Epigenetics and Autism Prevention

Autism One Conference
Chicago, Illinois
May 25, 2016

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Walsh Research Institute

- Public Charity
- Expertise in Brain Disorders
- Physician Training
- Research

Mounting Evidence that Autism is an Epigenetic Disorder

- More than 20 published studies,
- Most epigenetic disorders involve methylation imbalances and excess oxidative stress, both hallmarks of ASD,
- Autism fits the criteria for an epigenetic gene regulation disorder.

Apparent Epigenetic Gene-Regulation Disorders

- Cancer
- Heart Disease
- Autism (suspected)
- PTSD (suspected)
- Schizophrenia (suspected)

Characteristics of an Epigenetic Disorder

- Cases of sudden onset after normalcy
- Persistence of condition after onset
- A multitude of characteristic symptoms
- Heritable illness that violates laws of genetics
- Abnormal methylation
- Severe oxidative overload.

Recipe for an Epigenetic Disorder

- Genetic predisposition
- Environmental insult

Epigenetic Disorders
High Degree of Clinical Difficulty

- Numerous dysregulated genes,
- Many systems need correction: Immune function, biochemistry, G.I. Tract, oxidative stress, brain function, etc.
- Progress usually partial in nature; complete recovery relatively difficult to achieve.

The Bad News and Good News

- Most epigenetic disorders are complex and very difficult to treat.
- However, epigenetic disorders appear relatively easy to prevent.
- **If autism is epigenetic, prevention protocols could sharply reduce prevalence.**

The Bermuda Triangle of Autism

Undermethylation

Oxidative Stress

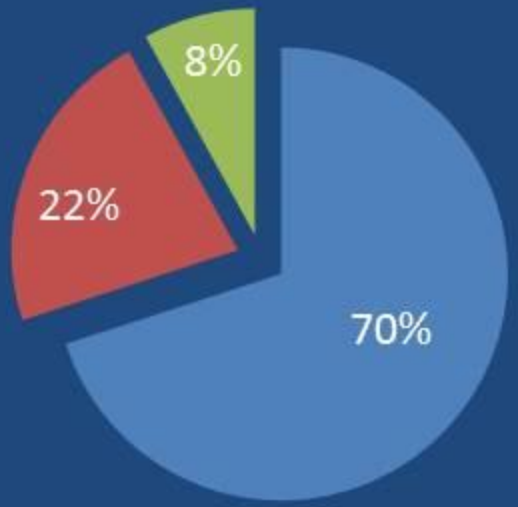
Epigenetics

Methylation Disorders – Two Types

UNDERmethylation

OVERmethylation

Incidence of Methylation Disorders in the General Population



Normal Methylation = 70%

Under Methylation = 22%

Over Methylation = 8%

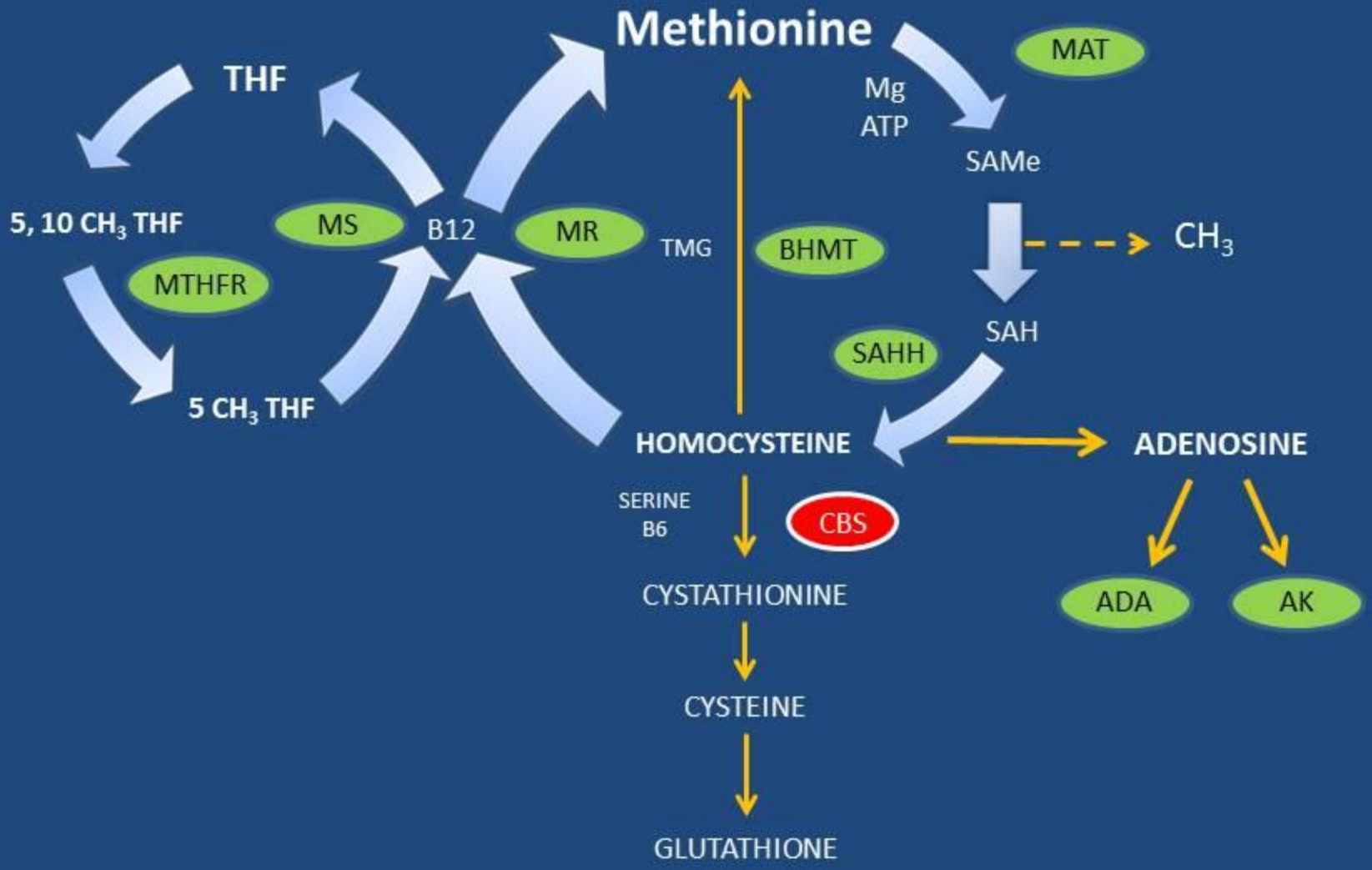
Year 1999 Discovery

Undermethylation present in 95% of ASD patients.

Primary Causes of UNDERmethylation

- **Enzyme Mutations (SNPs) in Methylation Cycle**
- **Overload of S-adenosylhomocysteine (SAH)**
- **Protein Deficiency or Malabsorption**

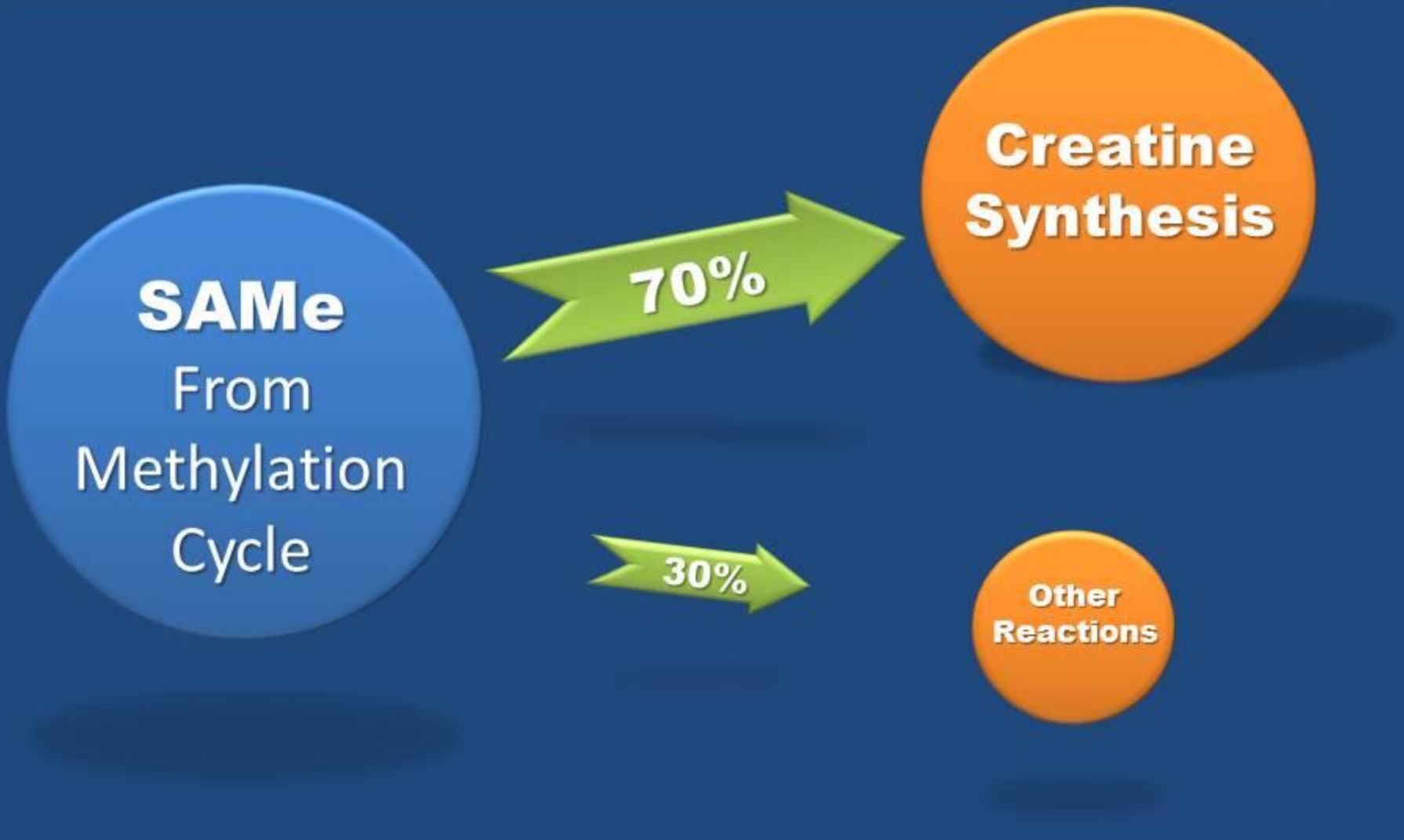
Methylation Cycle Enzymes



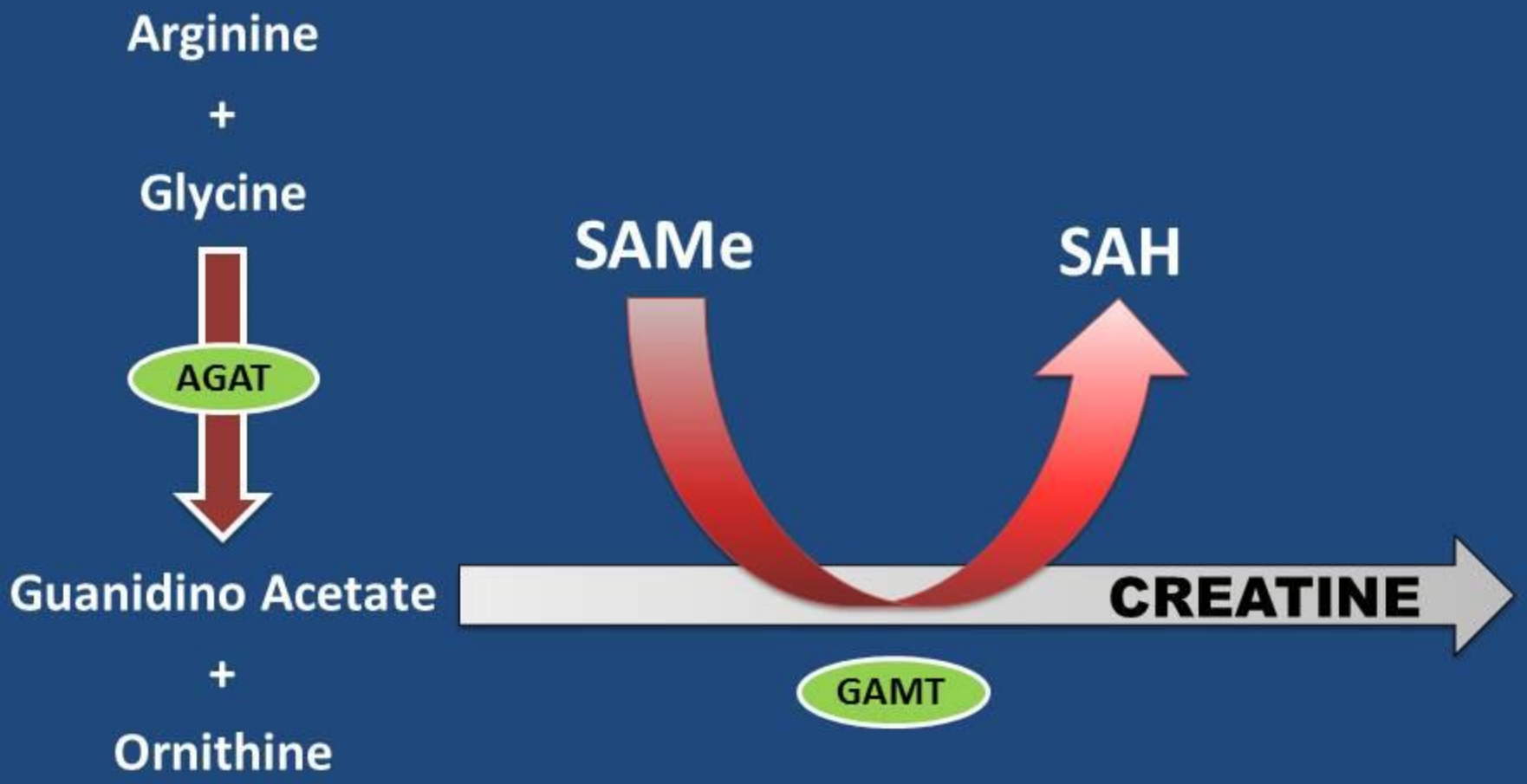
Primary Cause of OVERmethylation

Impaired SAMe Utilization

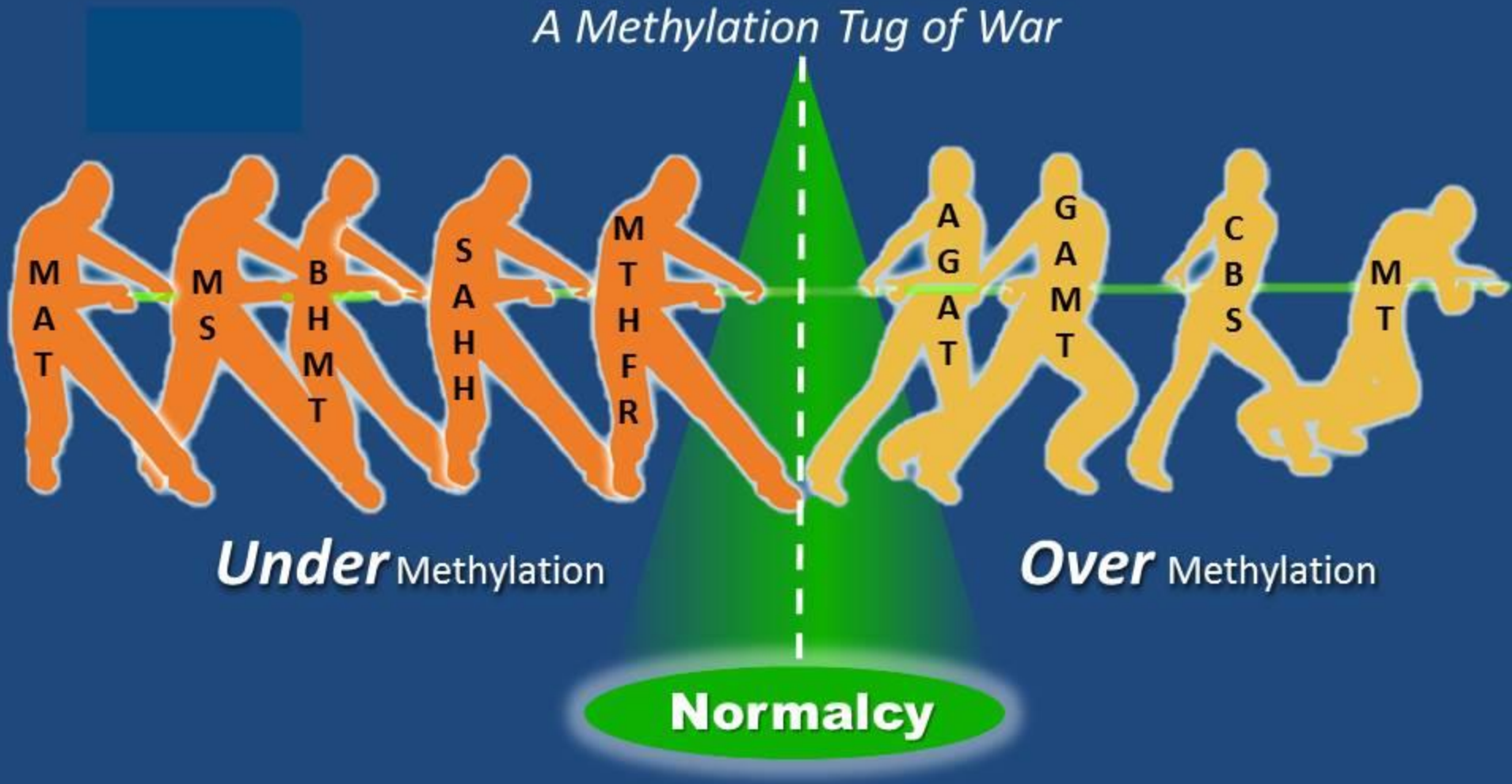
SAMe Utilization



Creatine Synthesis



Enzyme Mutations and Methylation



The vast majority of ASD children and adults are undermethylated.

UNDERMethylation: Symptoms & Traits
(Partial List)

- Strong willed; Oppositional to authority
- Very competitive in career or sports
- Family history of high accomplishment
- OCD tendencies, perfectionistic
- High libido, seasonal allergies (75%)
- Addictive tendencies
- Relatively high incidence of autism, drug abuse, anorexia, ODD, ADHD, depression

Oxidative Stress and Autism

Autism Database

- 6,500 patients
- > 750,000 blood/urine chemistries
- > 500,000 medical history factors.

Pervasive Biochemical Abnormalities in Autism

- Undermethylation
- Severe oxidative overload
- Depressed Glutathione & Cysteine
- Elevated Toxic Metals
- Copper/Ceruloplasmin Dysregulation
- Depleted Zinc & Metallothionein
- Elevated Pyrroles
- Low B-6, C, and Selenium

Note: ***Each of these imbalances is associated with elevated***
OXIDATIVE STRESS.

Consequences of Oxidative Overload

1. Hypersensitivity to Hg & other toxic metals,
2. Hypersensitivity to casein, and gluten,
3. Poor immune function,
4. Inflammation of the brain & G.I. tract,
5. Depletion of glutathione & metallothionein.

Consequences of Oxidative Overload in the G.I. Tract

- Destroys enzymes that break down casein & gluten,
- Increases candida/yeast levels,
- Reduces Zn levels and production of stomach acid,
- Produces inflammation,
- Results in a leaky intestinal barrier, allowing toxics to enter the bloodstream.

Many Effective Autism Therapies Have Antioxidant Properties

- Transdermal or Injected Glutathione
- Chelation with DMSA, DMPS, EDTA
- N-Acetylcysteine (NAC)
- Metallothionein Promotion
- Zn, Se, CoQ-10, Vitamins A,C,D,E
- Alpha Lipoic Acid
- Risperdal

Universal Factors in Autism

Methylation Imbalance

Severe Oxidative Stress

These factors are often dominant in epigenetic gene-regulation disorders.

EPIGENETICS

DNA's Role in Cell Nourishment

- About 25 trillion cells nourished by gene expression
- DNA contains about 20,000 genes, each capable of producing one specific protein
- Every cell has identical DNA, but every tissue, organ, and cell line needs a unique combination of proteins
- **This is accomplished by epigenetic gene regulation!**

Two Epigenetic Processes

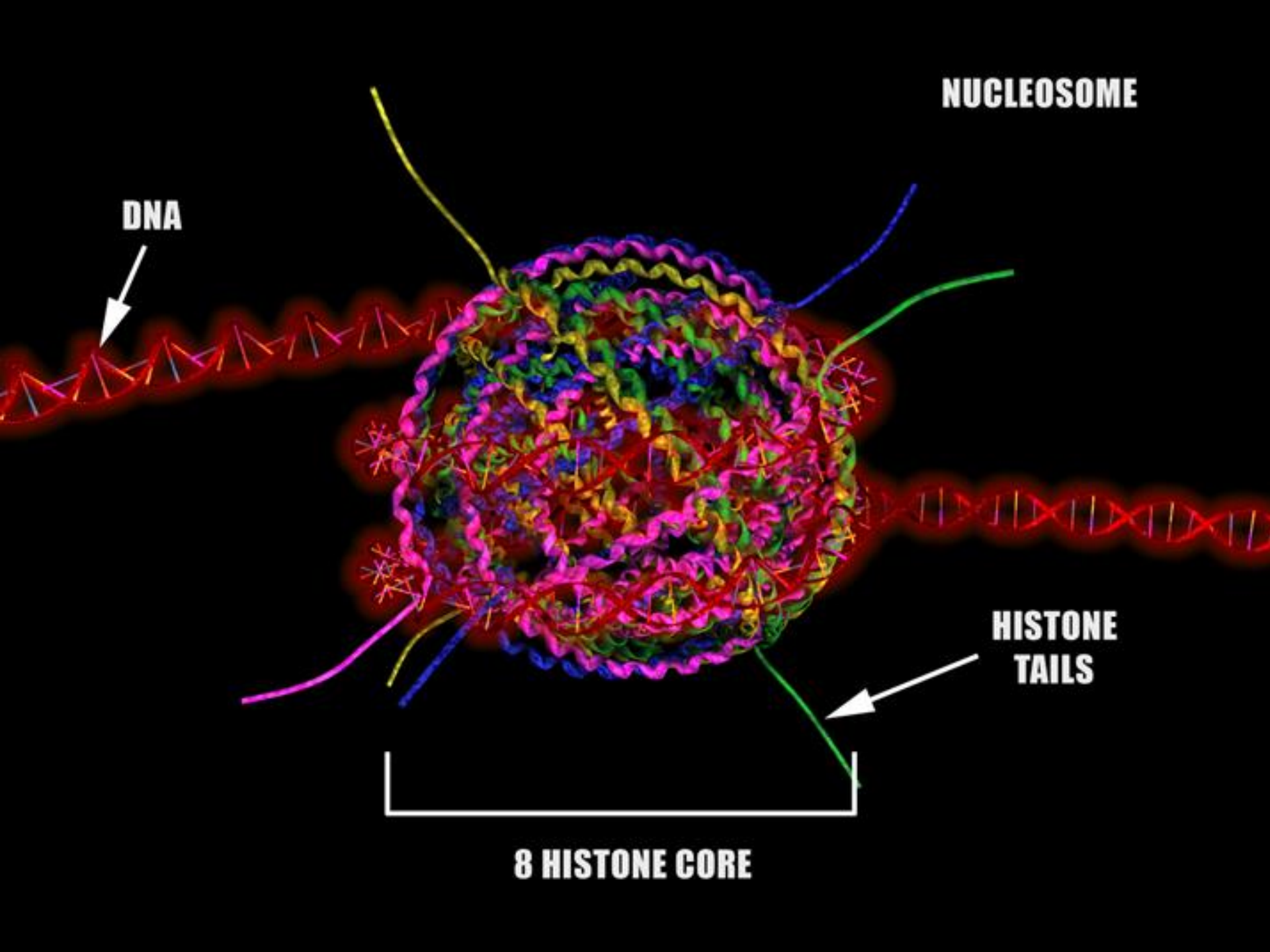
1. In-utero methylation of cytosine at specific DNA regions can efficiently regulate gene expression.

2. Histone modification by reactions with Acetyl-CoQ10, SAMe or other biochemicals.

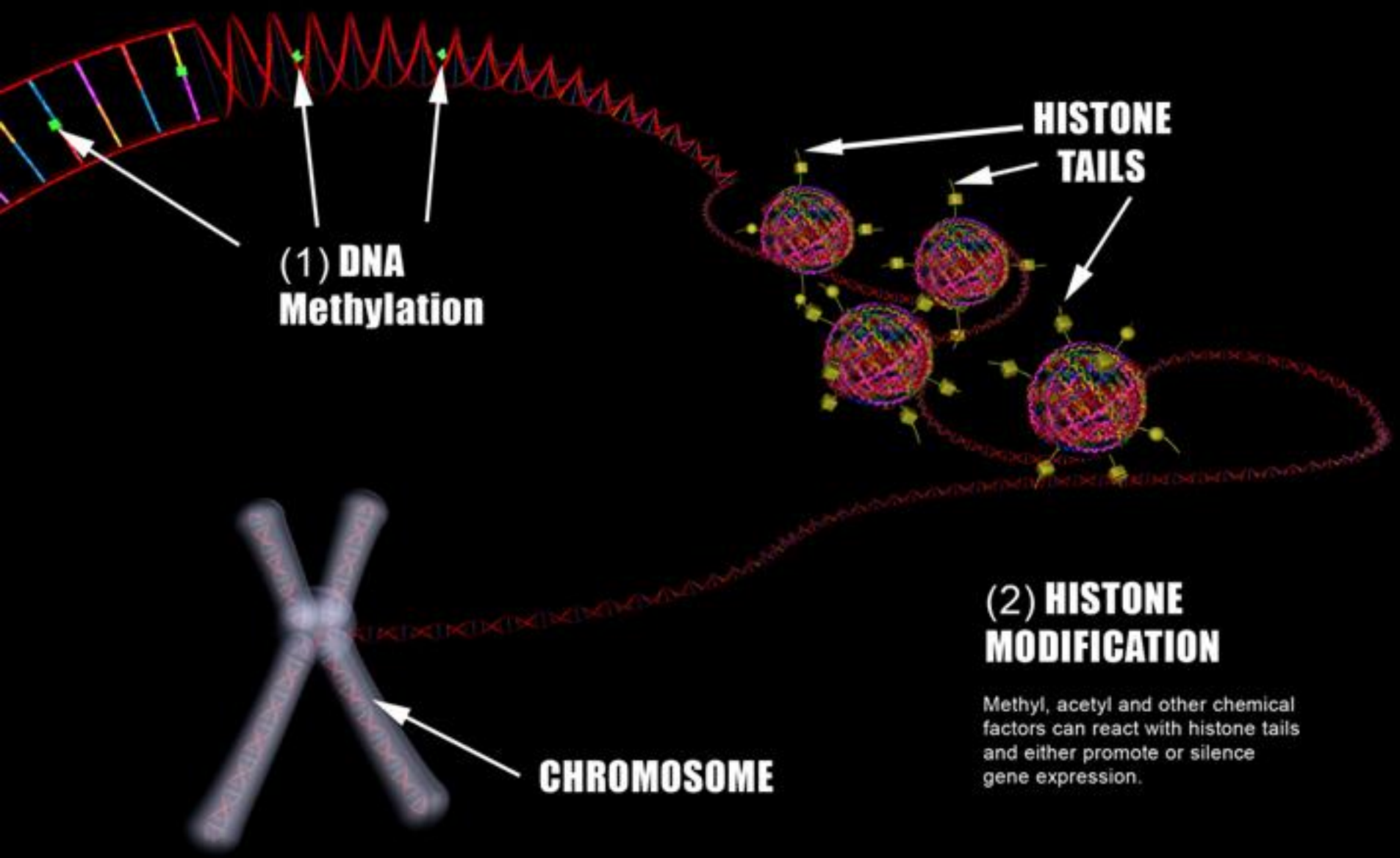
Methylation plays a major role in both processes.

Histones – Support Structures for the Fragile DNA

- Composed of 8 linear proteins twisted together like a ball of yarn,
- Originally believed to serve only as structural support for DNA packaging,
- Later found to inhibit or promote gene expression, depending on chemical reactions at histone tails.


NUCLEOSOME
DNA
HISTONE
TAILS
8 HISTONE CORE

The Two Main Components of the Epigenetic Code



Methyl Acetyl Competition

- Competition between methyl and acetyl groups often determines whether genes are expressed or silenced.
- Acetyl bookmarks promote expression.
- Methyl bookmarks inhibit expression.

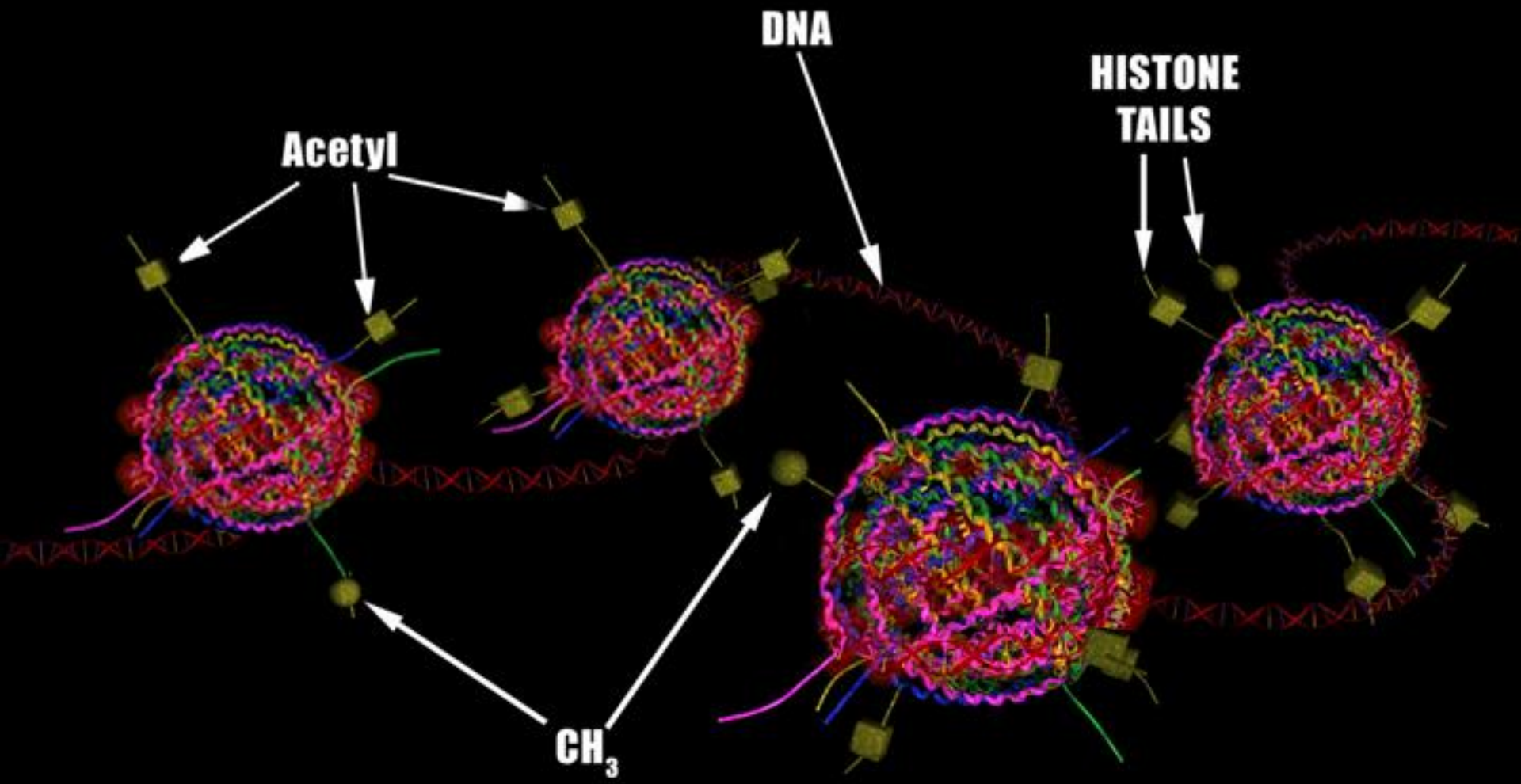
Gene Expression Requires Uncoiling of DNA

- Gene expression involves direct interaction of RNA polymerase and transcription factors with DNA. These large molecules cannot gain access to DNA/histone regions that are densely compacted,

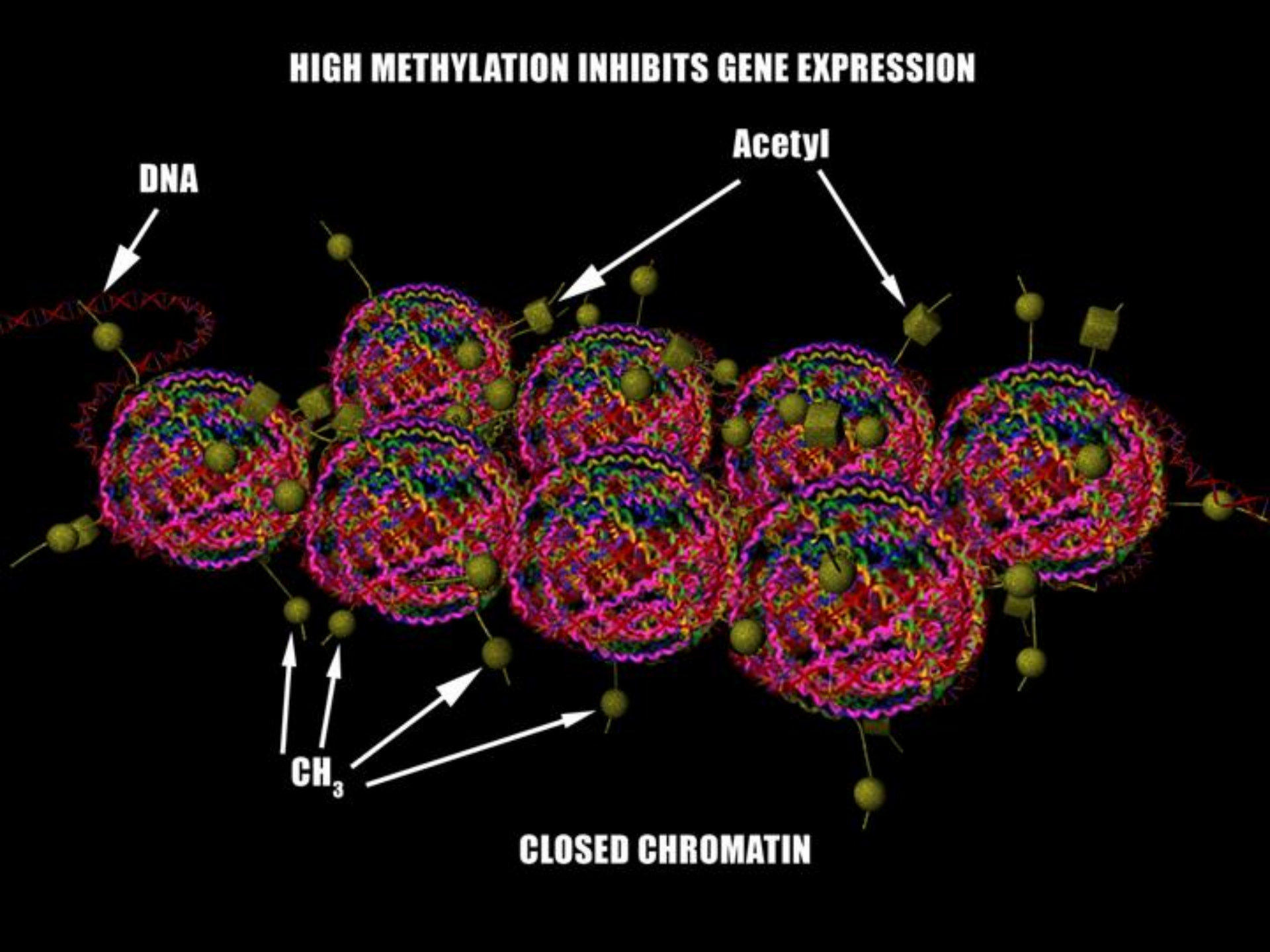
- The gentle attachment of DNA to histones involves electrostatic attraction – DNA is a weak acid and histones are mild bases (pH above 7.0).

- Acetylation decreases histone pH, causing uncoiling of DNA; methylation increases histone pH, increasing DNA/Histone.

LOW METHYLATION PROMOTES GENE EXPRESSION



OPEN CHROMATIN


HIGH METHYLATION INHIBITS GENE EXPRESSION
Acetyl
DNA
CH_3
CLOSED CHROMATIN

IN-UTERO UNDERMETHYLATION MAY BE RESPONSIBLE FOR AUTISM PREDISPOSITION

An Epigenetic Model of Autism

- Undermethylation during gestation causes weakened protection against oxidative stress and vulnerability to autism.
- Environmental insults produce severe oxidative stresses that alter expression of numerous genes during the critical period of early development.
- The result is autism, a complex gene-regulation disorder that can persist for a lifetime.

In-Utero Undermethylation and Vulnerability to Autism

1. Reduced expression of “natural” antioxidants such as GSH peroxidase, SOD, catalase, MT, etc.

2. SNP mutations that weaken key antioxidants

3. Impaired DNA repair capability

Constant Assault on DNA

- Adults have about 30 trillion DNA molecules.
- Assault by toxics, ROS, cosmic radiation, etc.
- Each DNA strand is seriously damaged between 10,000 and 1 million times daily.
- DNA single-strand and double-strand breaks, mismatched bases, chemically-altered bases, etc.

DNA Damage

2015 Nobel Prize in Chemistry
Modrich, Lindahl, Sancar

- Groundbreaking research on DNA repair,

- Potentially the most important scientific advance since Watson and Crick's discovery of the DNA double helix.

The Miracle of DNA Repair

- Constant effective DNA repair essential to life,
- Exquisitely complex repair mechanisms now well understood,
- DNA repair requires expression of many genes,
- In-utero undermethylation may weaken DNA repair and increase autism vulnerability.

Epigenetic Disorders – Environmental Insults Overwhelm DNA Repair

- Loss of DNA integrity,
- Altered gene expression that may last a lifetime,
- Complex disorders involving numerous malfunctioning genes.

A Clue From Cancer Research

- Severe oxidative stress can permanently alter gene expression and produce cancer.
- Autism may arise from a similar mechanism – severe oxidative stress that alters gene regulation.
- Intensive cancer research now aimed at epigenetic therapies to restore proper gene expression.
- Epigenetic therapies for ASD appear very promising.

ADVANCED EPIGENETIC THERAPIES

Epigenetic Therapy Approaches

1. Therapies to normalize epigenetic marks for DNA and histones

2. Bromodomain and chromodomain therapies

3. microRNA therapies

High complexity and technical difficulty!

Bromodomains

- 110 amino-acid RNA-motif sequence on specific transcription factors that enable gene expression,
- Readers of lysine acetylation at histones,
- Important factor in gene regulation,
- Bromodomain therapies are under active development for cancer.

Chromodomains

- Sequence of 40-50 amino acid residues in certain transcription factors that “read” and interact with methylated histones,
- Important aspect of gene regulation,
- Chromodomain protein 8 (CHD8) insufficiency implicated in ASD risk.

MicroRNA (The Traffic Cop)

- Small non-coding RNA molecules in nucleus,
- Can degrade transcribed mRNA strands or prevent their exit from the nucleus,
- Important aspect of gene regulation.

AUTISM PREVENTION

A Strategy for Autism Prevention

1. Identification of vulnerable newborns,
2. Antioxidant therapy for at-risk children,
3. Monitoring of DNA integrity until age 4.

Oxidative Assault on DNA

- The DNA nucleotide most vulnerable to oxidation is guanine,
- Existing lab tests can identify degree of guanine oxidation and vulnerability to autism regression.
- Extreme oxidative stress can overwhelm DNA repair of oxidized guanine lesions.

Lab Tests to Monitor DNA Integrity

8-oxo-deoxyguaninosine

8-oxo-guanine

malondialdehyde

etc.

Protection of Children at High Risk for Autism

- Minimize exposure to toxic metals and other sources of oxidative stress,
- Routine lab testing of DNA integrity,
- Dedicated antioxidant therapy until age 4.

Summary

- Autism spectrum disorders appear to be epigenetic gene-regulation conditions,
- Promising epigenetic therapies are under development,
- Effective autism prevention may be available with today's technology.

THANK YOU!

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Over his impressive career, Dr. Walsh has worked with 30,000 patients with conditions ranging from autism to schizophrenia to Alzheimer's. His book is an essential tool for anyone who would prefer to heal the brain with nutrients rather than drugs.

Teri Arranga, editor-in-chief, *Autism Science Digest*

NUTRIENT POWER

HEAL YOUR BIOCHEMISTRY AND HEAL YOUR BRAIN

WILLIAM J. WALSH, PhD