et al., *Nat. Med.*, vol. 21, no. 3, pp. 263–9, Feb. 2015.

Pissios et al., *Mol. Metab.*, vol. 2, no. 3, pp. 306–13, Jan. 2013.

Varela-Rey et al., *Alcohol Res.*, vol. 35, no. 1, pp. 25–35, Jan. 2013.

Curr Opin Clin Nutr Metab Care. 2013 Jan;16(1):102-8. doi: 10.1097/MCO.0b013e32835ad2ee.

The nutritional burden of methylation reactions.

Bertolo RF[1], McBreairty LE.

Author information

[1]Department of Biochemistry, Memorial University of Newfoundland, St John's, Newfoundland and Labrador, Canada. rbertolo@mun.ca

Abstract

PURPOSE OF REVIEW: Methyl group metabolism is a metabolically demanding process that has significant nutritional implications.

d methionine can
scusses the

roportion of the
y provision could
synthesis is
nocysteinemia

ions are

upregulated. These situations can impact methionine availability for protein synthesis, which can reduce growth. The methionine requirement can likely be spared by methyl donor and methylated product supplementation.

Recent evidence has clearly demonstrated that transmethylation reactions can consume a significant proportion of the flux of methionine. **In particular, synthesis of creatine and phosphatidylcholine consume most methyl groups and their dietary provision could spare methionine**.

Importantly, methionine can become limiting for protein and phosphatidylcholine synthesis when creatine synthesis is upregulated.

Other research has shown that betaine and choline seem to be more effective than folate at reducing hyperhomocysteinemia and impacting cardiovascular outcomes suggesting they may be limiting.

Methylation Superfoods

Beets
Spinach
Sea vegetables
Daikon radish
Shiitake

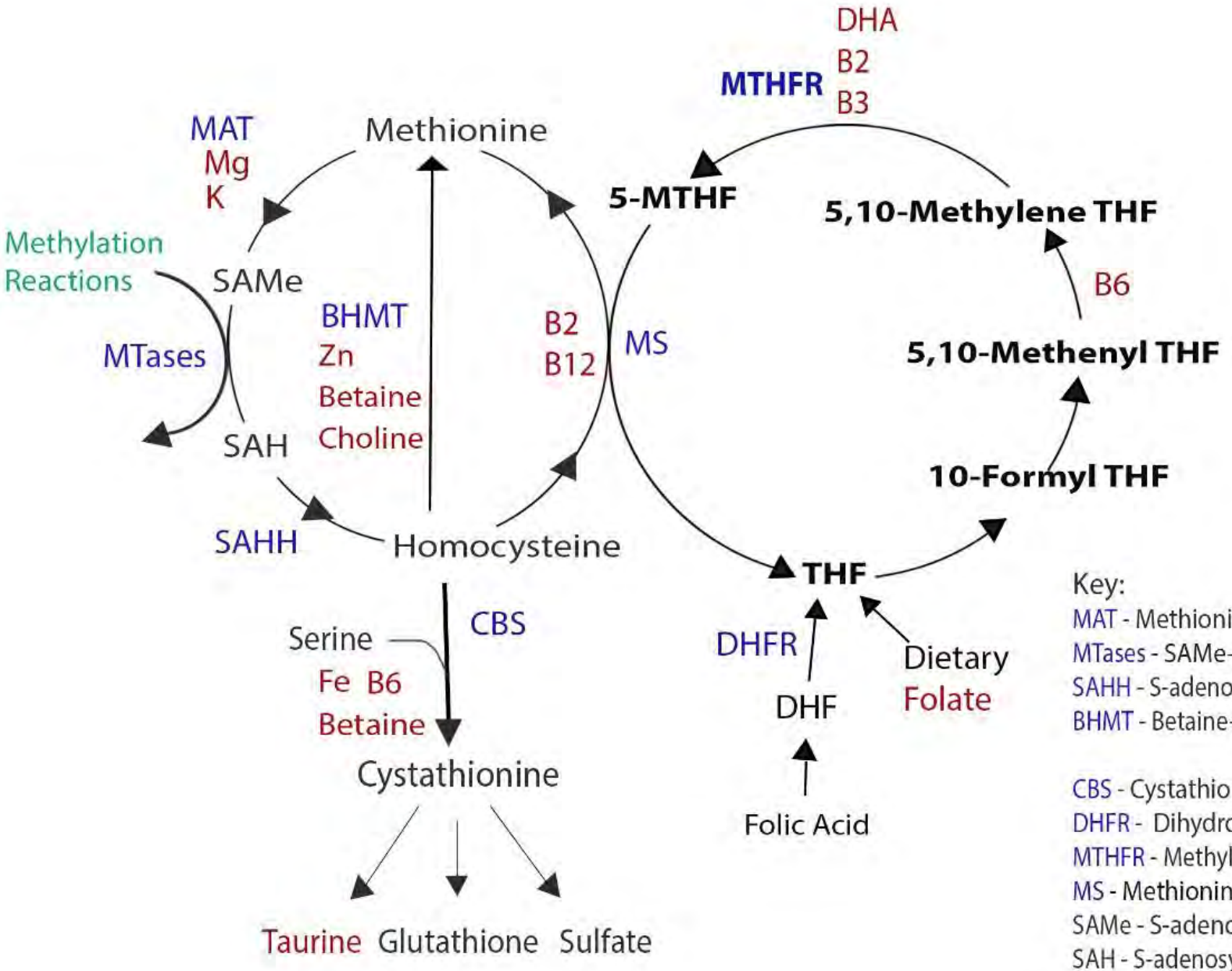
Salmon
Fish roe
Whitefish
Oysters
Eggs

Pumpkin seeds
Sesame seeds
Sunflower seeds
Liver

More Helpful Methylation Foods

- Sun-dried tomatoes
- Artichokes
- Asparagus
- Lambsquarters
- Mustard greens
- Turnip greens
- Leeks
- Okra
- Garlic
- Horseradish
- Fish
- Meats
- Nuts
- Seeds
- Spices
- Herbs
- Cocoa
- Fermented soy
- Beans and legumes
- Whole grains: amaranth, buckwheat, bulgur, kamut, quinoa, oats, dark rye, spelt, teff
- Blackstrap molasses

Nutrient cofactors and allosteric activators in methylation pathways



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
MTHFR - Methylenetetrahydrofolate reductase
MS - Methionine synthase
SAMe - S-adenosyl methionine
SAH - S-adenosyl-L-homocysteine
THF - Tetrahydrofolate
DHF - Dihydrofolate
5-MTHF - L-5-methyltetrahydrofolate

Creating A Methylation Food Plan

Category	Eat this…	Not this…
Vegetables and fruits	Red: apples (with skin), **BEETS**, bell peppers, blood oranges, cranberries, cherries, grapefruit (pink), goji berries, grapes, onions, plums, pomegranate, radicchio, radishes, raspberries, strawberries, sweet red peppers, rhubarb, rooibos tea, tomato (including **sun-dried tomatoes**), watermelon. Orange: apricots, bell peppers, cantaloupe, carrots, mango, nectarine, orange, papaya, persimmons, pumpkin, squash (acorn, butternut, winter), sweet potato, tangerines, turmeric, yams. Yellow: apple, Asian pears, banana, bell peppers, corn, ginger root, lemon, millet	Deep-fried vegetables. Potato chips, fries, processed vegetable snacks.

Table continues across all food categories…

Nutrient	Sample Menu 1 (Daily Average)	Sample Menu 2 (Daily Average)	RDA (adult male/female)
Folate	625 mcg	626 mcg	400/400 mcg DFE[1]
Folic acid	0 mcg	0 mcg	400/400 mcg DFE[1]
Vitamin B12	4.8 mcg	5.6 mcg	2.4/2.4 mcg
Betaine	321 mg	233 mg	-
Choline	455 mg[2]	414 mg[2]	550/425 mg
Riboflavin (Vitamin B2)	1.8 mg	1.9 mg	1.3/1.1 mg
Niacin (Vitamin B3)	19 mg	22 mg	16/14 mg
Vitamin B6	2.7 mg	2.8 mg	1.3/1.3 mg
Zinc	13.4 mg	13.9 mg	11/8 mg
Magnesium	605 mg	569 mg	420/320 mg
Omega 3 fatty acids	5.3 g	4.9 g	-
Total calories	1792 kcal	1743 kcal	-
% calories from carbohydrates	35%	30%	-
% calories from fats	47%	52%	-
% calories from protein	18%	18%	-

7-day Menu Plans with Nutrient Calculations

40+ recipes

Options:

Gluten-free

Dairy-free

Paleo

*Choline values underrepresented since many foods in the USDA database have not been evaluated for choline content

Gabe, 55 YO Male

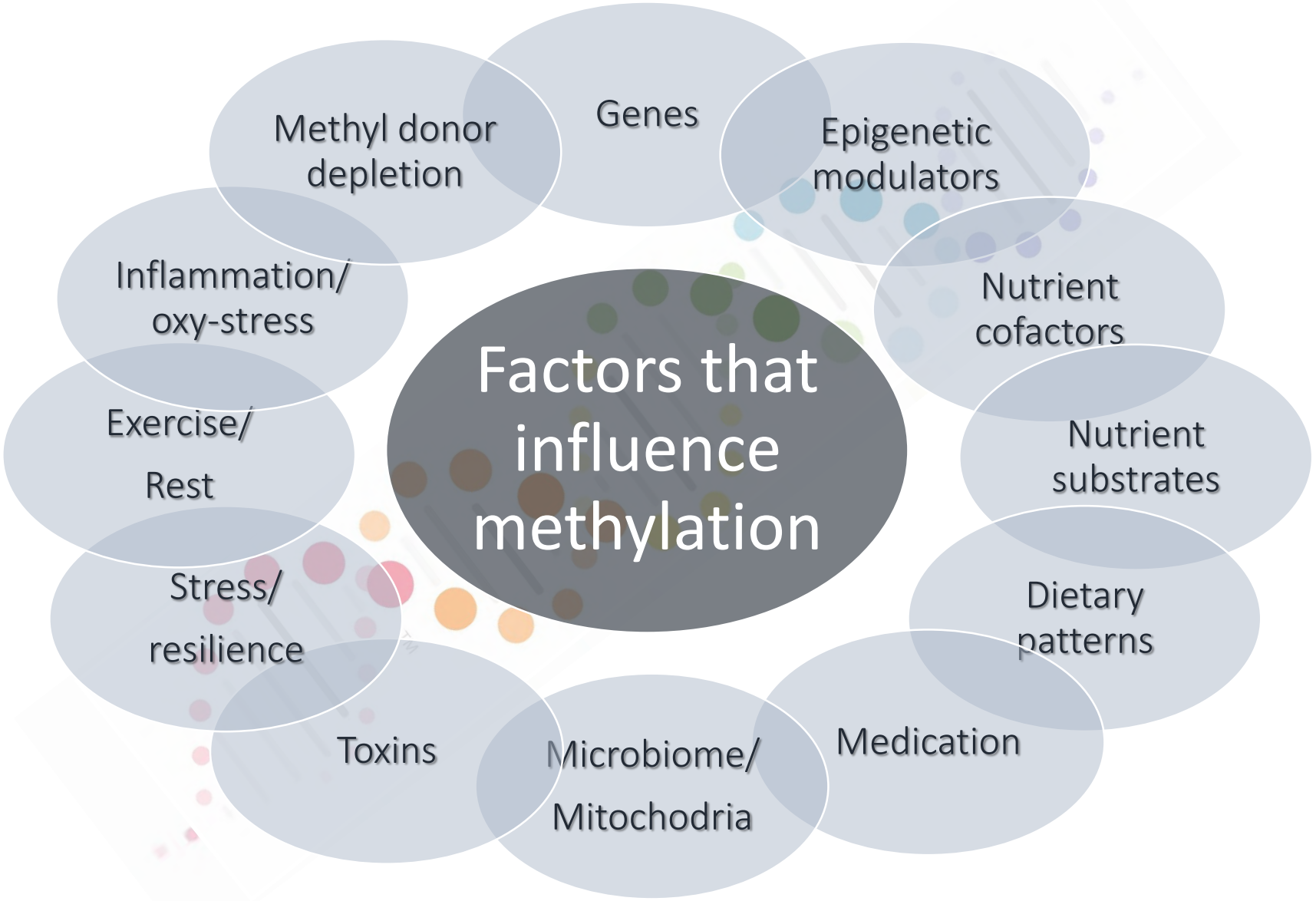
Dx: Mycotoxin exposure, Sjogren's. CC: Myalgia

- Methyl donors and many supplements significantly worsen symptoms
- Select labs
  - Baseline homocysteine 14.9
  - Serum B12 350
  - MMA NL
  - BHMT -/- MTHFR -/- COMT V158M +/-
- Our MDL plan:
  - Stress reduction: Fisher Wallace CES, Epsom salts baths, daily meditation
  - Exercise: 5x/week, 30-45 min, rowing & weights
  - Diet: Methylation Protocol—Romilly
  - Detoxification: IQ HEPA filtration
- Outcome discussion

Gabe, 55 YO Male

Dx: Mycotoxin exposure, Sjogren's. CC: Myalgia

- Dietary focus
  - High food-based methylation nutrients (Methylation Menu Plan) coupled with GFCF, lower FODMAPs (SIBO – inflammation), and 'detox' foods
    - Emphasis on high quality proteins (grass-fed/organic meats, low-mercury wild fish, organic eggs), dark leafy greens, beets (including beet powder), sea vegetables, nuts and seeds, herbs and spices
    - Handouts on low mercury fish, freezing vegetables/meals
  - Reduce food-related toxicity: organic, minimize plastic packaging, no microwaving in plastic, avoid food additives
  - Hydration
- Initial temporary increase in myalgia but moved through without incident
- After 1 month on program, pain had lessened, homocysteine trending down at 11.7. Motivated to continue.


Factors that influence methylation
Genes
Methyl donor depletion
Epigenetic modulators
Inflammation/ oxy-stress
Nutrient cofactors
Exercise/ Rest
Nutrient substrates
Stress/ resilience
Dietary patterns
Toxins
Microbiome/ Mitochodria
Medication

Supporting Methylation Through Diet and Lifestyle

- A safer, more nuanced way to support the homeodynamic balance of methylation activity
- How we use dietary and lifestyle support in clinical practice:
  - Alongside cautious/cyclical folate and methylation nutrient supplementation to enhance efficacy
  - As an alternative intervention for individuals who do not tolerate methyl donor supplementation
  - As a stand-alone intervention
  - Integrated with other needed non-methylation interventions

Thank You!

Full Methylation Diet and Lifestyle program available via **eBook**, at www.drkarafitzgerald.com/practitioners/eBook.
Use the following code for a 10% discount: BNI10

Get the latests methylation info through our **monthly professional and consumer newsletters** and through **Facebook, Twitter and Instagram**.