Epigenetics and the Aging Brain
Epigenetics and the Aging Brain

• The human brain - anatomy and function
• The aging brain
• The Alzheimer’s brain
• Epigenetics
• Nutrition and Brain Health
Epigenetics

- Chromatin – a conglomerate of protein and DNA
- Compaction of our genome is essential due to its enormous length
- Small modifications of chromatin have local and global effects on the availability of genetic information
- Many extrinsic influences impose chromatin modifications
Epigenetic Modifications
Epicatechin  Genistein  Resveratrol  Catechin  Curcumin

Green tea  Soy  Grape  Cocoa  Curcuma
Epigenetic story time


Genetically identical! What gives?
Nutritionally derived phenotype

Novel Major Royal Jelly Proteins: reproductive nutrients

Phenyl butyrate: epigenetic HDAC inhibitor

Chronic inflammation: Common denominator and likely precursor to disease

Nature or nurture: Let food be your epigenetic medicine in chronic inflammatory disorders

Katarzyna Szarc vel Szcic\textsuperscript{a,b}, Matladi N. Ndlovu\textsuperscript{a,c}, Guy Haegeman\textsuperscript{a}, Wim Vanden Berghe\textsuperscript{a,b,*}

Biochemical Pharmacology 80 (2010) 1816–1832
Epigenetic principles and mechanisms underlying nervous system functions in health and disease

Mark F. Mehler

Institute for Brain Disorders and Neural Regeneration, Departments of Neurology, Neuroscience and Psychiatry and Behavioral Sciences, The Rose F. Kennedy Center for Research in Intellectual and Developmental Disabilities and The Einstein Cancer Center, Albert Einstein College of Medicine, Bronx, NY, USA

ABSTRACT

Epigenetics and epigenomic medicine encompass a new science of brain and behavior that are already providing unique insights into the mechanisms underlying brain development, evolution, neuronal and network plasticity and homeostasis, senescence, the etiology of diverse neurological diseases and neural regenerative processes. Epigenetic mechanisms include DNA methylation, histone modifications, nucleosome repositioning, higher order chromatin remodeling, non-coding RNAs, and RNA and DNA editing. RNA is centrally involved in directing these processes, implying that the transcriptional state of the cell is the primary determinant of epigenetic memory. This transcriptional state can be modified not only by internal and external cues affecting gene expression and post-transcriptional processing, but also by RNA and DNA editing through activity-dependent intracellular transport and modulation of RNAs and RNA regulatory supercomplexes, and through trans-neuronal and systemic trafficking of functional RNA subclasses. These integrated processes promote dynamic reorganization of nuclear architecture and the genomic landscape to modulate functional gene and neural networks with complex temporal and spatial trajectories. Epigenetics represents the long sought after molecular interface mediating gene-environmental interactions during critical periods throughout the lifecycle. The discipline of environmental epigenomics has begun to identify combinatorial profiles of environmental stressors modulating the latency, initiation and progression of specific neurological disorders and more selective disease biomarkers and graded molecular responses to emerging therapeutic interventions. Pharmacoepigenomic therapies will promote accelerated recovery of impaired and seemingly irrevocably lost cognitive, behavioral, sensorimotor functions through epigenetic reprogramming of endogenous regional neural stem cell fate decisions, targeted tissue remodeling and restoration of neural network integrity, plasticity and connectivity.

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<table>
<thead>
<tr>
<th>Drugs</th>
<th>Epigenetic effect</th>
<th>Description</th>
<th>Clinical trials</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>DNMT inhibitors</td>
<td>5-azacytidine; a chemical analogue of cytidine that affects DNA methylation as a false substrate</td>
<td>Phases I, II and III: myelodysplastic syndromes such as leukemia</td>
<td>[60]</td>
</tr>
<tr>
<td>Decitabine</td>
<td>DNMT inhibitors</td>
<td>5-aza-2’-deoxycytidine, a chemical analogue of cytidine that affects DNA methylation as a false substrate</td>
<td>Phases I, II and III: myelodysplastic syndromes such as leukemia, cervical, and non-small-cell lung cancer</td>
<td>[60]</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>HDAC inhibitors</td>
<td>Cyclic tetrapeptide</td>
<td>Phases I and II: hematological tumors such as leukemia and lymphoma</td>
<td>[78,79]</td>
</tr>
<tr>
<td>Phenylbutyrate</td>
<td>HDAC inhibitors</td>
<td>Aliphatic acid</td>
<td>Phases I and II: hematological tumors such as leukemia and lymphoma and colorectal cancer</td>
<td>[78,79]</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>HDAC inhibitors</td>
<td>Aliphatic acid</td>
<td>Phase I: hematological tumors such as leukemia and lymphoma</td>
<td>[78,79]</td>
</tr>
<tr>
<td>Suberoylanilide</td>
<td>HDAC inhibitors</td>
<td>Hydroxamic acid</td>
<td>Phases I and II: hematological tumors, such as leukemia and lymphoma, solid tumors</td>
<td>[78,79]</td>
</tr>
<tr>
<td>hydroxamic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resveratrol</td>
<td>SIRT1 activator</td>
<td>A natural compound enriched in grapes and red wine</td>
<td>Phase I and II: diabetes, obesity, Alzheimer’s disease and cancers</td>
<td>[118,119]</td>
</tr>
<tr>
<td>Genistein</td>
<td>Inhibitor of both DNMTs and HDACs</td>
<td>Active epigenetic diet found in soybean products</td>
<td>Preclinical: diabetes and cancer</td>
<td>[61,63,122,123]</td>
</tr>
<tr>
<td>EGCG</td>
<td>Inhibitor of both DNMTs and HDACs</td>
<td>Active epigenetic dietary compound enriched in green tea</td>
<td>Phase I: diabetes, cardiovascular disease and cancer</td>
<td>[61,62,124,125]</td>
</tr>
<tr>
<td>Sulforaphane</td>
<td>HDAC inhibitor</td>
<td>Active epigenetic dietary compound enriched in broccoli sprouts</td>
<td>Preclinical</td>
<td>[80,121]</td>
</tr>
</tbody>
</table>

*DNMT, DNA methyltransferase; HDAC, histone deacetylase; SIRT1, Sir2 homolog 1; EGCG, epigallocatechin gallate.
Bioactive nutrient components influence human epigenome

Inhibition of DNMT/Nrf2 Pathway: **Anticancer**

- Anti-estrogenic effect: Inhibit DNMT and HDAC
- Anti-breast cancer

Anti-inflammatory

- Inhibits expression of iNOS, COX-2, and NF-κB via Sirt1 Pathway

Anti-inflammatory

- Reduces peripheral DNA methylation: Pro-cancer OR protects against CVD

- Decrease HDAC, HATs DNMTs effects: Anti-cancer

**Vanden Berghe et al. 2012; Tammen et al. 2013**
Aging and Caloric Restriction

Only intervention to extend life span for humans
Sirtuins – Longevity and Health

Diagram showing the functions of SIRT1, including neuroprotection, cardioprotection, and effects on insulin secretion, adipogenesis, gluconeogenesis, and energy expenditure. The diagram also highlights SIRT activating compounds (resveratrol), SIRT inhibitors (nicotinamide, sirtinol, others), and the role of UCP-2, NFκB, PPARγ, PGC-1α, and BAT (brown adipose tissue) in these processes.

Chemical structures of Butein, Quercetin, and Resveratrol are also shown.
Epigenetic regulation of caloric restriction in aging

Yuanyuan Li\textsuperscript{1,3*}, Michael Daniel\textsuperscript{1} and Trygve O Tollefsbol\textsuperscript{1,2,3,4,5}

Table 1 Summary of aging-related diseases affected by caloric restriction in experimental animal models and clinical trials\textsuperscript{*}

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Findings</th>
<th>Rodents</th>
<th>Nonhuman primates</th>
<th>Humans</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>CR prevents a broad range of cancer incidences, including breast and gastrointestinal cancer.</td>
<td>Y</td>
<td>Y</td>
<td>Y/?</td>
<td>[17,13,23]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>CR improves glucose homeostasis and prevents diabetes.</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>[18,13,23,24]</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>CR lowers blood pressure and favorably alters lipid profile, resulting in significantly reducing the risk of cardiovascular disease and related complications.</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>[19,13,22-24]</td>
</tr>
<tr>
<td>Neurodegenerative diseases</td>
<td>CR reduces aging-associated neuronal loss and neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease.</td>
<td>Y</td>
<td>Y</td>
<td>Y/?</td>
<td>[20,13,23]</td>
</tr>
<tr>
<td>Immune deficiencies</td>
<td>CR delays the onset of T-lymphocyte-dependent autoimmune diseases.</td>
<td>Y</td>
<td>Y/?</td>
<td>Y/?</td>
<td>[21]</td>
</tr>
</tbody>
</table>

\textsuperscript{*}CR, caloric restriction; Y, CR has effects on relevant physiological changes; Y/?, not resolved or not reported.

Li et al. BMC Medicine 2011, 9:98
http://www.biomedcentral.com/1741-7015/9/98
Dietary histone deacetylase inhibitors:
From cells to mice to man

Roderick H. Dashwood\textsuperscript{a,} and Emily Ho\textsuperscript{b}

Abstract

Sulforaphane (SFN) is an isothiocyanate found in certain vegetables, and specifically in broccoli sprouts. This anticarcinogen was first identified as a potent inducer of detoxifying enzymes in the liver, but it also acts in tumors. In animal models, SFN inhibits the activation of the NF-κB transcription factor and the expression of COX-2. In human prostate cancer, SFN inhibits the growth of tumors in mouse models, with evidence for altered levels of COX-2. In human subjects, a single ingestion of 68 g broccoli sprouts increased the activity of COX-2 in peripheral blood mononuclear cells 3-6 h after consumption.

<table>
<thead>
<tr>
<th>Dietary agents</th>
<th>Structure</th>
<th>Epigenetic effect on Cancer</th>
<th>Picture of the sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin (Parsley)</td>
<td><img src="image1" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Fang et al. 2007)</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Alpinia zerumbet (Zerumbet catappa)</td>
<td><img src="image3" alt="Structure" /></td>
<td>HDAC inhibitor (Lee et al. 2012; Drenth et al. 2008)</td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>Curcumin (Turmeric)</td>
<td><img src="image5" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Lee et al. 2009; Fang et al. 2007; Po and Parmeck 2010; HDAC and HAT inhibitor (Chen et al. 2009; Li et al. 2009; Kang et al. 2008; Cai et al. 2009; Brinkhuis et al. 2004))</td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>Epigallocatechin-3-gallate (EGCG) (Green tea)</td>
<td><img src="image7" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Fang et al. 2005; Kato et al. 2008; Sugdy et al. 2010; Lee et al. 2005)</td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>Genistein (Soybean)</td>
<td><img src="image9" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Majid et al. 2008; Kakuno et al. 2005; Fang et al. 2008; Li et al. 2009)</td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td>Lycopene (Tomato)</td>
<td><img src="image11" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Majid et al. 2008; Kakuno et al. 2005; Fang et al. 2008; Li et al. 2009; King-Batson et al. 2008; Majid et al. 2008)</td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>Resveratrol (Red grapes)</td>
<td><img src="image13" alt="Structure" /></td>
<td>DNA methyltransferase inhibitor (Papoutsis et al. 2010; Stelanska et al. 2010)</td>
<td><img src="image14" alt="Image" /></td>
</tr>
<tr>
<td>Silymarin (Milk thistle)</td>
<td><img src="image15" alt="Structure" /></td>
<td>SIRT1 activator (Eebergen et al. 2008; Wang et al. 2008; Beatty et al. 2009)</td>
<td><img src="image16" alt="Image" /></td>
</tr>
</tbody>
</table>
Epigenetics and Brain Health

Human Micro Biome
Our gut bacteria play a key role in the bioavailability of botanicals
Healthy botanicals are conducive for a health gut microbiota

Blood Brain Barrier Crossing
Most compounds to not readily cross from the periphery into the brain
Many botanicals defy chemistry and physiology
Polyphenols enter the CNS

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>Amount (μg/g feed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthocyanin</td>
<td></td>
</tr>
<tr>
<td>Delphinidin</td>
<td>98.2</td>
</tr>
<tr>
<td>Cyanidin</td>
<td>18.0</td>
</tr>
<tr>
<td>Petunidin</td>
<td>42.6</td>
</tr>
<tr>
<td>Peonidin</td>
<td>3.8</td>
</tr>
<tr>
<td>Malvidin</td>
<td>104.6</td>
</tr>
<tr>
<td>Flavanol</td>
<td></td>
</tr>
<tr>
<td>Monomer</td>
<td>65.7</td>
</tr>
<tr>
<td>Dimer</td>
<td>52.3</td>
</tr>
<tr>
<td>Procyanidin</td>
<td>35.9</td>
</tr>
</tbody>
</table>

B

Concentration (nmol/g tissue): Hippocampus, Cortex

Concentration (μM): Plasma
# Botanical phenolics and brain health

**Albert Y. Sun**\(^1,2\), **Qun Wang**\(^1\), **Agnes Simonyi**\(^3\), and **Grace Y. Sun**\(^2,3\)

## Effects of common botanicals on AD, PD and stroke

<table>
<thead>
<tr>
<th>Polyphenol/plant name</th>
<th>Model</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blueberry</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Joseph et al. 2003)</td>
</tr>
<tr>
<td>EGCG</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Rezai-Zadeh et al. 2005)</td>
</tr>
<tr>
<td>Garlic</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Chauhan 2003)</td>
</tr>
<tr>
<td></td>
<td>TgCRND8 mice</td>
<td>+</td>
<td>(Chauhan &amp; Sandoval 2007)</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Stackman et al. 2003)</td>
</tr>
<tr>
<td></td>
<td>TgAPP/PS1 mice</td>
<td>+</td>
<td>(Garcia-Alloza et al. 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Tchantchou et al. 2007)</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Chen et al. 2006)</td>
</tr>
<tr>
<td>Ginsenoside Rb1 or M1</td>
<td>Aβ infusion (i.c.v.) mice</td>
<td>+</td>
<td>(Tohda et al. 2004)</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>Tg2576 mice</td>
<td>+</td>
<td>(Hartman et al. 2006)</td>
</tr>
</tbody>
</table>

Frontline immunoepigenetic diet?

Silibine: HAT, HDACi

Folate: SAMs

Fistein: SIRT1a

Diallyl sulfide: HDACi

Theophylline: HDACi

Quercetin: HDACi, DNMTi, SIRT1a

Szarc vel Szic et al. 2010
Blueberries - Cognition - Aging

Morris Water Maze:
A test system to assess spatial memory

Blueberries - Cognition - Aging

Krikorian R et al., (2010) Blueberry Supplementation Improves Memory in Older Adults. J. Agric. Food Chem. DOI:10.1021/jf9029332
Rod Like Actin Inclusions

- Inflammatory Cytokines
- Amyloid beta
- HIV gp120

- NADPH oxidase
- Prion Protein
- Oxygen Radicals
- Actin Inclusions

Spring 2017

OLLI
Nonpolar BB Extracts Blunt Inflammatory and Oxidative Stress

Whole BB extract

Simple physicochemical property (polarity)

Bioassay

Blueberry Botanicals block formation actin inclusion

![Graph showing percent neurons with rods](image)

- Untreated
- TNFα
- Aβd/t

- Ctrl
- Veh
- 0.5
- 1.5
- 5
- 15
- Veh
- wo
- no
- +UA

% Neurons with a rod length of X

X = rod length (pixels)

- UA 0 min
- UA 10 min
- UA 20 min
- UA 40 min
- UA 60 min

Spring 2017

OLLI
Cereon Biotechnology develops epigenetic intervention and prevention strategies to rescue or protect cognitive health by blunting inflammatory and oxidative stress in the aging and diseased central nervous system through nutraceuticals obtained from the pharmacopia of the boreal forest and arctic tundra and novel proprietary derivative compounds.

www.cereonbiotech.com
Epigenetics and Gene Activation for Improved Health and Longevity

Excercise
- BDNF

Nutritional Factors
- Calorie Restriction
- Mediterranean Diet
- Polyphenols

Signaling molecules

Transcription factors

Environment
- Clean air, water and soil
- No smoking

Emotional Health
- Religion
- Meditation
- Spirituality

Anti-Inflammatory
Anti-oxidant, Anti-mutation
Meditate and change your genome!

- Less of HDAC9.
- More histone acetylation and less histone methylation.
- Lower levels of certain stress related genes.

Meditation Increases Telomerase Activity and Improves Mental Health

*Study examines the positive impact of yogic meditation on caregivers of dementia sufferers*
United States
Guatemala
Chad
What should I do (i.e. eat) ?

• Focus on overall pattern rather than nutrients (Mediterranean Diet)
• Don’t be afraid of saturated fats (10% daily)
• Increase omega-3 fats (plant oils, fish)
• Reduce refined carbohydrate intake
• Reduce sugars (HFCS)
• Avoid trans fats
• Promote fruit and vegetables
• Go NUTS
• Use lots of herbs
• Chocolate and alcohol in moderation YES
A useful help

Choose MyPlate.gov
What I do

- Obtain organic food
- Processes your food yourself
- Think rainbow
- Lower your glycemic index
- Adhere to the Mediterranean diet
- Think meat/fish as “the side order”
- Exercise (endurance, flexibility, strength)
- Mental activity (anything other than iPhone)
- Be happy
Thank you!