Presentation Plan

**Can environmental effects be passed on across generations?**

- The environment of the parents affects their offspring over their lifetime
- Environmental effects over many generations: the role of the epigenome
- Modeling inheritance of environmental effects across generations using worms
- Conclusions and take-homes
The Environment of the Parents Affects Their Offspring over Their Lifetime

**Question:**
Which of the following can lead to an individual becoming overweight? (raise your hand if you agree)

1) Eating too **little** food

2) Eating too much food

3) Your parents ate too little food **before** you were born

4) Your parents ate too much food **before** you were conceived

Exposure to Famine During Pregnancy Can Lead to Obesity Later in Life

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**The New England Journal of Medicine**

*Volume 279*  
*AUGUST 12, 1979*  
*Number 7*

**OBESITY IN YOUNG MEN AFTER FAMINE EXPOSURE IN UTERO AND EARLY INFANCY**


Abstract: In a historical cohort study of 100,000 19-year-old men exposed to the Dutch famine of 1944-45 and examined at military induction, we tested the hypothesis that prenatal and early postnatal nutrition determines subsequent obesity. Outcomes were opposite depending on the time of exposure. During the last trimester of pregnancy and the first months of life, exposure produced significantly lower obesity rates (P<0.0001). This result is consistent with the inference that nutritional deprivation affected the development of hypothalamic centers regulating food intake and growth, and that subsequent increased food availability produced an accumulation of excess fat in an organism growing to its predetermined maximum size. (N Engl J Med 295:349-353, 1976)
Evidence That a Fatty Diet Pre-Conception Can Alter Your Metabolism

High Fat Diet $\rightarrow$ Metabolic disorder

Obesity $\rightarrow$ Weight gain

Qi Chen
Michelle Lane

How Could This Work?
What is the Epigenome?

Conrad Waddington introduced the term *epigenetics* in the early 1940s.

He defined epigenetics as “the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.”

“The study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence”

*Arthur Riggs*

What is the Epigenome?
Epigenetics and the Epigenome

At the molecular level, the epigenome consists of:

- DNA methylation (5mC)
- Histone modifications (many different kinds)
- Small RNAs

The Epigenome as Mediator of Trans-Generational Effects

DIET
STRESS
CHEMICALS
MANY OTHERS
Agreeing on a Definition of “Transgenerational”

DNA Methylation Can Mediate Chemical Exposure Effects
Can DNA Methylation Transmit Information across Generations?

Small Sperm RNAs as Mediators of Metabolic Disorder
Hypothesis

Histone modifications may also carry environmental information across generations

C. elegans as a Model System
**C. elegans as a Model System**

- Transparent
- Short generation time
- Extensive size of germline
- Suitable for 96-well plate format
- Established genetic, epigenetic and reproductive model
- Conservation of genes and pathways

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**C. elegans Shows a High Degree of Conservation of Histone Modifications**

Wormbook
Studying Transgenerational Effects in *C. elegans*

In two weeks

<table>
<thead>
<tr>
<th>F1 (Embryo)</th>
<th>F2 (Germline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₀ (hermaphrodite)</td>
<td>F₁</td>
</tr>
</tbody>
</table>

Multigenerational Exposure

Environmental Factor

Transgenerational Effect

A Reporter for Epigenetic Germline Silencing

(NL2507, pkls1582[let-858::GFP + rol-6[su1006]]

(Schaner CE and Kelly WG, 2006)
Studying Transgenerational Effects in *C. elegans*

P₀ (hermaphrodite) → F₁ → F₂ → F₃

Environmental Factor

Multigenerational Exposure

Transgenerational Effect

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**Bisphenol A**

\[
\text{HO} \quad \text{Bisphenol A (BPA)} \quad \text{OH}
\]

Plasticizer widely used in the plastic industry.

- Plastic bottle
- Food-can liners
- Dental composite
- Thermal paper

At high doses, has demonstrated reproductive and developmental toxicity,

**Known epigenetic effects in adult germ cells and other cell types**
Transgenerational Desilencing of the Epi-Reporter Following Exposure to BPA (100 μM)

N=5-10, 20 worms each, *P<0.05, **P<0.01, ***P<0.001

Camacho et al., unpublished
Transgenerational Desilencing of the Epi-Reporter Following Exposure to BPA (100 μM)

Camacho et al., unpublished

Ancestral BPA Exposure Causes Transgenerational Reproductive Dysfunctions

Camacho et al., unpublished
Ancestral BPA Exposure Reduces H3K9me3 and H3K27me3 Levels in the F3

Camacho et al., unpublished
Dissecting the Genetic Requirement for BPA Transgenerational Effects

RNAi Against *jmjd-2* and *jmjd-3/utx-1* Rescues H3K9me3 and H3K27me3 at the F3

Camacho et al., unpublished
RNAi Against *jmjd-2* and *jmjd-3/utx-1* Rescues BPA Effects at the F3

Camacho et al., unpublished

BPA's Transgenerational Desilencing Effect Is Likely Mediated by the Female Program

**N**=5, 30 worms each **P**≤0.01. Expression of the *pkIs1582* integrated array was then monitored in F3 germlines.
Main Conclusions of BPA Transgenerational Studies in *C. elegans*

- BPA exposures leads to transgenerational repetitive array desilencing, embryonic lethality and germline apoptosis
- Effects are inherited through the female germline program
- Effects are correlated with lower H3K9me3 and H3K27me3 in the germline
- They are dependent on the activity of Jumonji histone demethylases

**Are We Doomed or Is It an Opportunity for Change?**
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