Trace Metals and Placental Methylation

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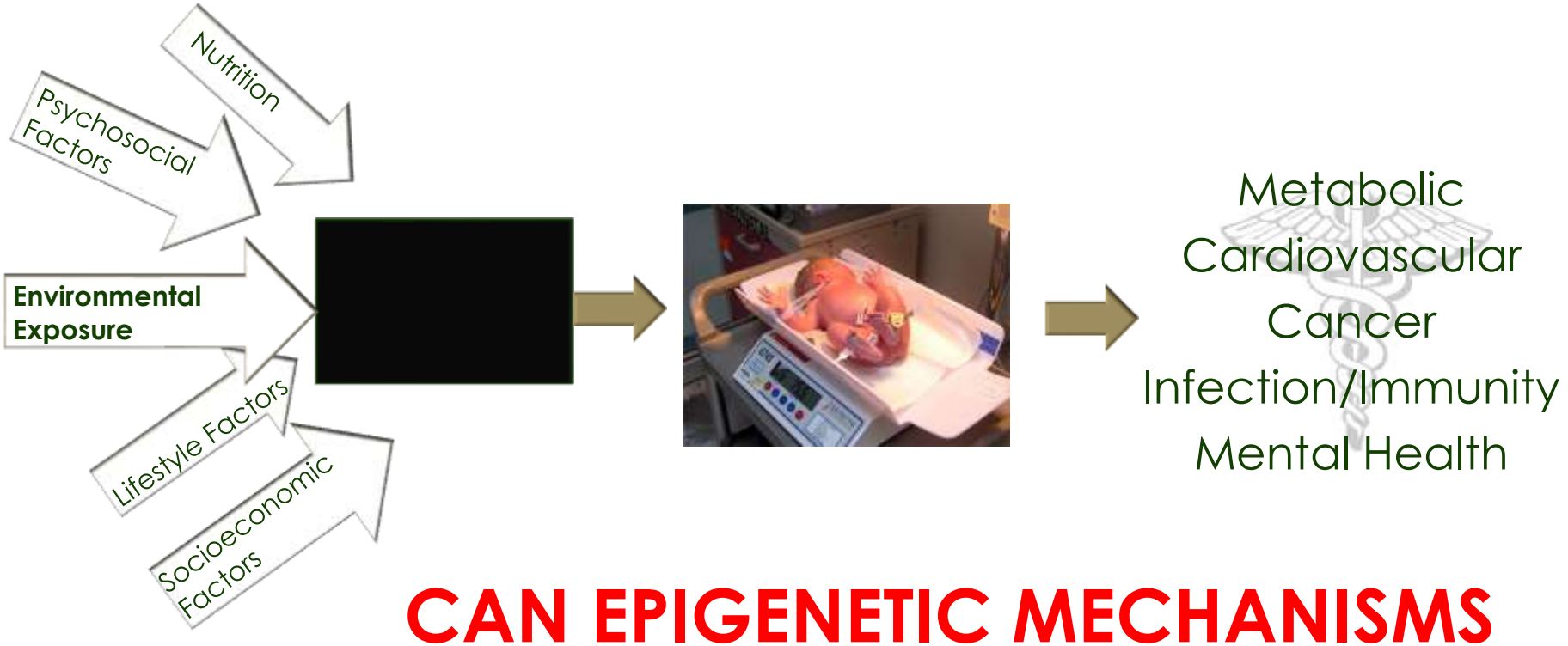
Developmental Origins



CAN EPIGENETIC MECHANISMS FILL THE BLACK BOX?

Epigenetics

- Heritable and Stable Control of Gene Expression Potential Beyond the DNA Sequence
  - Heritable: can pass on to successive cells
    - Does not alter the genetic sequence
  - Stable: cannot **easily** be altered
    - Potentially reversible
  - Controls Gene Expression *Potential*
    - On, Off, Level?

Modes of Epigenetic Regulation

- **DNA Methylation**
- Histone post-translational modification
- Imprinting

Transcription Control

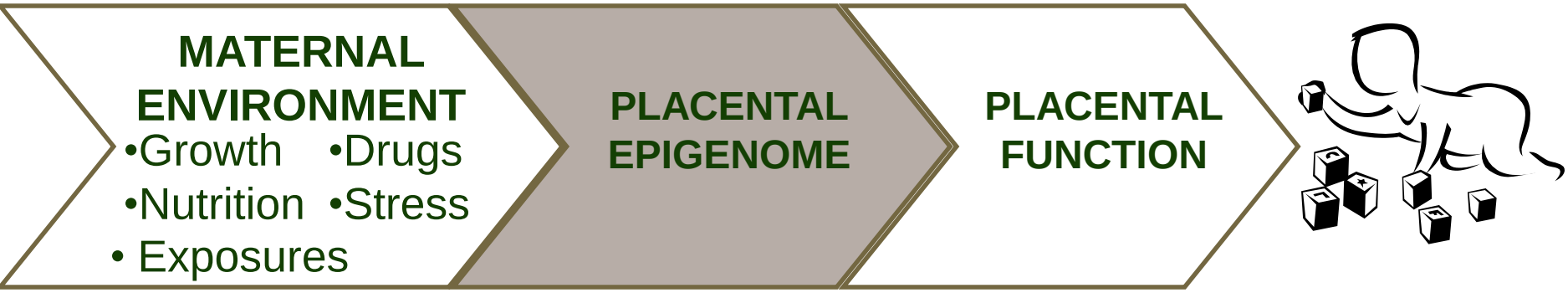
- RNA-mediated regulation

Post-transcription Control

Where we study epigenetic mechanisms matters

- **Epigenetic Patterning is highly tissue specific**
- **Represents functional alteration**
- **Placenta**
  - First complex organ to form
  - Regulates intrauterine environment
  - Transport
    - Nutrients
    - Water
    - Gas
    - Waste products
  - Immuno-endocrine
    - Hormones
    - Growth factors

Role of Placental Epigenome



- Demonstrate placental molecular features integrate environmental signals
- Link variability in molecular features to Infant Outcomes (and beyond!)

DNA Methylation in Placenta

- Mechanism to control gene expression
  - Highly tissue specific
  - Placenta has specific DNA methylation profile
  - Pattern is set during in utero development
- Altered Methylation linked to environmental exposures
- Variability linked to disease risk
- Genome-wide DNA methylation
  - Opportunity to identify novel genes or pathways targeted by exposures
  - Can then examine if these alterations predict downstream outcomes
  - Use Genome-Wide Array Based Approaches
    - Illumina Infinium Methylation450K Array

Study Population: Rhode Island Child Health Study

- 899 mother-infant pairs enrolled at Women and Infants Hospital, Providence RI from 2009-2014
- Healthy Pregnancies with no complications
- Health Term Infants
- Oversampled for SGA (small) and LGA (large) infants. Matched to AGA (appropriate)
- Performed neurobehavioral assessments on newborns during hospital stay using the NICU Network Neurobehavioral Scales
- Obtaining maternal and infant toenails to measure metals

Pregnancy → **Delivery**

Mom
- Medical Chart Review
- Questionnaire

Infant
- Clinical Characteristics
- NNNS Assessment

- Maternal blood
- Toenail Samples

- Placenta
- Cord Blood
- Toenails

Linking Molecular Character with Exposures and Outcomes

Exposures of interest: Mercury

- Crosses placenta
- Interferes with placental function
- Neurobehavioral effects associated with prenatal and childhood exposure
- Exposure through diet (seafood), dental amalgams, industrial pollution

Discovery Study of Hg associated placental DNA Methylation

Used Genome-wide Array to Measure DNA methylation at >450,000 sites in DNA from placenta

Identified 339 Loci whose Methylation was associated with Hg exposures

Asked if methylation of any of these genes was associated with a neurobehavioral profile that could suggest a risk for later problems

Many within genes associated with neurologic outcomes

- Neurodevelopment and behavior
- Schizophrenia
- ADHD
- Movement disorders
- Autism

6 CpG Hg-associated loci are associated with NNNS High Excitability Profile

Illumina CpG Designation	Gene Symbol	P Value	UCSC CpG Island Designation
cg13267931	***EMID2***	8.25×10^{-6}	**Island**
cg14874750	***EMID2***	6.06×10^{-5}	**Island**
cg23424003	***EMID2***	7.30×10^{-5}	**Island**
cg27179533	***EMID2***	5.46×10^{-5}	**Island**
cg27528510	***EMID2***	9.00×10^{-5}	**Island**
cg14048874	***EMID2***	0.0023	**Island**
cg14175932		2.84×10^{-5}	
cg17128947	***CPLX1***	0.0054	**Island**
cg25385940	***TTC23***	0.0059	**N Shore**
cg10470368		0.0075	

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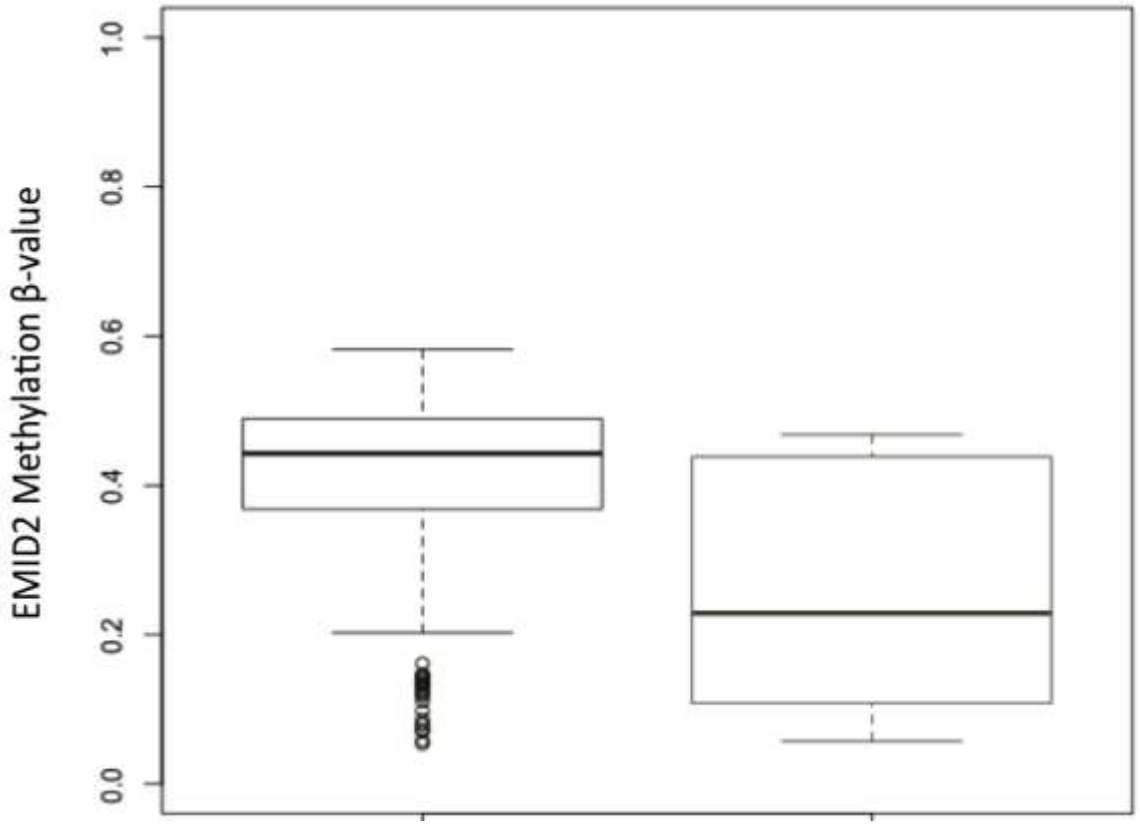
Placental hypomethylation of *EMID2* associated with Risk Behavioral Profile



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EMID2

- Collagen protein, unknown placental function
- Genetic variation in EMID2 mediates side effects on vision and hearing in response to an antidepressant (Adkins et al. 2012)
- More work needed to understand the functional role of this gene in placenta

Focus on Placenta

- Critical organ involved in regulating intrauterine environment and programming numerous fetal functions
- Alterations to genes or pathways can have long-term consequences on development
- DNA methylation are susceptible to environmental signals
  - Toxicant Exposures
  - Maternal Factors/Lifestyle
  - Stress, Psychosocial adversity
- DNA methylation can be linked to critical newborn outcomes
  - Growth
  - Neurobehavioral development
- Can help us to understand how toxicants work, why they lead to long-term health effects, and how we can intervene!

Acknowledgments

Dartmouth

Dave Armstrong
Corina Lesseur Perez
Allison Paquette
Allison Appleton
Dylan Guerin
Brian Jackson
Margaret Karagas & Children's Center Team

Oregon State

Andy Houseman

Mt. Sinai

Jia Chen
Luca Lambertini

Women and Infants

Barry Lester
James Padbury

Brown

Jennifer Maccani
Karl Kelsey

Funding

NIMH R01MH094609
NIEHS R01ES022223
NIEHS P01 ES022832; EPA RD83544201

THE CHILDREN'S ENVIRONMENTAL HEALTH & DISEASE PREVENTION RESEARCH CENTER AT DARTMOUTH