Transgenerational Epigenetic Inheritance and Systemic Racism in America

A Presentation to AB 3121 Task Force to Study and Develop Reparations Proposals For African Americans

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It is well established that personal experiences of trauma, adversity, and discrimination can "get under the skin" and increase risk for a whole host of negative mental and physical health outcomes.

Emerging research now also confirms that negative exposures in one generation, can be passed down to affect the health and well-being of future generations through transgenerational epigenetic inheritance.

What is transgenerational Epigenetic Inheritance?

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It is how the negative effects of adversities and traumas in one generation can be passed down to affect the health and well-being of future generations. Grandchildren and great grandchildren can be negatively impacted by ancestral traumas -- even when they have not been directly exposed to any harm themselves.

Transgenerational Epigenetic Inheritance: Key Concepts

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Kaufman et al., 2021

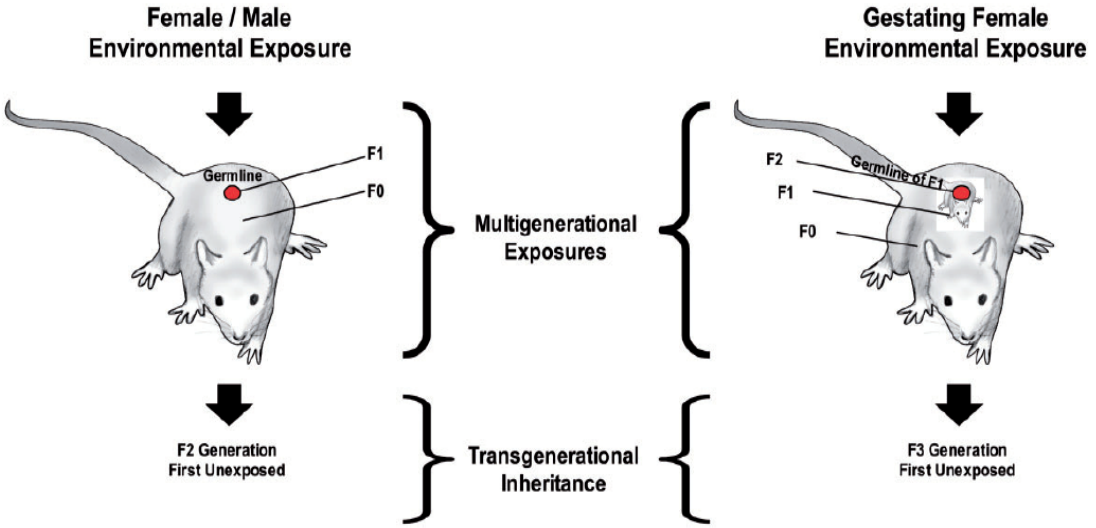
- Epigenetic modifications are chemical modifications to the genes that affect the likelihood of a given gene product being made -- with gene products being things like proteins and hormones that our bodies need to stay healthy.
- Epigenetic modifications are NOT gene mutations. Gene mutations interrupt the codes used to make the gene products so they may not be built right.
- Epigenetic modifications just turn genes on and off, but do not affect the codes used to create the gene products.

Transgenerational Epigenetic Inheritance: Key Concepts (con't)

- Epigenetic mechanisms are one of the ways experiences of trauma get "under the skin."
- For the environmentally induced epigenetic modifications to be inherited across generations, they must be contained in the germline – the sperm or the egg -- as these are the only two cells used to create subsequent life.

Animal Paradigm Used to Study Transgenerational Epigenetic Inheritance

Transgenerational epigenetic inheritance requires the negative outcomes associated with the exposure in the original generation (F0) be evident in subsequent generations with no history of exposure; the F2 generation if the F0 was male; the F3 generation if the F0 was female and pregnant at time of exposure



Reprinted from Nilsson et al., 2018

Code:

F0=first exposed generation

F1=Offspring/children

F2=Grandchildren

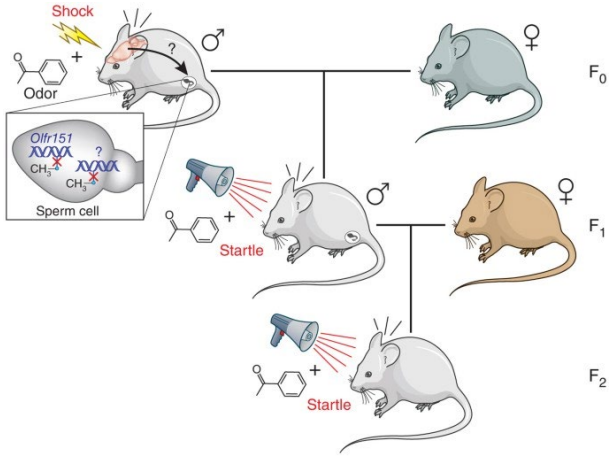
F3=Great grandchildren

Transgenerational Epigenetic Transmission

Experiment 1: Fear Conditioning

a behavioral analog for trauma exposure

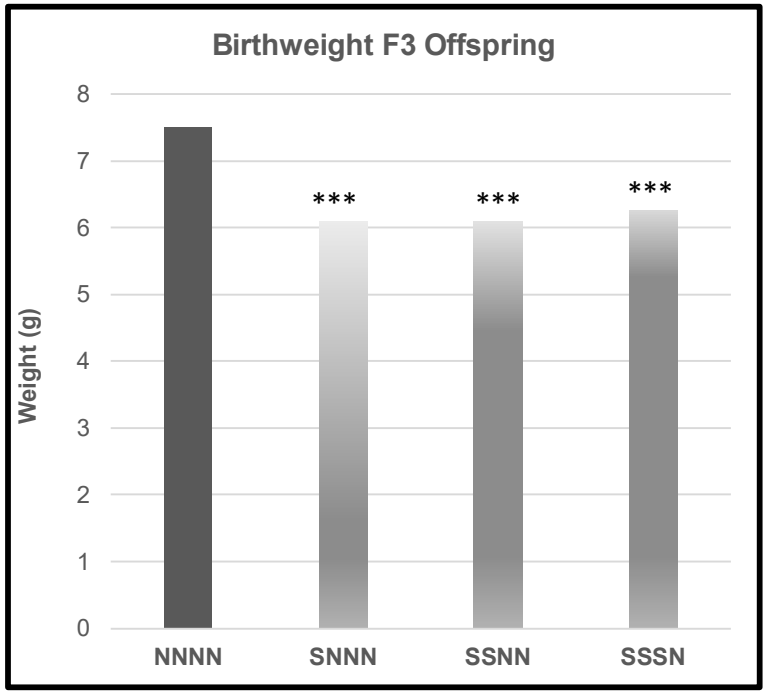
- Fear Conditioning F0 mice: Pair shock and odor (Dias & Ressler, 2014)
- F1 (e.g., children) and F2 (e.g., grandchildren) generations had an increased behavioral sensitivity (e.g., fear) to the F0-conditioned odor, but not to other odors, despite no prior exposure to the odor or shocks.



- F0 mice subjected to fear conditioning and their F1 offspring were also found to have epigenetic marks in their sperm in a gene critical to olfactory perception.
- F0-fear conditioning was also associated with changes in brain regions involved in olfactory perception in the F1 and F2 generation offspring of F0 fear conditioned mice.
- IVF experiment further supports the role of sperm epigenetics

Transgenerational Epigenetic Transmission

Experiment 2: Stress During Pregnancy



Code:

NNNN=No stress across four generations

SNNN=F0 Transgenerational stress

SSNN & SSSN= Multigenerational stress

Yao et al., 2014

- **F0 pregnant rats exposed to stress from gestational days 12-18**
- **4 generations studied**
- **Stress reduced maternal weight gain in the F0 cohort and each successive generation**
- **Stress decreased gestational length beginning in the F1**
- **Stress increased maternal blood glucose levels by the F2 cohort**
- **Decreased offspring weight by F1 -- greatest F3 offspring of transgenerationally stressed mothers (SNNN)**

Transgenerational Epigenetic Transmission
Experiment 2: Stress During Pregnancy (con't)

Yao et al., 2014

- Offspring of prenatally, multigenerationally, and trans-generationally stressed mothers had developmental delays
- A multigenerational history of prenatal stress was associated with changes in genes implicated in brain plasticity, parturition/childbirth, and preterm birth

The documentation of an impact of transgenerational and multigenerational stress on preterm birth is particularly interesting given racial disparities in rates of preterm birth, and recent findings that adequate prenatal care does not reduce racial disparities, with African American women who engage in adequate prenatal care still at elevated risk for preterm birth.

Thurston et al., 2021

Transgenerational Epigenetic Transmission

Experiment 3: High Fat Diet

de Castro Barbosa et al., 2016

- **F0 male rats were fed either a high-fat or normal chow-diet for 12 weeks and then mated to normal chow-fed females to create F1 and F2 generation offspring.**
- **The F1 (e.g., children) and F2 (e.g., grandchildren) offspring of the F0 males fed the high-fat diet had reduced birth-weight when compared to the offspring of chow-fed F0 males; with low birth-weight a documented risk factor for obesity and type 2 diabetes.**
- **F0 male rats fed the high-fat diet and their F1 male offspring had common sperm epigenetic changes in genes implicated in the regulation of glucose homeostasis, insulin sensitivity, and a predisposition to Type 2 diabetes.**
- **A history of a high fat/poor diet can impact the health of descendants across multiple generations.**

Transgenerational Epigenetic Transmission

Experiment 4: Lead Exposure

Meyer et al., 2020

- **Meyer and colleagues used zebrafish to study the transgenerational repercussions of lead exposure.**
- **F0 embryos were exposed for 24 hours to waterborne lead. The F0 generation zebrafish were then raised to adulthood and F1 and F2 generation offspring, who had no direct lead exposure, were then studied.**
- **The dosage of lead exposure used in this investigation was previously found to generate learning impairments in zebrafish, and similar learning impairments were found to be present in the F2 offspring of F0 lead exposed zebrafish.**
- **F2 offspring of F0 lead exposed zebrafish had altered expression in genes involved in brain development (e.g., synaptic function and plasticity, neurogenesis) and epigenetic processes -- genes which may be involved in lead-induced neurobehavioral deficits and/or their inheritance.**

Summary: Part I

- Emerging research confirms that negative exposures in one generation, can be passed down to affect the health and well-being of future generations through transgenerational epigenetic inheritance – the transgenerational transmission of experience-dependent chemical modifications to the genes.
- While most of the research to date has been conducted in animals, studies in humans have shown ancestors exposure to trauma, poor nutrition, and toxic chemicals can impact the health of descendants across several generations, and some of the epigenetic modifications noted in animal studies have also been reported in humans.

Summary: Part I (con't)

- For the environmentally induced epigenetic modifications to be inherited across generations, they must be contained in the germline (e.g., sperm, egg), which has now been demonstrated in multiple studies.
- The causal significance of these epigenetic changes have also been demonstrated with in-vitro fertilization studies.
- The biological relevance of the genes regulated by the epigenetic marks identified in the studies of transgenerational epigenetic inheritance provide compelling support for the role of these mechanisms in the transmission of experience-dependent traits and health problems.

Preventing the Transmission of the Negative Effects of Ancestral Traumas

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Animal Studies

- Fear Conditioning/Trauma -> Extinction Training/Treatment (Aoued, Ressler, Dias, et al., 2019)
- High Fat Diet -> Healthy Diet and Exercise (McPherson et al., 2015)
- Prenatal Stress -> Exercise and Enrichment (Bustamante et al., 2013;Schander et al., 2020)
- In-utero Lead Exposure -> Enrichment (Cao et al., 2008)

Preventing the Transmission of the Negative Effects of Ancestral Traumas

Human Studies

- Harlem Children's Zone programs and Carolina Abecedarian Project (HCZ, 2021;Slopen, 2021;Winkleby, 2007)
- Stanford Medical Youth Science Program (Easterlin et al., 2019)
- Strong African American Families Prevention Program (Hanson, Brody et al,, 2018; Kaufman et al., 2021)

Preliminary data suggest the negative impact of ancestral traumas can be prevented, with a role for trauma-informed services, culturally-adapted prevention and intervention programs, and enrichment opportunities strongly indicated.

True change and healing, however, will require acknowledgement of the harms that were done, and broader systemic policy level changes.