The Toxic Sins of Our Ancestors

Lecture Plan

1) Your family, their behavior, and your health
2) Can environmental effects be passed on across generations?
3) What is the epigenome?
4) Modeling environmental effects on the epigenome across several generations using worms!
5) Our results
6) Conclusions and take-homes
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Your Family, Their Behavior, and Your Health!

Question:
Which of the following has a scientifically proven effect on becoming overweight? (Raise your hand if you agree.)

1) Eating too little food throughout your life
2) Eating too much food throughout your life
3) Your parents ate too much food before you were born
4) Your parents ate too little food before you were born
A Disease May Originate from an Exposure Many Years Earlier in Life

Birth Cohorts in Relation to Famine Exposure

Obesity Prevalence Rates Among Birth Cohorts in Famine and Control Areas

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A Disease Could Originate from an Exposure Several Generations Before

Many months

Michael Skinner’s Work and Its Associated Controversy

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility
Matthew D. Anway, Andrea S. Cupp, Mehmet Uzumcu, Michael K. Skinner
Science, 2005.
**Spermatogenesis is Impaired Transgenerationally**

A. Control adult male F3

B. VZ adult male F3

*Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility*
Matthew D. Anway, Andrea S. Cupp, Mehmet Uzumcu, Michael K. Skinner

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**How Does It Work?**
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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.”

That definition has now shifted and is generally considered to be:

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

or

*The structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states.*

**QUESTION:** What are the differences between these definitions?

What is the Epigenome?
Can Alteration of Histone Marks be Transgenerationally Transmitted?

The Function of DNA Methylation

- Protecting the genome from transposition
- Genomic imprinting
- X inactivation
- Tissue specific gene expression
DNA Methylation: Establishment and Resetting

Hypothesis

Histone modifications may also carry information across generations.
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**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
C. elegans Shows a High Degree of Conservation of Histone Modifications

Wormbook

A Reporter for Epigenetic Germline Silencing

(NL2507, pkIs1582[let-858::GFP + rol-6(su1006)]

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

![Diagram showing multigenerational exposure and effect](image)

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Bisphenol A

Plasticizer wildly 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
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
Transgenerational Desilencing of the Epi-Reporter Following Exposure to BPA (100 µM)

BPA Exposure Causes a Transgenerational Increase in Embryonic Lethality

N=10-20, **P<0.01, ***P<0.001
Ancestral Response is a Poor Predictor of F3 Desilencing Status

<table>
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<th>% GFP EXPRESSION</th>
<th>DMSO (GFP-)</th>
<th>BPA (GFP-)</th>
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Ancestral Response is a Poor Predictor of F3 Desilencing Status

N=5-10, 20 worms each, *P<0.05, **P<0.01, ***P<0.001
The Reporter Desilencing in the F3 is Dependent on *jmjd-2/jmjd-3/utx-1* Activities

F3 reporter desilencing

F3 Embryonic Lethality is Strongly Dependent on *jmjd-3/utx-1* Activities
Conclusions

• BPA exposure causes a heritable germline chromatin desilencing effect.
• This effect correlates with an increase in embryonic lethality.
• Both chromatin desilencing and embryonic lethality transgenerational phenotypes are dependent on the proper regulation of repressive histone marks.

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