Autism as a Multifactorial Disease

Dr. Amy A. Yasko
Ph.D., ND, NHD, AMD, HHP, FAAIM
“What do schizophrenia, diabetes and autism have in common? The answer is that many different factors act together to influence their development. As well as fundamentals like age and gender, other genetic and environmental factors…may play a role in the onset of these so-called multifactorial diseases.”

*Multifactorial Diseases: Choose your targets*
*BIOPEOPLE, Summer 2004*
Multifactorial Disease

- Environmental
- Genetic
- Infectious
- Stress

DISEASE
Autism as a Multifactorial Disease

- Multifactorial Diseases are caused by a combination of factors acting together. This can include infections and environmental events occurring in genetically susceptible individuals. Basic parameters like age and gender, along with other genetic and environmental factors, play a role in the onset of determining vulnerability to these diseases.

- What we currently call "autism" is actually a medical condition caused by infections and environmental events occurring in genetically susceptible individuals. Infections would only lead to autism if they occur in individuals with the appropriate types of genetic susceptibility that render them vulnerable.

- The basis for this susceptibility in autism may result from single or multiple mutations in the methylation pathway, combined with complex interactions between thimerosal and this pathway. These imbalances in methylation lay the appropriate groundwork for the further assault of environmental and infectious agents to result in autism.

- As a result of the decreased activity in the methylation pathway, there is a shortage of methyl groups in the body for a variety of important functions.
• All of these changes, when they occur in utero or in very young children, can alter brain development, and can also set up metabolic changes that cause ongoing compromise of brain function.

• The metabolically caused changes in brain function can, however, be treated if problems driving these metabolic changes are treated and corrected.

• This would suggest that autism is a medical condition associated with a defect in the methylation pathway, with brain and behavior changes that lead to observable autistic behaviors occurring as a downstream consequence of these medical abnormalities, and that it should be characterized as such.

• Continuing with this analogy, perhaps autism should be reclassified as a defect in methylation that results in neuroinflammatory disease.
IOM Report May 17, 2004

Immunization Safety Review: Vaccines and Autism
In recent years, a number of chronic diseases have been linked, in some cases definitively, to an infectious etiology: peptic ulcer disease with *Helicobacter pylori*, cervical cancer with several human papillomaviruses, Whipple's disease with *Tropheryma whippelii*, Lyme arthritis and neuroborreliosis with *Borrelia burgdorferi*, AIDS with the human immunodeficiency virus, liver cancer and cirrhosis with hepatitis B and C viruses, to name a few. The proven and suspected roles of microbes does not stop with physical ailments; infections are increasingly being examined as associated causes of or possible contributors to a variety of serious, chronic neuropsychiatric disorders and to developmental problems, especially in children.
Infectious Agents and Schizophrenia

• “Most cases of schizophrenia are caused by infections and other environmental events occurring in genetically susceptible individuals.”

• “Infections relating to schizophrenia occurring in this context would not...lead to disease in individuals who do not have the appropriate genetic susceptibility.”

• There was an association between infection with HSV2 and higher rates of schizophrenia.

• The authors found increased levels of antibodies to *Toxoplasma gondii* in individuals with recent onset schizophrenia.

On a related note:

• Parasitic infection impairs the immune response to the tetanus vaccine.
  (Infection and Immunity May 2004 )
Multifactorial Disease

- Environmental
- Genetic
- Infectious
- Stress
Prenatal Lead Exposure, -Aminolevulinic Acid, and Schizophrenia

Mark G.A. Opler,1 Alan S. Brown,1,2 Joseph Graziano,3 Manisha Desai,4 Wei Zheng,3 Catherine Schaefer,5 Pamela Factor-Litvak,6 and Ezra S. Susser2,6

1Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, New York, USA; 2New York State Psychiatric Institute, New York, New York, USA; 3Department of Environmental Health Sciences and 4Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA; 5Division of Research, Kaiser Permanente Health Care, Oakland, California, USA; 6Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, USA

Schizophrenia is a severe mental disorder of unknown etiology. Recent reports suggest that a number of environmental factors during prenatal development may be associated with schizophrenia. We tested the hypothesis that environmental lead exposure may be associated with schizophrenia using archived serum samples from a cohort of live births enrolled between 1959 and 1966 in Oakland, California. Cases of schizophrenia spectrum disorder were identified and matched to controls. A biologic marker of lead exposure, -aminolevulinic acid ( -ALA), was determined in second-trimester serum samples of 44 cases and 75 controls. -ALA was stratified into high and low categories, yielding 66 subjects in the high category, corresponding to a blood lead level (BPb) ≥ 15 µg/dL, and 53 in the low category, corresponding to BPb < 15 µg/dL. Using logistic regression, the odds ratio (OR) for schizophrenia associated with higher -ALA was 1.83 [95% confidence interval (CI), 0.87-3.87; p = 0.1]. Adjusting for covariates gave an OR of 2.43 (95% CI, 0.99-5.96; p = 0.051). This finding suggests that the effects of prenatal exposure to lead and/or elevated -ALA may extend into later life and must be further investigated as risk factors for adult psychiatric diseases.

BH$_2$ is inhibited by lead, leading to BH$_4$. BH$_4$ can be converted into serotonin and dopamine.
Glutamic acid \rightarrow 5 \text{ amino levulinic acid} \rightarrow \text{heme}

- Inhibited by lead
- Lead increases the level of glutamate
- Red blood cells
- Cytochromes
Effect of Lead on Gaba Release

Braga MF, Pereira EF, Albuquerque EX.
Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore,

• Thus, it is most likely that the neurotoxic effects of Pb2+ in the mammalian brain involve a decrease in release of neurotransmitters.

• Given that synaptic activity is a key mechanism for the establishment of stable synaptic connections early in the development, it is possible that, by interfering with spontaneous transmitter release, Pb2+ has lasting effects on neuronal maturation and plasticity.
What’s in a name?

• From 1800 to 1938 autism was referred to as childhood schizophrenia
• Should it now be characterized as NeuroInflammatory Disease?
Atherosclerosis v.s. Autism

- Genetic
  - MTHFr
- Infectious
  - Chlamydia pneumonia
  - Streptococcus
- Stress
  - Inflammatory Mediators
  - Glutamate
    - Improper Calcium Regulation
    - Improper CO₂ Regulation
- Environmental
  - Cholesterol
- Cardiovascular Inflammatory Disease

- Genetic
  - MTHFr
- Infectious
  - Viral: MMR, Herpes
  - Bacterial
- Stress
  - Inflammatory Mediators
  - Glutamate
    - Improper Calcium Regulation
    - Improper CO₂ Regulation
- Environmental
  - Heavy Metals
- Neuroinflammatory Disease
Glutamate is the gun.
Calcium is the bullet.
Glutamic Acid → Vitamin K → γ Carboxyglutamic Acid

- CO₂ build up / improper Ca++ regulation
- Increased risk of coronary artery calcification
- p38 MAP kinase inflammation pathway
Glutamate and Calcium

Glutamate → calcium flow into neurons

Calcium flow → nerve damage

Nerve damage → inflammation
Bacterial infection
Antibiotics
Lack normal flora
Pancreatic malfunction
Improper fat absorption

Stress

MAP38 Kinase

Cell death

Mg ↓, Ca ↑

IL6 ↑

Methylation

Myelination

Vit K ↓
Multifactorial Disease

- Environmental
- Genetic
- Infectious
- Stress

DISEASE
Cell : Cell Communication

RNA
Heal Your Body Naturally:

The Power of RNA

By Dr. Amy Yasko and Dr. Garry Gordon

A layman's guide to RNA and its use for optimal health.
Effect of **Nerve Calm RNA NutriSwitch™** on Excitotoxins

26 month old Female

Seizure Activity

![Graph showing seizure activity](chart.png)
The Effect of **Glucose Support RNA NutriSwitch™** on Glucose Levels

80 yr. old Male

Glucose Support RNA NutriSwitch

Fasting Glucose
Effect of **Health Foundation RNA NutriSwitch™**

Initial CRP = 14
Prednisone = 15 mg

CRP = 0
Prednisone = 0 mg

Graph showing the decrease in CRP levels from 3/28/02 to 10/15/02 after starting Health Foundation RNA NutriSwitch™.
Effect of Lipid Support RNA NutriSwitch™ Formula on Triglycerides

26 month old Female

Triglycerides

Start RNA NutriSwitch

Data points:
- 9/13/2003
- 9/17/2003
- 9/26/2003
- 10/1/2003
- 10/17/2003
- 10/23/2003
- 10/30/2003
- 12/16/2003
- 2/3/2004
- 3/8/2004
Effect of Lipid Support RNA NutriSwitch™ on Cholesterol
43 yr. old Male

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<tr>
<th>Date</th>
<th>Total Cholesterol</th>
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<td>Nov. 6, 2003</td>
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<td>Jan. 14, 2004</td>
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<tr>
<td>May 21, 2003</td>
<td>150</td>
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Effect of Lipid Support RNA NutriSwitch™ on LDL
43 yr. old Male
Effect of Lipid Support RNA NutriSwitch™ on Liver Enzymes

![Bar chart illustrating the effect of lipid support RNA NutriSwitch™ on liver enzymes compared to with statin drugs. The chart shows a decrease in ALT and AST levels when using lipid support RNA NutriSwitch™.](image-url)
The Effect of **Kidney Support**

**RNA Nutriswitch™**

![Bar Chart]

- **Start Kidney Nucleotides**
- **5/13/2002**
- **7/25/2002**

**Graph Details**

- **Y-axis**: BUN and Creatinine levels
- **Colors**: Green for BUN, Light Blue for Creatinine

**Comparison**

- Before: BUN = 16, Creatinine = 3
- After: BUN = 12, Creatinine = 2

Note: Data points are fictional for illustrative purposes.
The Effect of **Bowel Support RNA NutriSwitch™** on Intestinal Permeability

- Normal Range: 5-30
- Start Bowel Support NutriSwitch
- % Mannitol Recovery
The Effect of Prostate Plus RNA NutriSwitch™

Start Prostate Plus Nucleotides

PSA
Heal Your Body Naturally:

It Starts With Just One Drop

By Dr. Amy Yasko and Dr. Garry Gordon

Suggested programs used around the world for over 35 health conditions.
The Puzzle of Autism: Putting It All Together
A Guide to Transforming the Treatment Of Autism

For Parents and Physicians

Garry F. Gordon MD, DO, MD(H) and Amy Yasko PhD, ND, NHD, AMD, HHP, FAAIM
Thallium (ug/g Creatinine)

Safe Range: 1.1
Tungsten (ug/g Creatinine)

Safe Range: 1.5
Aluminum (ug/g Creatinine)

Safe Range: 60
Mercury (ug/g Creatinine)

Safe Range: 5
Safe Range: 5

Lead (ug/g Creatinine)
We have the same unique DNA in every cell in our body.
IF the IDENTICAL genetic information is in every cell in the body, what determines how different cells differentiate?
DNA

Transcription

RNA-1

Protein-1

Translation

RNA-2

Protein-2
By MODULATING the levels of RNA, one has the ability to SPECIFICALLY affect the levels of ANY protein in the body.
NATURALLY Occurring Regulatory Process

- Plants
- Bacteria
- Animals
HUMANS TYPICALLY EAT SEVERAL GRAMS OF NUCLEOTIDES IN THEIR DIET EACH DAY
<table>
<thead>
<tr>
<th></th>
<th>Adenine (mg/10 g)</th>
<th>Guanine (mg/100 g)</th>
<th>Hypoxanthine (mg/100 g)</th>
<th>Xanthine (mg/100 g)</th>
<th>Total purines (mg/100 g)</th>
<th>RNA (mg/100 g)</th>
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<tr>
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<td>74</td>
<td>61</td>
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<td>Beef kidney</td>
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<td>47</td>
<td>63</td>
<td>61</td>
<td>213</td>
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<td>16</td>
<td>38</td>
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<td>12</td>
<td>26</td>
<td>112</td>
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<td>78</td>
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<tr>
<td>Chicken heart</td>
<td>32</td>
<td>41</td>
<td>12</td>
<td>138</td>
<td>223</td>
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<td>Anchovies</td>
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<td>185</td>
<td>6</td>
<td>212</td>
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<td>Clams</td>
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<td>24</td>
<td>12</td>
<td>86</td>
<td>136</td>
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<td>Mackerel</td>
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<td>26</td>
<td>5</td>
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<td>Salmon</td>
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<td>80</td>
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<td>Sardines</td>
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<td><strong>Dried legumes</strong></td>
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<td>Garbanza bean</td>
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<td>Lentils</td>
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<td>51</td>
<td>15</td>
<td>42</td>
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<td>82</td>
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<td>16</td>
<td>222</td>
<td>306</td>
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<tr>
<td>Pinto bean</td>
<td>46</td>
<td>39</td>
<td>25</td>
<td>34</td>
<td>144</td>
<td>485</td>
</tr>
</tbody>
</table>
RNA CONTAINING FOODS CURRENTLY ON THE MARKET

Breast milk has been reported to contain 1-12 mg/dL of DNA and 10-60 mg/dL of RNA.

broken down into components:
Nucleotides & Ribose
RNA Nucleotides

Natural RNA (or DNA)
broken down

Nucleotides
Purines & Pyrimidines
+ Ribose

Allopathic Use of RNA

Synthetic RNA (or DNA)
Does not break down
According to the 1999 FDA Dietary Supplement Industry Report:

“Nucleic acids: large molecules that are encoded with genetic instructions... and the oral tablet and capsule forms are non-toxic.”
According to the FDA, “Introduced nucleic acids, in and of themselves, do not raise safety concerns. Thus, for example, the introduction of a gene encoding an anti-sense ribonucleic acid (RNA) would not raise concerns about either the gene or the anti-sense RNA. Any safety considerations would focus on the intended effects of the anti-sense RNA. Hence, continuing the example, if the anti-sense RNA were used to suppress an enzyme, then just as for any other method intended to suppress an enzyme, such as deletion or nonsense mutation, the metabolic effects on the host plant of such enzyme suppression should be considered at the conceptual stage of development and monitored, when appropriate and feasible.” …
...Furthermore, the Working Policy states that even the transfer of genetic material in the form of nucleic acids is not subject to FDCA Section 409 because “nucleic acids are present in the cells of every living organism, including every plant and animal.” Nucleic acids that are expressed in GRAS microbes, such as yeast are also GRAS.

Department of HHS FDA Docket No. 92N-0139.  
FSHN 101 Food Biotechnology.
RNA Nucleotides

The concept of the body requiring dietary nucleotides when “under stress”, or “limited nutrients” or “rapid growth” conditions could easily comprise many, if not all, of the chronic conditions that plague us today.
Inflammatory Mediators:
- COX2
- NFKB
- TNF
- LO

Glutamate Reactive Oxygen Species (ROS)

Lead amplifies excitotoxin damage

Nerve Calm RNA NutriSwitch™

Metals RNA NutriSwitch™ & EDTA

Inflammatory Mediators:
- COX2
- NFKB
- TNF
- LO

Health Foundation RNA NutriSwitch™ & Stress Foundation RNA NutriSwitch™
Autism as a Multifactorial Disease

Multifactorial Diseases are caused by a combination of factors acting together. This can include infections and environmental events occurring in genetically susceptible individuals. Basic parameters like age and gender, along with other genetic and environmental factors, play a role in the onset of determining vulnerability to these diseases. I have proposed (in my recently published book,"The Puzzle of Autism") that what we currently call "autism" is actually a medical condition caused by infections and environmental events occurring in genetically susceptible individuals. Infections would only lead to autism if they occur in individuals with the appropriate types of genetic susceptibility that render them vulnerable. I believe that the basis for this susceptibility in autism may result from single or multiple mutations in the methylation pathway, combined with complex interactions between thimerosal and this pathway. These imbalances in methylation lay the appropriate groundwork for the further assault of environmental and infectious agents to result in autism. While it is possible to envision a number of genetic mutations that would result in this underlying genetic susceptibility, so far specific mutations in one or both MTHFr alleles, as well as methionine synthase mutations have been found to be associated with autistic phenotypes. I suspect that the majority of cases of children who are autistic will be determined to contain homozygous or heterozygous mutations in the MTHFr C677T or A1298C alleles, in addition to potential defects elsewhere in this pathway. As a result of this decreased activity in the methylation pathway, there is a shortage of methyl groups in the body for a variety of important functions.
Methylation is related to neurotransmitter levels; methylation of intermediates in tryptophan metabolism can affect the levels of serotonin. Intermediates of the methylation pathway are also shared with the pathway involved in dopamine synthesis. Consequently, imbalances in the methylation pathway will also affect the neurotransmitter dopamine. In addition to its direct role as a neurotransmitter, dopamine is involved in methylating phospholipids in the cell membranes. Membrane fluidity is important for a variety of reasons including proper signaling of the immune system as well as protecting nerves from damage. The building blocks for DNA and RNA require the methylation pathway. Without adequate DNA and RNA it is difficult for the body to synthesize new cells. This would result in a decreased level of new T cell synthesis. De novo T cell synthesis is necessary to respond to viral infection, as well as for other aspects of the proper functioning of the immune system. T cells are necessary for antibody producing cells in the body (B cells) as both T helpers and T suppressors to appropriately regulate the antibody response. In addition, the decreased level of methylation can result in improper DNA regulation. DNA methylation is necessary to prevent the expression of viral genes that have been inserted into the body's DNA. Loss of methylation can lead to the expression of inserted viral genes. Proper levels of methylation are also directly related to the body's ability to both myelinate nerves and to prune nerves. Myelin is a sheath that wraps around the neuronal wiring to insulate and facilitate faster transmission of electrical potentials.
Without adequate methylation, the nerves cannot myelinate in the first place, or cannot remyelinate after insults such as viral infection or heavy metal toxicity. A secondary effect of a lack of methylation and hence decreased myelination is inadequate "pruning" of nerves. Pruning helps to prevent excessive wiring, or unused neural connections and reduces the synaptic density. Without adequate pruning the brain cell connections are misdirected and proliferate into dense, bunched thickets. All of these changes, when they occur in utero or in very young children, can alter brain development, and can also set up metabolic changes that cause ongoing compromise of brain function.

The metabolically caused changes in brain function can, however, be treated if problems driving these metabolic changes are treated and corrected. This would suggest that autism is a medical condition associated with a defect in the methylation pathway, with brain and behavior changes that lead to observable autistic behaviors occurring as a downstream consequence of these medical abnormalities. And that it should be characterized as such. An analogy can be made to the medical condition of cardiovascular disease. There too, a mutation in the MTHFr C677T allele establishes sets up an individual to be a genetically susceptible individual. The combination of infectious agents (IOM Report June 2004), the inflammatory cascade that is triggered as a result of infection, along with this genetic mutation and other environmental stressors leads to cardiovascular disease in individuals with the appropriate genetic background. Continuing with this analogy, perhaps autism should be reclassified as a defect in methylation that results in neuroinflammatory disease.

Dr. Amy Yasko Neurological Research Institute 2004
How Does Methylation Control Synthesis of Proteins?

One of the ways the cells control which genetic information they will use is to chemically modify the DNA. The illustration shows an enzyme (diagrammed in ribbons) adding methyl groups to some of the DNA (balls in the form of a double helix). This inactivates that part of the chromosome. It’s as if we were to put glue on the edges of some of the books in the library; those pages would become unavailable to readers.
CpG methylation, chromatin structure and gene silencing-a three-way connection.

EMBO J. 1998 Sep 1;17(17):4905-8. Razin A.

- There is a three-way connection between DNA methylation, gene activity and chromatin structure.
- Methylation plays a pivotal role in establishing and maintaining an inactive state of a gene by rendering the chromatin structure inaccessible to the transcription machinery.
Targeted Methylation

Introducing methylated DNA at specific genomic loci affects local histone acetylation.

By Jonathan Weitzman

Methylation of DNA at CpG dinucleotides represses gene transcription. Methylation plays an important role in development, imprinting, X-chromosome inactivation and tissue-specific gene expression, but the mechanisms of methylation-induced repression are still unclear. In the December Molecular and Cellular Biology, Schubeler et al. show that localized histone deacetylation can explain methylation-induced repression (Mol Cell Biol 2000, 20:9103-9112). The authors used an elegant technique called recombinase-mediated cassette exchange (RMCE) to introduce in vitro-methylated DNA at defined chromosomal positions. They used the Cre recombinase to insert methylated or unmethylated forms of the human β-globin gene promoter driving a green fluorescent protein (GFP) reporter gene. Methylation repressed GFP expression, and was stable in cells over at least 12 weeks in culture. Methylation did not affect DNA replication or global chromatin remodeling. However, methylation caused a hypoacetylation of histones H3 and H4 within the transgene. These observations support a model in which methylated DNA represses
Changes in DNA methylation profiles are common features of development and in a number of human diseases, such as cancer and imprinting disorders like Beckwith–Wiedemann and Prader–Willi/Angelman syndromes. This suggests that DNA methylation is required for proper gene regulation during development and in differentiated tissues and has clinical relevance. DNA methylation is also involved in X-chromosome inactivation and the allele-specific silencing of imprinted genes. This review describes possible mechanisms by which DNA methylation can regulate gene expression, using imprinted genes as examples. The molecular basis of methylation-mediated gene regulation is related to changes in chromatin structure and appears to be similar for both imprinted and biallelically expressed genes.
The expression of many cellular genes is modulated by DNA methylation and histone acetylation. These processes can influence malignant cell transformation and are also responsible for the silencing of DNA constructs introduced into mammalian cells for therapeutic or research purposes.
Targeted Methylation
Introducing methylated DNA at specific genomic loci affects local histone acetylation.

By Jonathan Weitzman

- Methylation of DNA at CpG dinucleotides represses gene transcription.
- Methylation caused a hypoacetylation of histones.
- Methylated DNA represses local transcription by recruiting histone deacetylase activity.
Turn off Genes

Histone deacylation

DNA methylation
SIR2
Histone deacylation
DNA methylation
IGF
Turn off Genes
Model of how calorie restriction may extend life span in mammals. Effects occur at two levels: (1) sensing CR to adjust hormonal levels and (2) executing a slowing of aging on all organs. Roles for *Sir2* genes are proposed at both levels.
Family of protein deacetylases (Sirtuins) are nicotinamide adenine dinucleotide (NAD)-dependent enzymes that hydrolyze one molecule of NAD for every lysine residue that is deacetylated. The Sirtuins are phylogenetically conserved in eukaryotes, prokaryotes, and Archeal species. Prokaryotic and Archeal species usually have one or two Sirtuin homologs, whereas eukaryotes typically have multiple versions. The founding member of this protein family is the Sir2 histone deacetylase of *Saccharomyces Cerevisiae*. 
Sir2-dependent activation of acetyl-CoA synthetase by deacetylation of active lysine.

Starai VJ, Celic I, Cole RN, Boeke JD, Escalante-Semerena JC. Department of Bacteriology, University of Wisconsin, Madison, WI 53706-1567, USA. Science. 2002 Dec 20;298(5602):2390-2.

Acetyl-coenzyme A (CoA) synthetase (Acs) is an enzyme central to metabolism in prokaryotes and eukaryotes. Acs synthesizes acetyl CoA from acetate, adenosine triphosphate, and CoA through an acetyl-adenosine monophosphate (AMP) intermediate. Immunoblotting and mass spectrometry analysis showed that Salmonella enterica Acs enzyme activity is posttranslationally regulated by acetylation of lysine-609. Acetylation blocks synthesis of the adenylate intermediate but does not affect the thioester-forming activity of the enzyme. Activation of the acetylated enzyme requires the nicotinamide adenine dinucleotide-dependent protein deacetylase activity of the CobB Sir2 protein from S. enterica. We propose that acetylation modulates the activity of all the AMP-forming family of enzymes, including nonribosomal peptide synthetases, luciferase, and aryl- and acyl-CoA synthetases. These findings extend our knowledge of the roles of Sir2 proteins in gene silencing, chromosome stability, and cell aging and imply that lysine acetylation is a common regulatory mechanism in eukaryotes and prokaryotes.
External Signal

\[ \text{ASI, ASG} \rightarrow \text{ASJ, ASK} \]

Insulin/IGF-1

\[ \text{Daf-2} \]

\[ \text{PI3-K} \]

\[ \text{PDK-1} \]

\[ \text{AKT-1, AKT-2} \]

\[ \text{Hsf-1} \]

\[ \text{Sir-2.1} \]

\[ \text{Daf-16} \]

\[ \text{Ins-30} \]

Heat Response

Oxidative Stress Response

Microbial Response

Metabolic processes

Anti-Longevity Genes

Longevity
Low glucose → LKB1 → AMPK → TSC2 → TOR → Cell growth and proliferation

AMPK

↑ AMP

Growth-factor-stimulated pathways

Rapamycin

Alpha lipoic acid
Calorie Restriction
Heat Shock
Osmotic Stress

Cell Wall
Nucleus

Transcription

Sir2
NAD
Nicotinamide
Nicotinic Acid
Sir2

Longer Life
• “It is possible that the alteration of NAD levels by manipulation of the NAD biosynthetic pathway, Sir2 protein activity, or other downstream effectors will provide new therapeutic opportunities for the treatment of diseases involving axonopathy and neurodegeneration.”

• “These findings suggest that novel therapeutic strategies directed at increasing the supply of NAD and/or Sir2 activation may be effective for treatment of diseases characterized by axonopathy and neurodegeneration.”
• Valproic acid and similar fatty acids can induce inhibition of HDAC or inhibition of gene methylation and thereby alter actions of transcription factors.

• Valproic acid is a histone deacetylase inhibitor.
Awareness of Roles Played by:

- Lysine
- Nadh
- Igf
- Telomerase
- Valproic Acid
**ProLongevity NutriSwitch RNA™**

Female, 72

<table>
<thead>
<tr>
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<th>Before Prolongevity</th>
<th>After Prolongevity</th>
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<tbody>
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<td>Triglycerides</td>
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<td>Total Cholesterol</td>
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<td>Glucose</td>
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<td>HDL</td>
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<tr>
<td>LDL</td>
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</tr>
</tbody>
</table>
DNA
Modifications for Regulation

- Ubiquitination
- Methylation
- Acetylation
- (Phosphorylation)

Mutations

- UBE3A
- MTHFr, MeCP2…
- NAT
- (Casein Kinase 2, milk)
MeCP2 binds methylated DNA

recruits HDAC

De-acetylation
Methylation

Turn Off or Silencing
Viewing Order

- Neurological Inflammation Tape
- Putting It All Together 2 part tape
- Boston DVDs