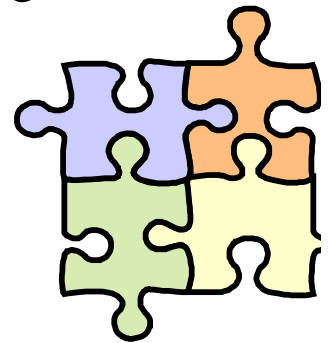
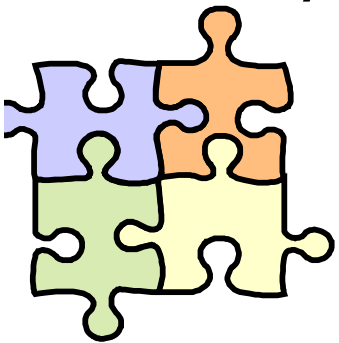


# Pro-Oxidant Environmental Exposures: Implications of Redox Imbalance in Autism

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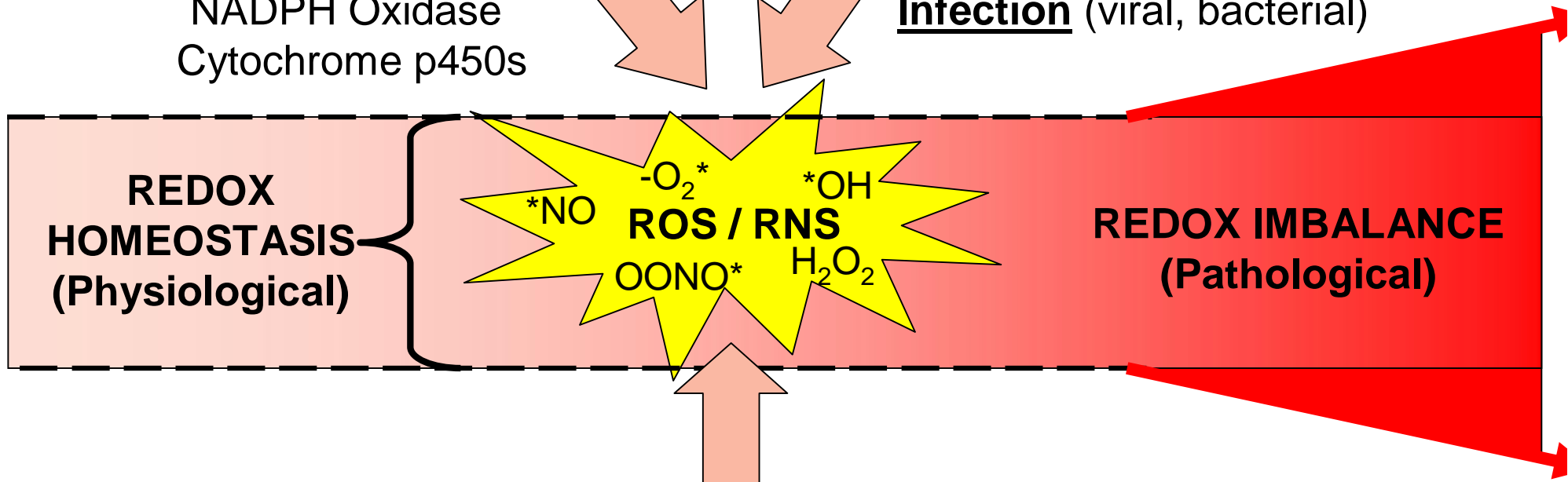


## ENDOGENOUS SOURCES

Mitochondria  
Peroxisomes  
Lipoxygenases  
NADPH Oxidase  
Cytochrome p450s

## EXOGENOUS SOURCES

UV light  
Ionizing Radiation  
Environmental Toxins  
Infection (viral, bacterial)

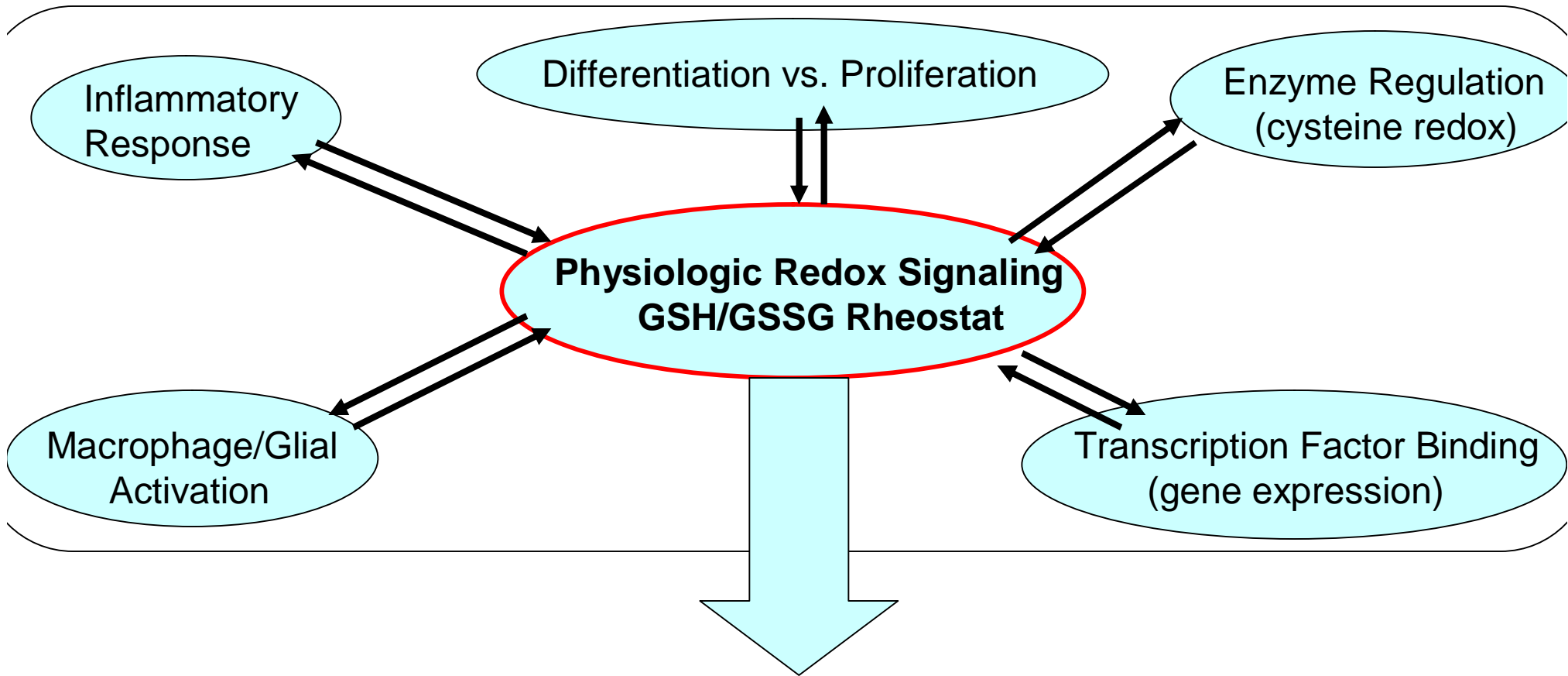


## ANTIOXIDANT DEFENSE

**Glutathione (GSH ↔ GSSG)**

Catalase, SOD, GSH peroxidase, Theoredoxin  
Metallothionein, Vitamins C, E, A, Flavinoids

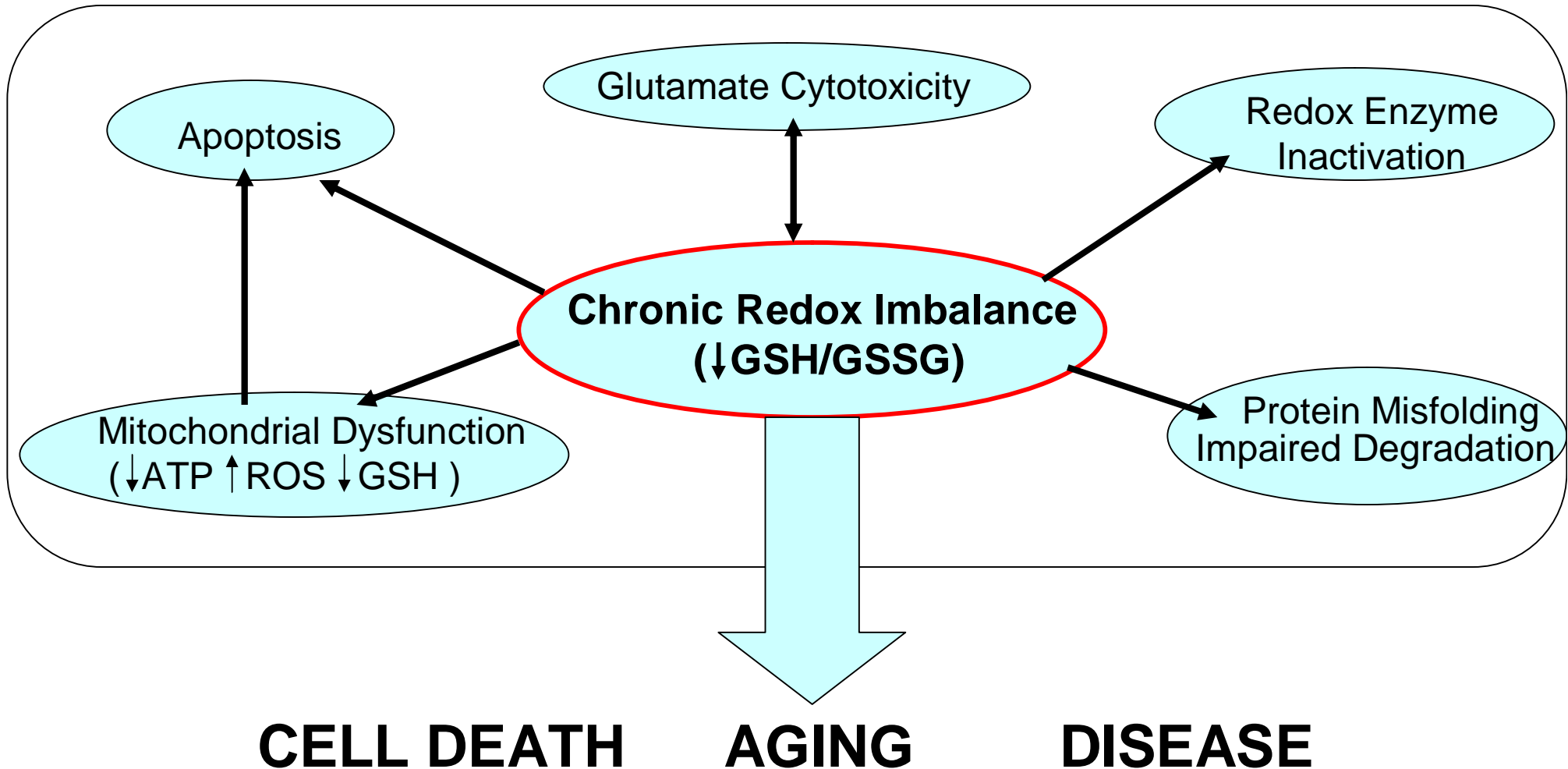
**Subtle changes in redox balance are reversible**  
**(With Adequate GSH Availability)**



**FUNCTIONAL METABOLISM AND HEALTH**

# Chronic GSH/GSSG Redox Imbalance Can Be Irreversible

Promotes a Self-Perpetuating Cycle of Oxidative Stress



Glutathione depletion and oxidative stress may be a final common pathway of toxicity for many common environmental exposures

**METALS**

- Mercury
- Aluminum
- Nickel
- Cobalt
- Cadmium
- Lead
- Arsenic
- Manganase

**SOLVENTS**

- Alcohol
- Chlorinated Solvents
- Benzene

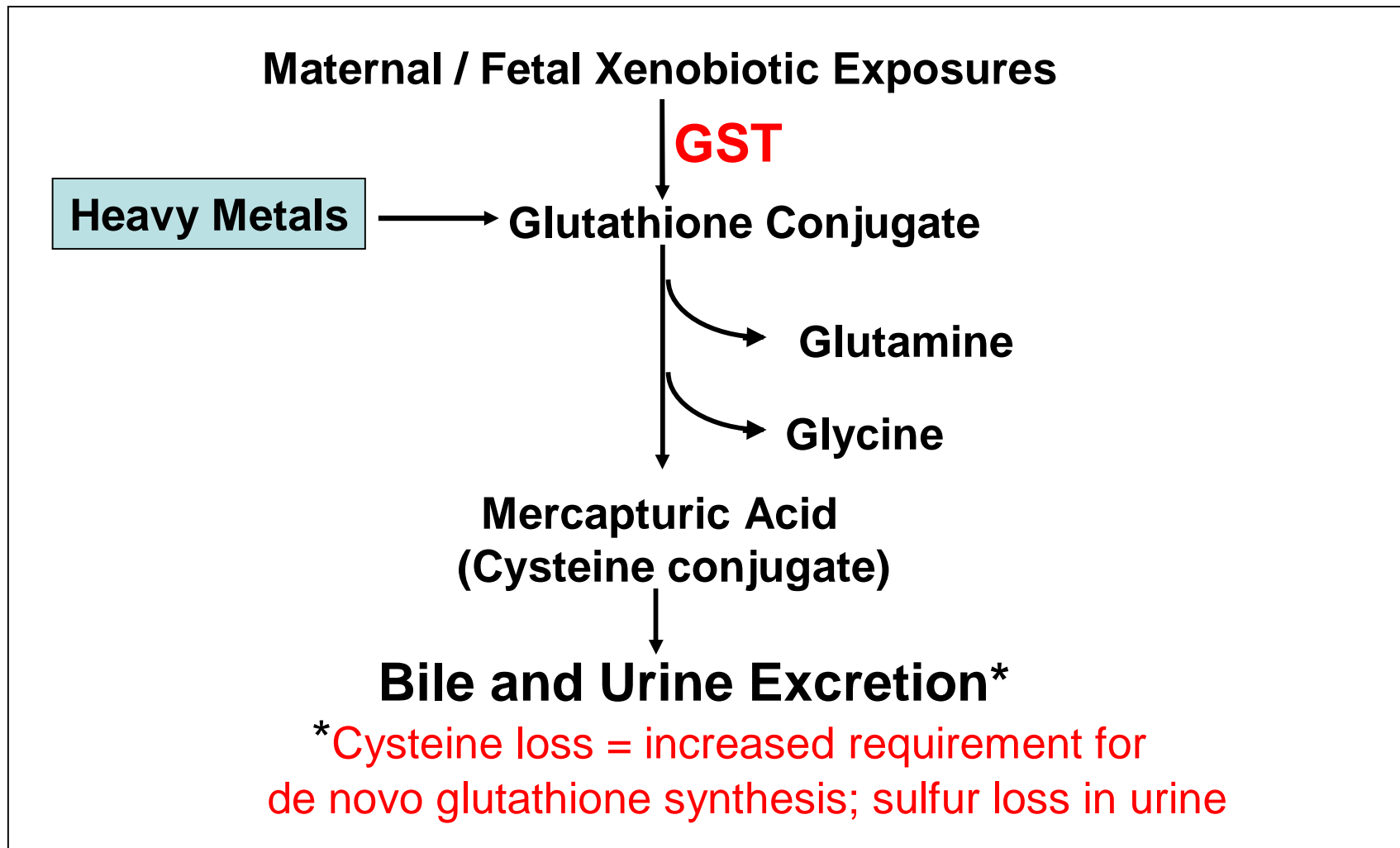
**INDUSTRIAL CHEMICALS**

- PCBs
- Pesticides
- Herbicides

All induce oxidative stress and GSH depletion

Multiple exposures are additive/synergistic!

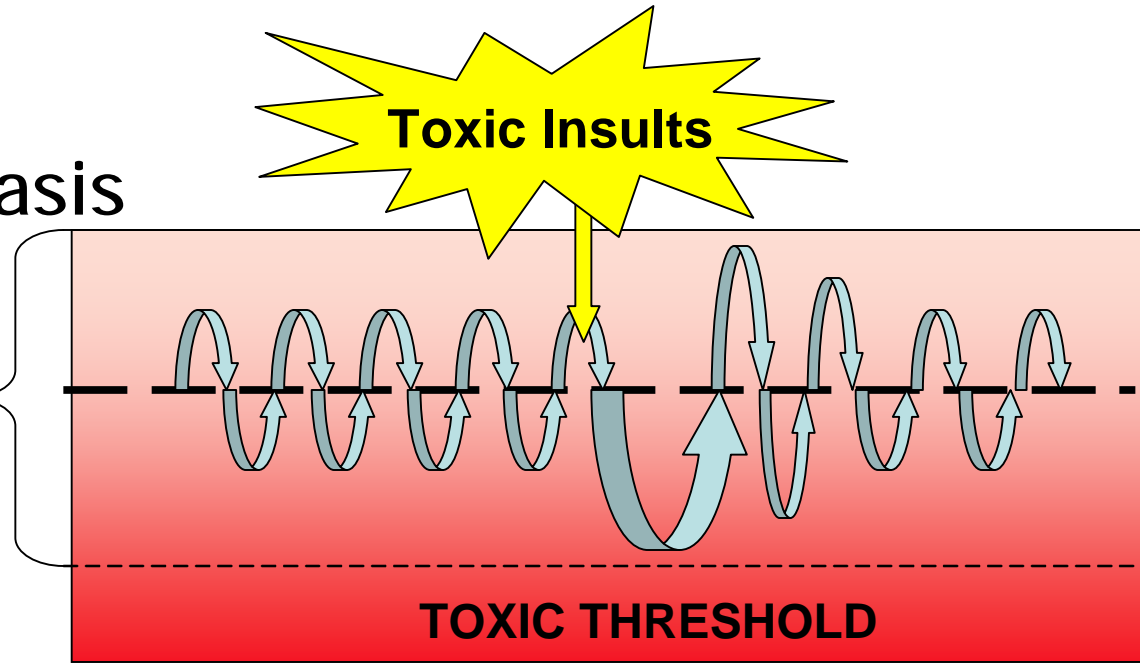
# DETOXIFICATION FUNCTIONS OF GLUTATHIONE



Detoxification: Hg, As, Pb, Cd bind to thiol (SH) group; Metal-cysteine conjugates excreted

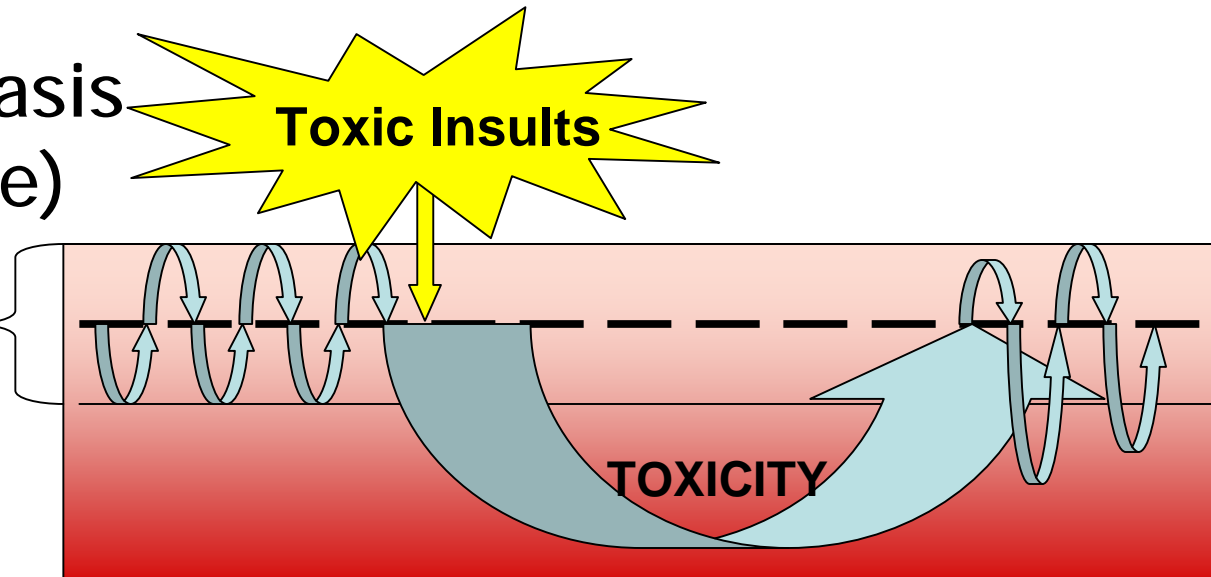
## Normal Homeostasis

↑ GSH/GSSG



## Fragile Homeostasis (limited reserve)

↓ GSH/GSSG



# Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism<sup>1,2</sup>

*S Jill James, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak, David W Gaylor, and James A Neubrandner*

**American Journal of Clinical Nutrition 80:1611-17 (2004)**

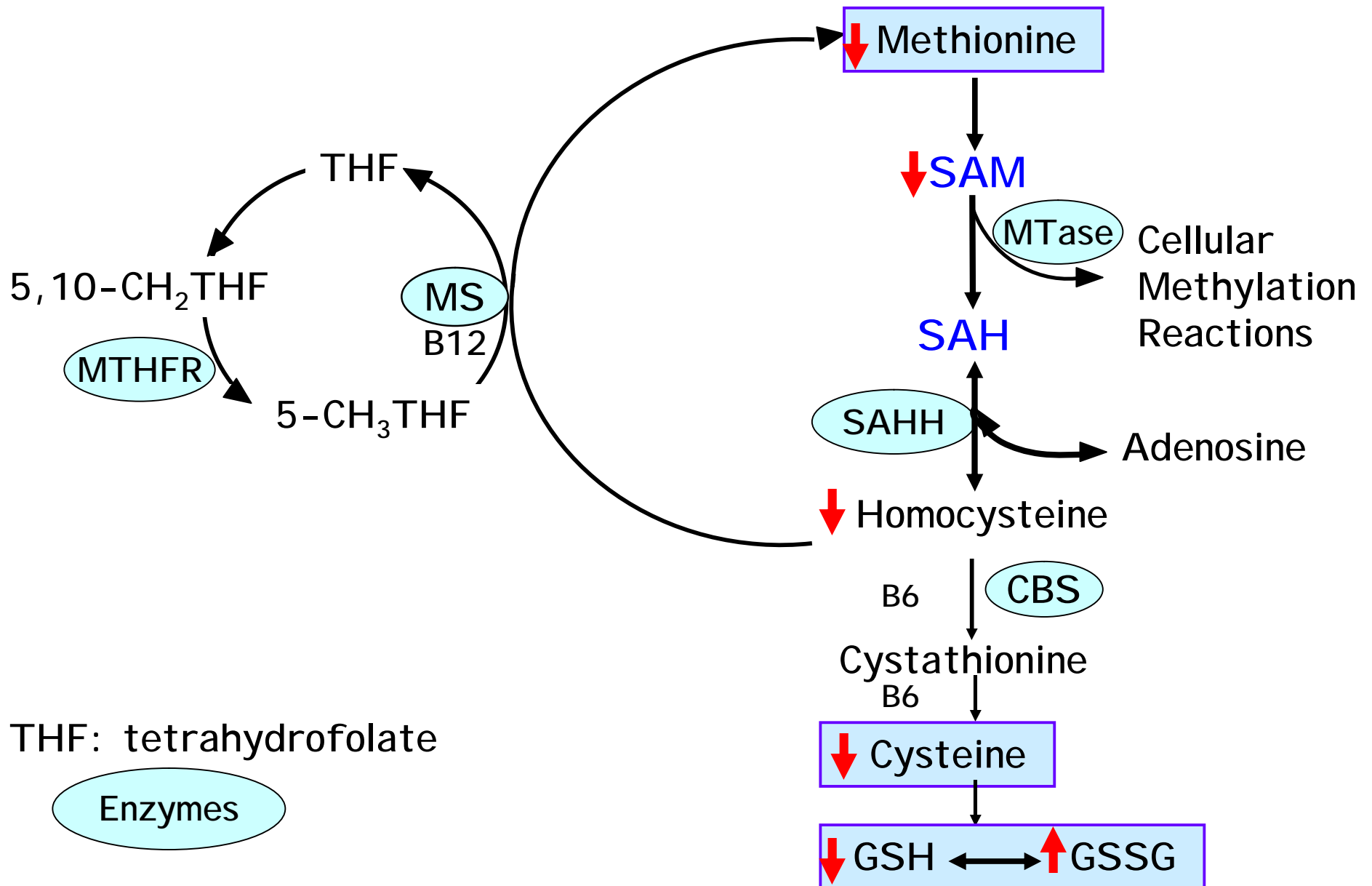
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## **Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism**

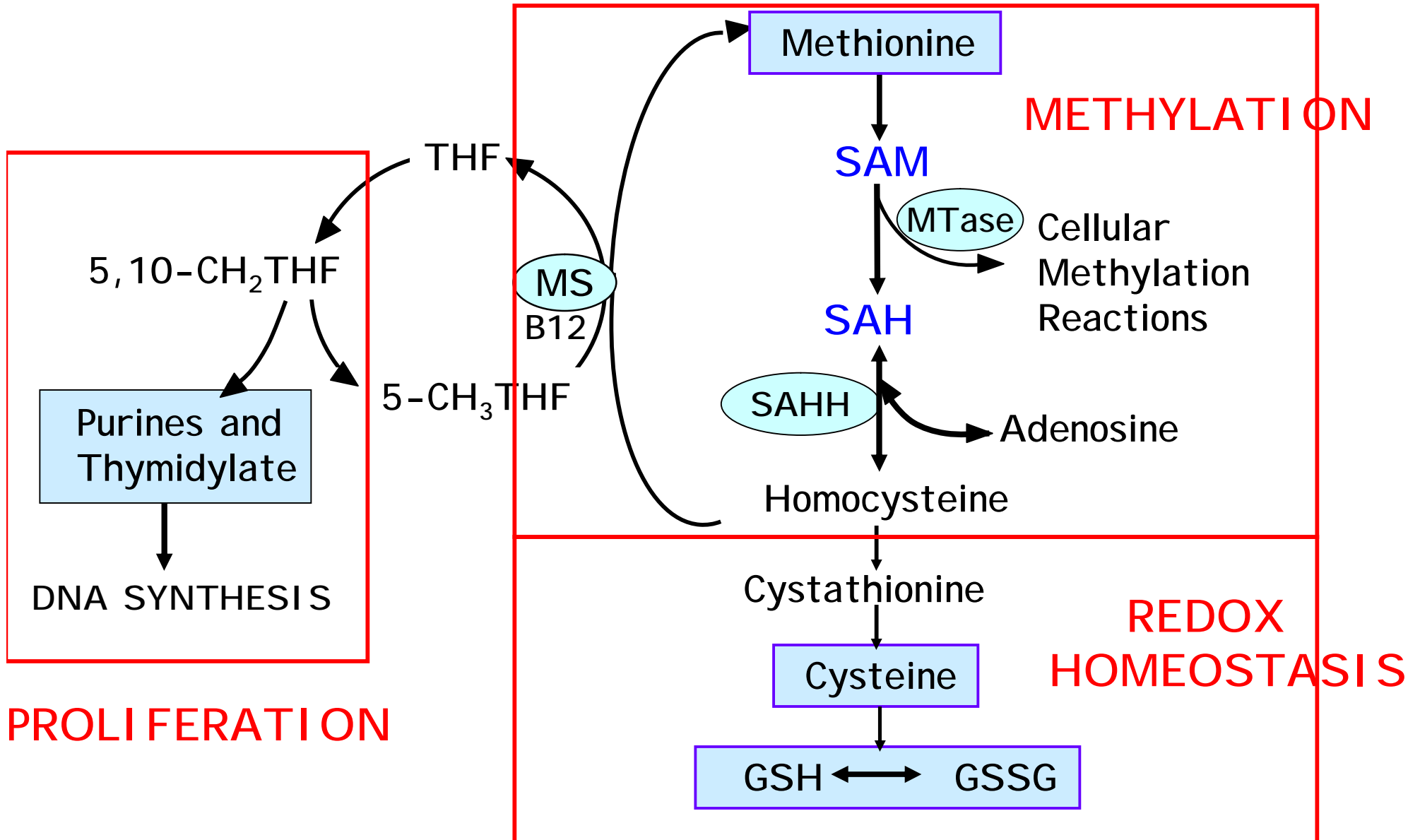
S. Jill James,<sup>1\*</sup> Stepan Melnyk,<sup>1</sup> Stefanie Jernigan,<sup>1</sup> Mario A. Cleves,<sup>1</sup> Charles H. Halsted,<sup>2</sup> Donna H. Wong,<sup>2</sup> Paul Cutler,<sup>3</sup> Kenneth Bock,<sup>4</sup> Marvin Boris,<sup>5</sup> J. Jeffrey Bradstreet,<sup>6</sup> Sidney M. Baker,<sup>7</sup> and David W. Gaylor<sup>8</sup>

**American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B937-956 (2006)**

# Evidence for Redox Imbalance in Autistic Children

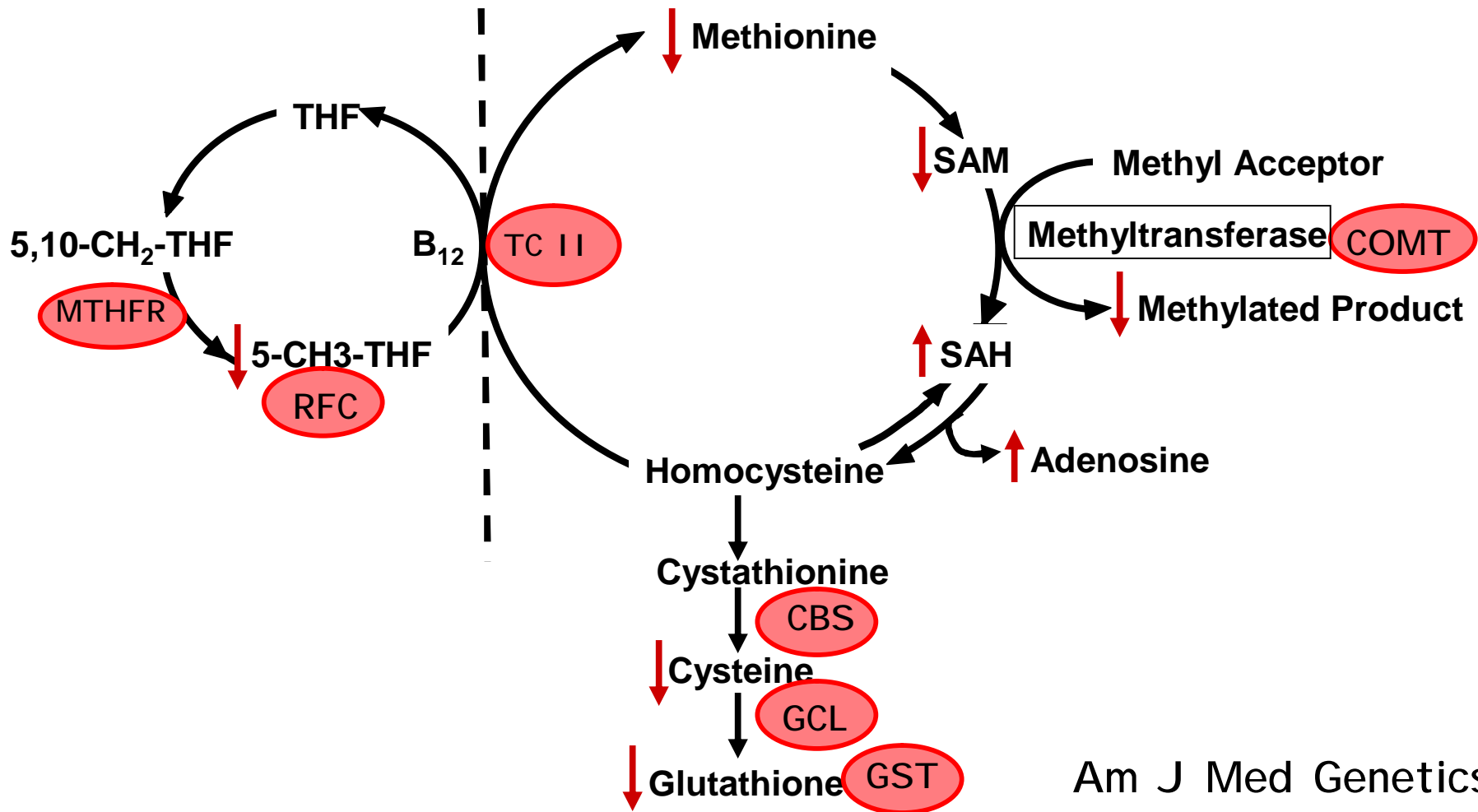


# Vital Importance of these Interdependent Metabolic Pathways



Is there a genetic basis for metabolic imbalance and increased vulnerability to oxidative stress in autistic children?

# A Targeted Approach to Autism Genetics: Using the Metabolic Endophenotype as a Guide to Candidate Genes



Am J Med Genetics, 2006

## Difficulties with purely genetic approach to autism

Estimated 15 to 100 different genes may be required for phenotype

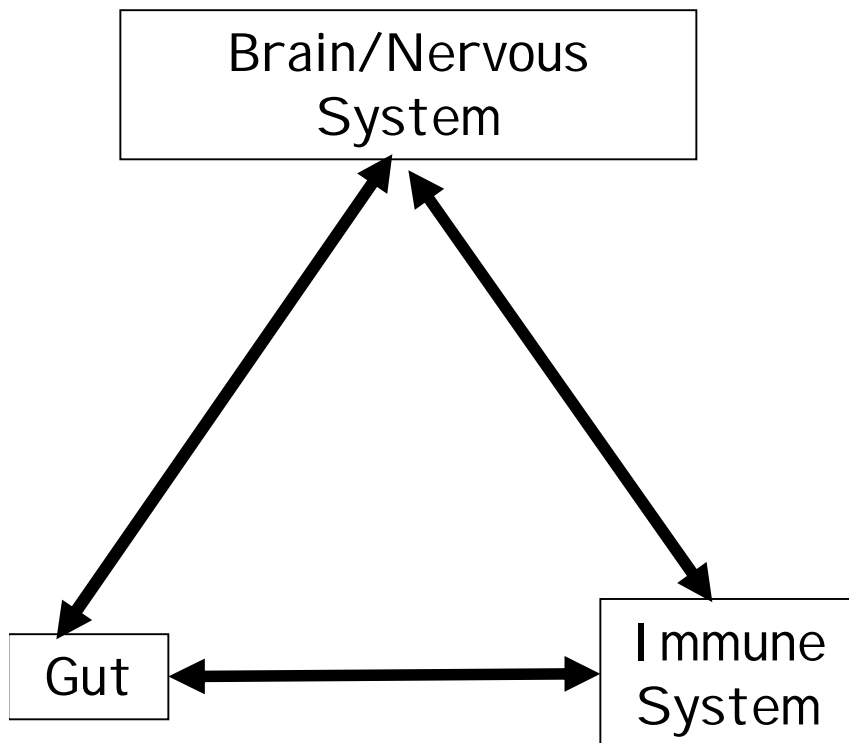
Different combinations of genes in different autistic individuals

If genetic susceptibility requires an environmental trigger, same genetic risk factors may be present in unaffected individuals

Genetics does not encompass timing and severity of environmental exposures and heterogeneity of response

# Looking Beyond the Brain

## The Autism Triad: Brain-Gut-Immune Axis



GUT  $\Rightarrow$  BRAIN: Vagus afferents; Gut neuropeptides

BRAIN  $\Rightarrow$  GUT: Endorphins; Neuropeptides

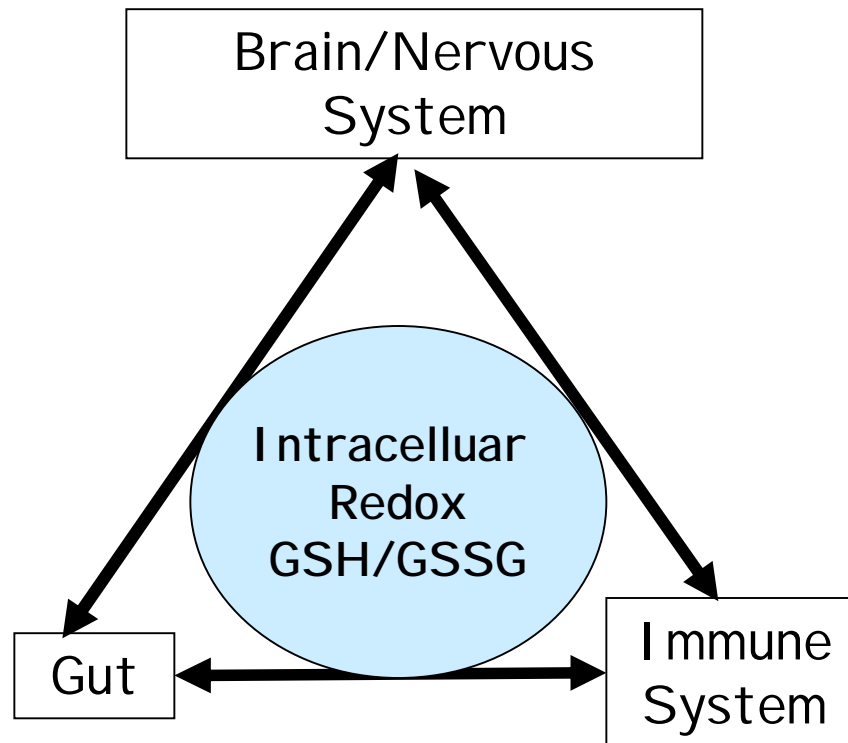
IMMUNE  $\Rightarrow$  BRAIN: Cytokines; microglia activation

BRAIN  $\Rightarrow$  IMMUNE: Endorphins; Neuropeptides; Cortisol

IMMUNE  $\Rightarrow$  GUT: Cytokines; GALT

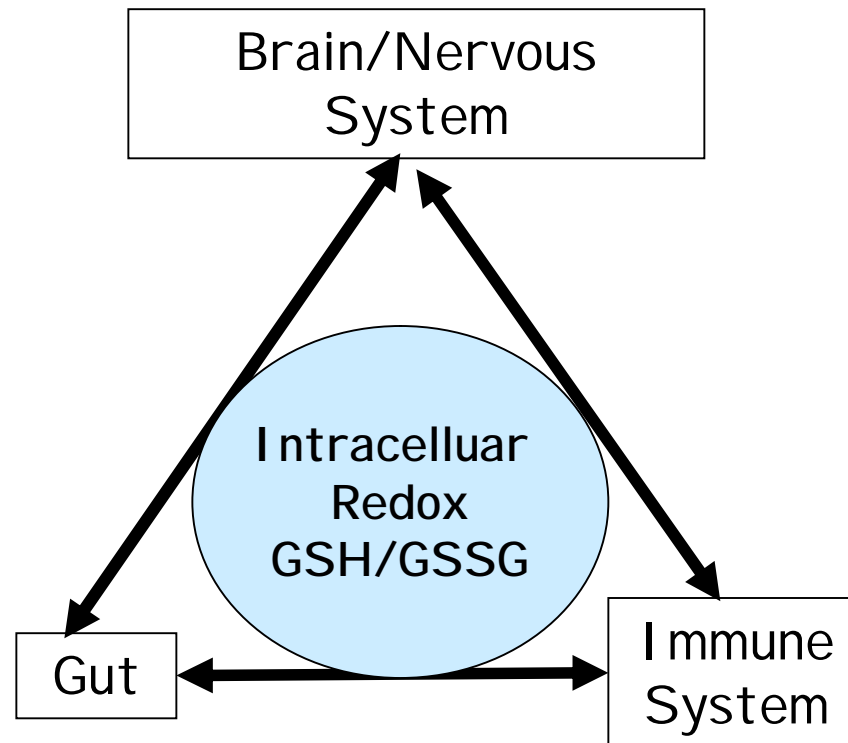
GUT  $\Rightarrow$  IMMUNE: Gut neuropeptides; microbial products

# The Autism Triad: Brain-Gut-Immune Axis



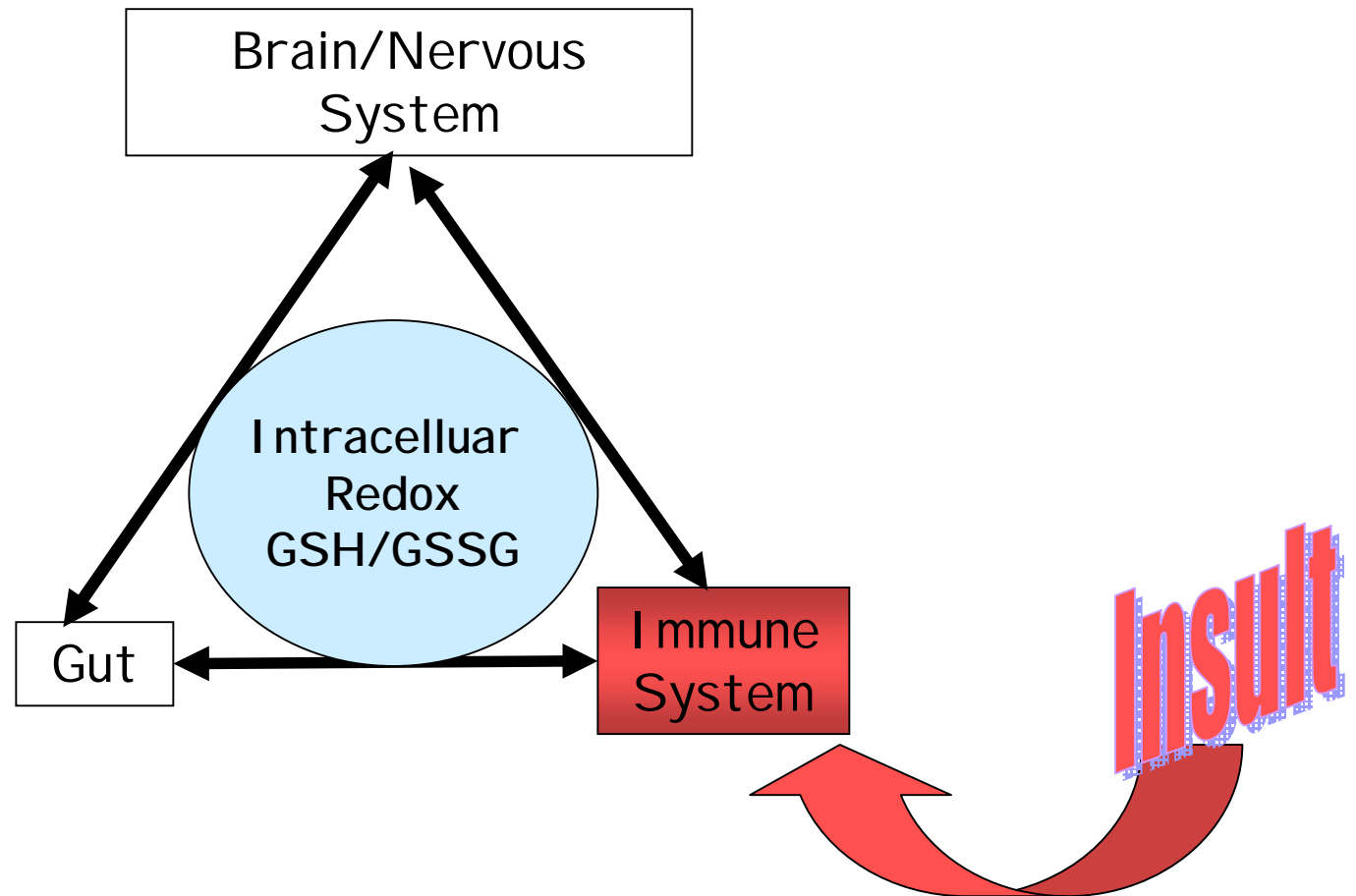
All 3 systems highly sensitive to oxidative stress especially during critical developmental windows

All 3 systems are developmentally immature at birth

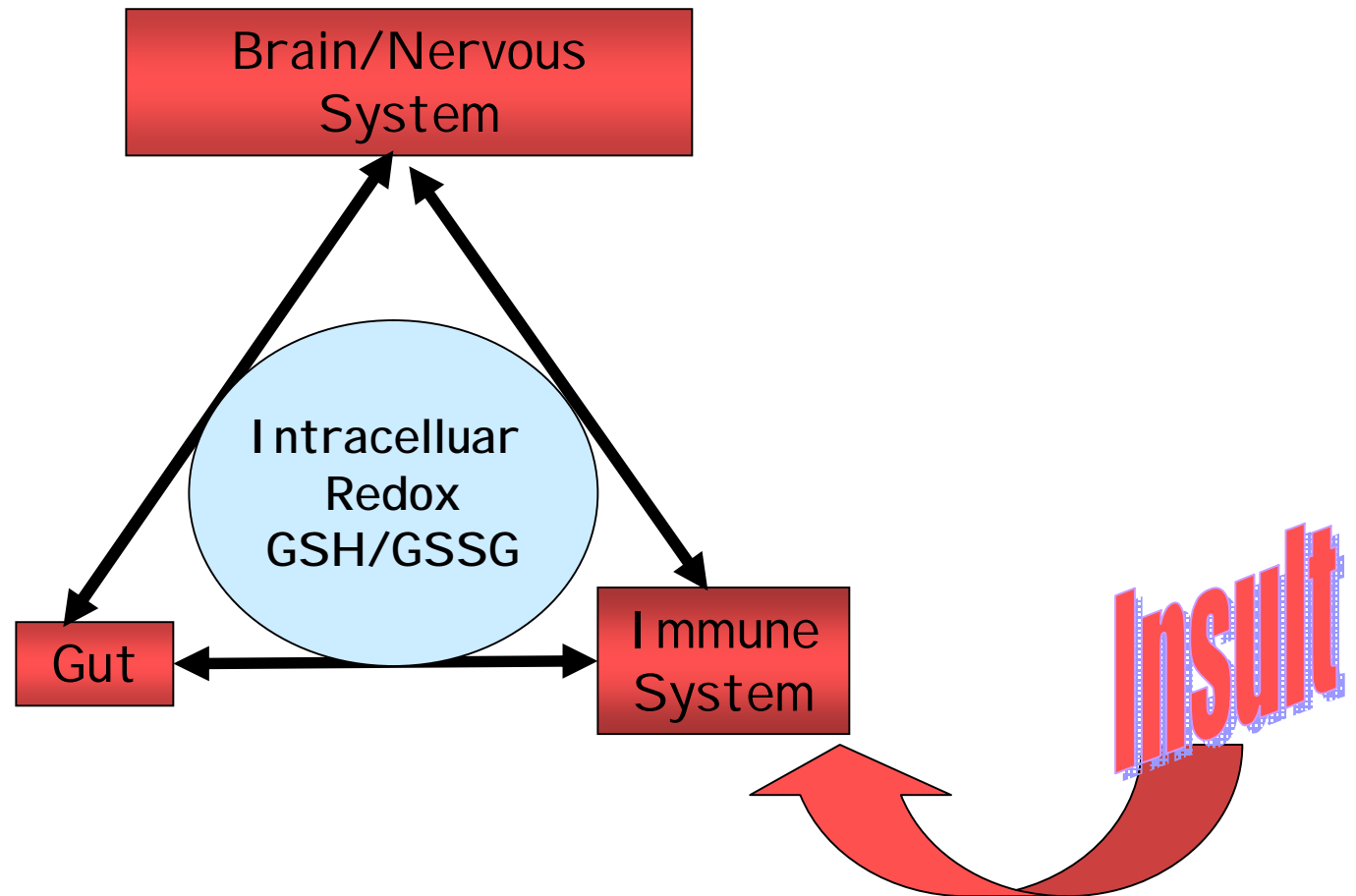


Developmental trajectories of all three systems depend on appropriate environmental signals

Toxic insult to one would indirectly affect the developmental trajectory and function of the others



Toxic insult to one would indirectly affect the developmental trajectory and function of the others



## New Questions

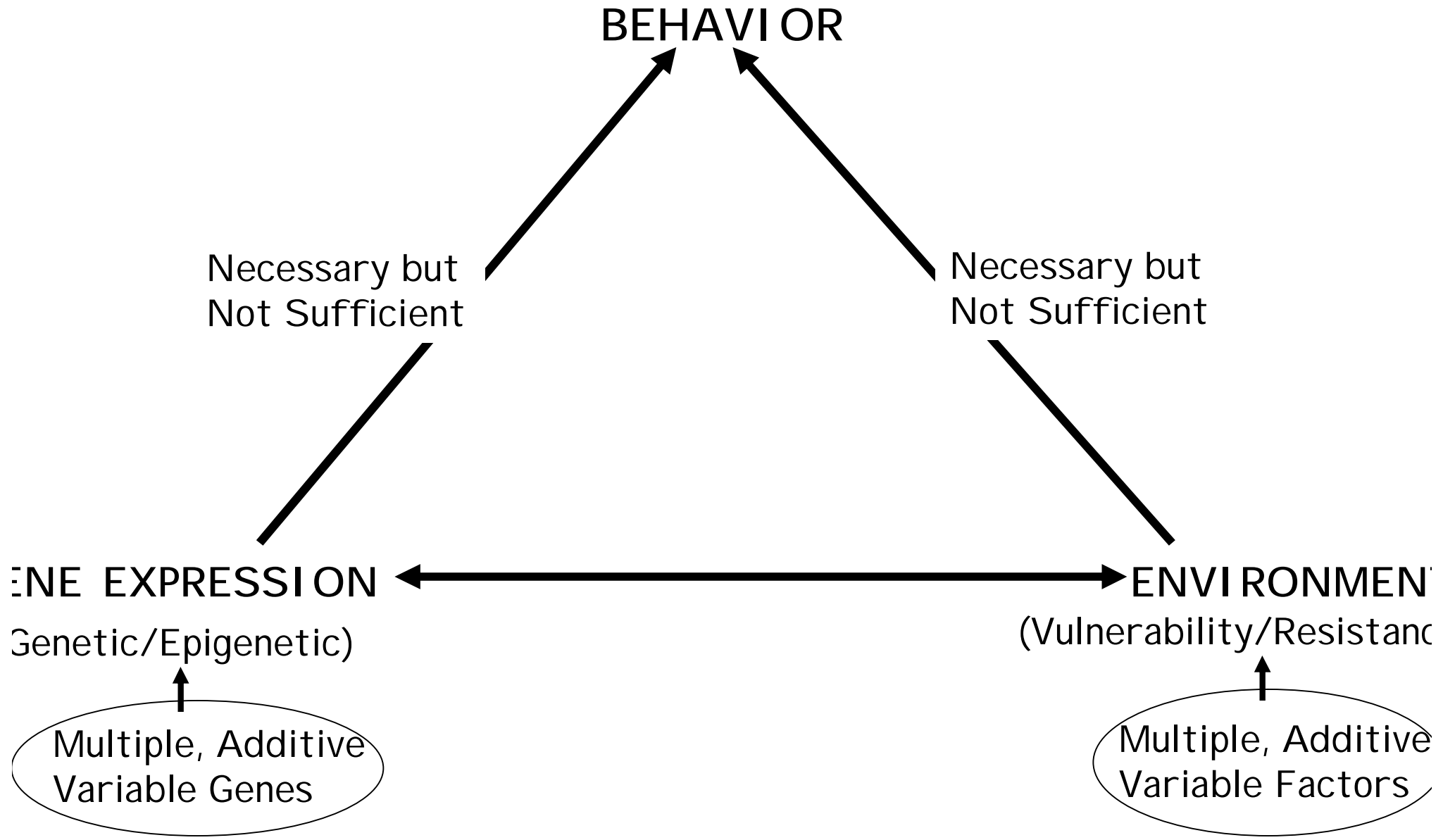
Do we need a broader paradigm for autism pathogenesis ?

A more systemic approach beyond neurologic impact?

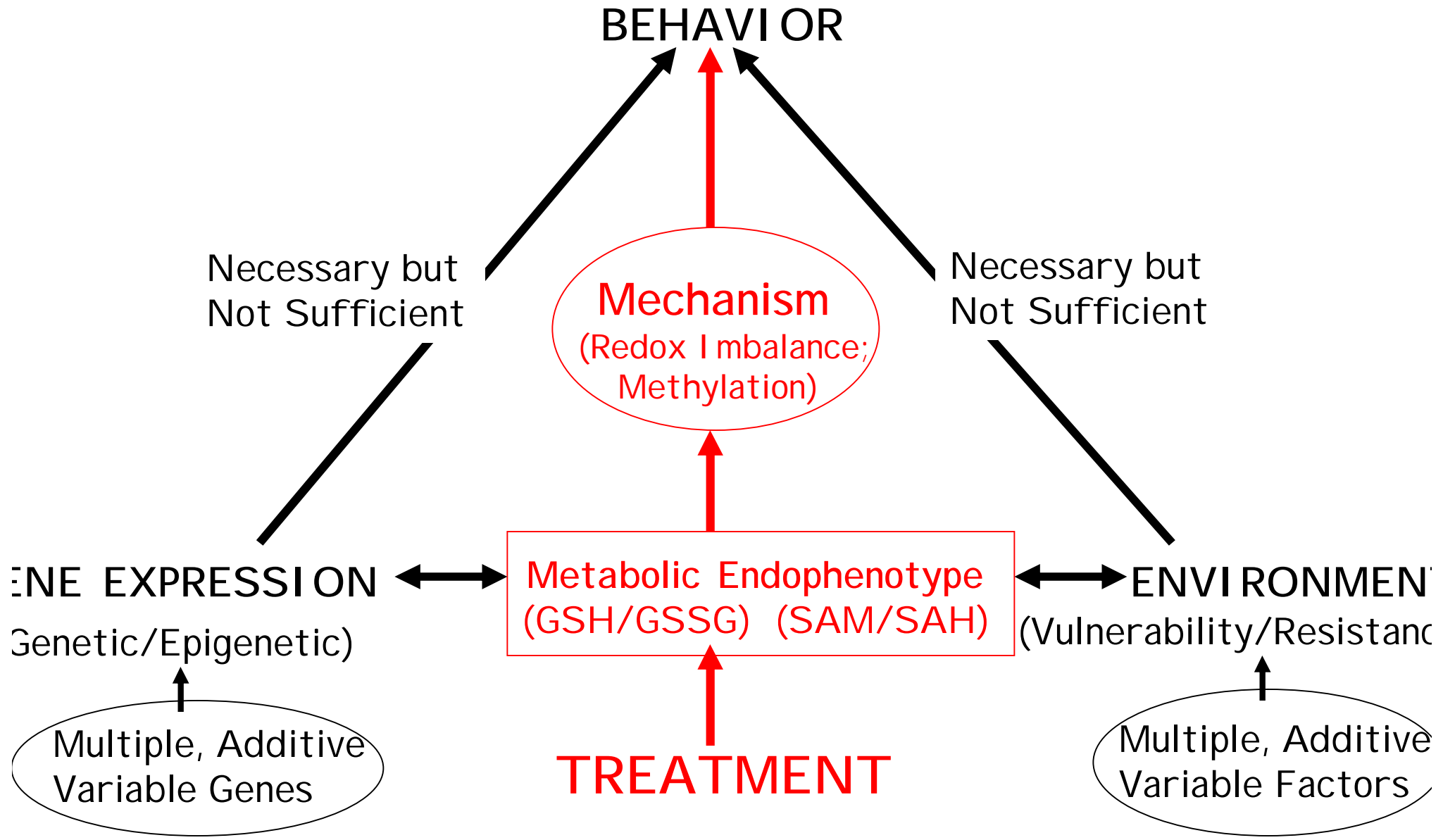
Could there be a component of metabolic encephalopathy that is treatable?

The oxidative stress hypothesis encompasses the possibility of a gut-brain-immune interaction and gene-environment interactions

# FROM EPIDEMIOLOGY TO MECHANISM



# FROM EPIDEMIOLOGY TO MECHANISM



# Future Research Agenda

## Targeted Metabolic Profiling

A targeted metabolic signature is an integrated reflection of genes, environment, and nutrition on a specific pathway of interest

Isolated metabolite evaluation lacks metabolic context

Global metabolomics not yet mature

A targeted metabolic profile provides metabolic context and insights into molecular mechanisms of the disease process, candidate genes, and treatment targets

## Recommendations

1. Focus on candidate metabolic pathways for clues to environmentally relevant candidate genes in autistic children, animal models and cell models; (e.g., redox; detox; immunologic, mitochondrial pathways)
2. Use metabolic biomarkers as targets for treatment strategies and efficacy; identify responders and non-responders to predict response to treatment; insights into novel treatment targets
3. Do comparative studies with CSF and plasma and urine for central and peripheral differences in autistic individuals

## Recommendations

4. Quantitative metabolite patterns may be able to distinguish subpopulations within the heterogeneity of autism
5. Evaluate high risk children with developmental delay, siblings, and discordant twins for predictive biomarkers to facilitate early detection and targeted intervention strategies
6. Infrastructure: NMR, LC/MS/MS; HPLC-Electrochemical Detection; Capillary Electrophoresis-TOF/MS