Epigenetic Transgenerational Inheritance

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Abstract

Epigenetic processes are the molecular mechanisms an organism uses to respond to environmental changes with changes in gene expression. Exposure to environmental factors or toxicants can result in epigenetic changes that cause changes in gene expression or increased disease incidence. Epigenetic changes can be inherited across generations, even after exposure to the environmental factors has ceased. This is known as epigenetic transgenerational inheritance. When a gestating female is exposed to an environmental factor, that F0 generation female, the F1 generation fetus, and the germ cells (sperm or eggs) that are inside the fetus that will produce the F2 generation, are also directly exposed. Therefore, examination of the F3 generation (great grand-offspring) is needed to assess transgenerational phenomena. If an adult male or non-pregnant female is exposed to an environmental factor, then the F0 generation adult and the germ cells that will generate the F1 generation are directly exposed, and examination of the non-exposed F2 generation (grand-offspring) is required to demonstrate a transgenerational phenomenon.

Glossary

Epigenetics Molecular factors and processes around DNA that regulate genome activity independent of DNA sequence, and which are mitotically stable.
Epimutation An altered epigenetic mark at a specific chromosomal site, often in response to exposure to an environmental factor.
Transgenerational epigenetic inheritance Germline (sperm or egg) transmission of epigenetic information between generations in the absence of any continued direct exposures or genetic manipulations.

Key Points

- Epigenetic Transgenerational Inheritance.

Introduction

It is self-evident that the environment has a strong effect on the biology of an organism. Changes in the environment or exposure to environmental toxicants can result in changes in gene expression and development of pathologies or phenotypic variation. Epigenetic factors are the molecular mechanisms an organism uses to respond to environmental changes with changes in gene expression. Although more traditional definitions exist (Skinner *et al.*, 2010; Skinner, 2011), a modern mechanistic definition of epigenetics is:

Molecular factors/processes around the DNA that regulate genome activity independent of DNA sequence, and that are mitotically stable.

The term epigenetics was coined by Dr. Conrad Waddington, University of Edinborough, in the 1940s to describe gene-environment observations that could not be explained with classic genetics (Waddington, 1942). In the 1970s DNA methylation was the first epigenetic molecular mark to be characterized. With DNA methylation a small (methyl) chemical group is attached to DNA, primarily at the cytosine base in animals (Holliday and Pugh, 1975; Singer *et al.*, 1979). In the 1990s the histone proteins that DNA is wrapped around were also found to be chemically modified to alter gene expression (Davie, 1998; Loidl, 1994). In the 2000s non-coding RNA molecules were identified that can act as epigenetic factors (Kornfeld and Bruning, 2014). The coiling, looping and general structure of DNA, termed chromatin structure, is also an epigenetic factor (Yaniv, 2014). Additional DNA cytosine modifications have also been described (Liu *et al.*, 2016). More recently RNA methylation has been shown to alter the RNA structure to recruit proteins that impact gene expression and cellular function. The currently known epigenetic molecular processes are DNA cytosine modifications, histone modifications, functional non-coding RNA, RNA methylation, and chromatin structure. All these epigenetic processes are important and have distinct roles in the regulation of how genes are expressed in the genome, independent of DNA sequence. New epigenetic marks and processes will also likely be identified in the future.

The vast majority of environmental factors and toxicants do not have the ability to alter DNA sequence or promote genetic mutations (McCarrey, 2012). In contrast, the environment can dramatically influence epigenetic processes to alter gene expression and development. Therefore, epigenetics provides a molecular mechanism for the environment to directly alter the biology of an organism (Jirtle and Skinner, 2007). An altered epigenetic mark at a specific chromosomal site in response to an environmental factor is termed an "Epimutation" (Skinner *et al*., 2010). Therefore, DNA sequence changes are genetic mutations, while environmentally altered epigenetic sites that influence genome activity are epimutations.

Epigenetic changes can be inherited across generations, and can result in changes in gene expression and phenotype in subsequent generations, even after exposure to the environmental changes or factors has ceased. "Epigenetic Transgenerational Inheritance" is defined as (Skinner *et al*., 2010; Skinner, 2014):

Germline (sperm or egg) transmission of epigenetic information between generations in the absence of any continued direct exposures or genetic manipulations.

An early study on the toxicant actions of the agricultural fungicide vinclozolin identified the epigenetic transgenerational inheritance phenomenon (Anway *et al*., 2005). F0 generation pregnant rats were exposed to vinclozolin at the time of fetal sex determination and direct effects on F1 generation adults were identified. F1 generation adult males developed a testis abnormality. When the F1 generation offspring were bred to generate the F2 generation (grand-offspring) the F2 generation adult males were found to have the same testis defects as the F1 generation. When the animals were bred to the transgenerational F3 and F4 generations, the adult testis defect continued in over 90% of all male progeny (Anway *et al*., 2005). As the animals aged, both males and females developed disease in a variety of organs (Anway *et al*., 2006). The frequency of the abnormality did not decline at each generation, but stayed high suggesting a non-Mendelian phenomenon not following classic genetic processes. When the male vinclozolin lineage animal was outcrossed to a wildtype female, the transgenerational phenotype was maintained at the same frequency, but a reverse outcross of a vinclozolin lineage female to a wildtype male resulted in loss of the phenotype (Anway *et al*., 2005). Therefore, a transgenerational phenomenon was observed that was transmitted through the male germline (sperm). Later experiments with other toxicant exposures (**Table 1**) have shown transmission through the female germline predominantly (Manikkam *et al*., 2014), such that the transgenerational phenotype is transmitted in a parent of origin allelic manner, similar to imprinted genes.

To understand transgenerational phenomena it is essential to distinguish between direct exposure effects versus germline (sperm or egg) mediated transgenerational events. When a gestating female is exposed, that F0 generation female, the F1 generation fetus, and the germ cells (sperm or eggs) that are inside the fetus and that will produce the F2 generation, are also directly exposed, **Fig. 1**. Therefore, any effects seen in the F0, F1 and F2 generations may be due to direct exposure toxicity as well as to environmentally induced epigenetic changes. Examination of the F3 generation (great grand-offspring) is minimally needed to assess transgenerational phenomenon, since direct exposure effects are not involved (Skinner, 2008), **Fig. 1**. In contrast, in the event an adult male or non-pregnant female is exposed to an environmental factor, then the F0 generation adult and the germ cells that will generate the F1 generation are directly exposed, and examination of the non-exposed F2 generation (grand-offspring) is required to demonstrate a transgenerational phenomenon. When multiple generations are directly exposed, this is referred to as a multigenerational exposure, which has been shown to have effects with a variety of exposures (Skinner *et al*., 2010). The ability to transmit information from one generation to the next requires the sperm or egg so transgenerational events are germ cell mediated (**Fig. 1**).

Consideration of environmentally induced epigenetic transgenerational inheritance is anticipated to have a significant role in all areas of biology. Knowledge of environmental epigenetics and epigenetic inheritance will help to better understand how environmental factors and toxicant exposures can influence our health and disease across generations. In addition, epigenetic transgenerational inheritance will have a critical role in evolution (Skinner, 2015). The environment can impact the phenotypic variation and adaptation through epigenetic transgenerational inheritance to impact natural selection and Darwinian evolution (Skinner and Nilsson, 2021).

Table 1 Environmentally induced epigenetic transgenerational inheritance

Environmental toxicants	
Vinclozolin (agricultural fungicide)	Permethrin and DEET (insect repellant)
Methoxychlor (agricultural pesticide)	DDT (pesticide)
Dioxin/TCDD (industrial contaminant)	Tributyltin (industrial toxicant and biocide)
Plastic compounds (BPA and phthalates)	Hydrocarbons (jet fuel)
Other types exposures	
Nutrition (high fat or caloric restriction)	Smoking and alcohol
Temperature and drought (plant health and flowering)	Stress (behavioral)

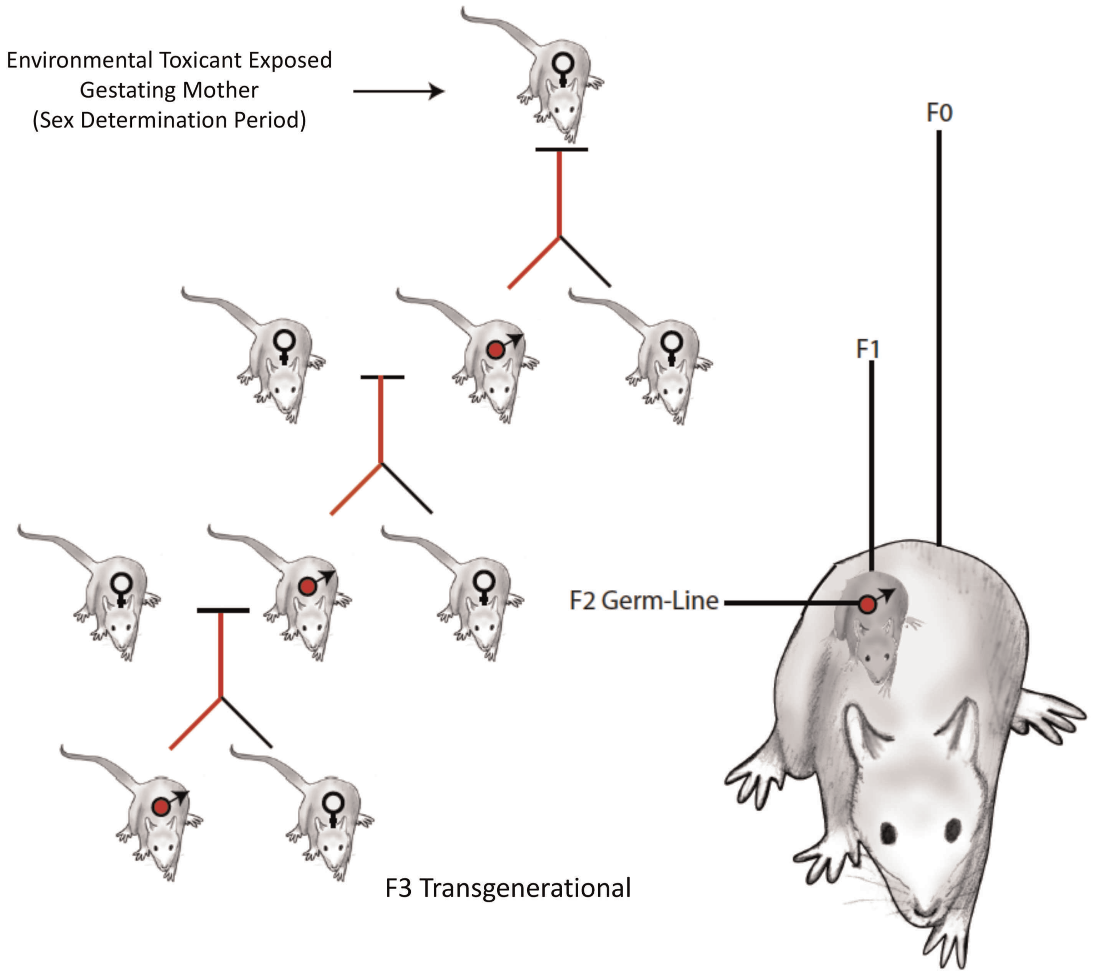

Fig. 1 Environmental factor exposure example showing an F0 generation pregnant animal exposed to a toxicant, and illustrating that the multigenerational F1 and F2 generations were also directly exposed, while the transgenerational F3 generation had no direct exposure. Adapted from Skinner, M.K., 2008. What is an epigenetic transgenerational phenotype? F3 or F2. Reproductive Toxicology 25, 2–6.

Conclusions

A wide variety of environmental toxicants (Nilsson *et al.,* 2022) and other factors (**Table 1**) promote epigenetic transgenerational inheritance of alterations in phenotypic variation and pathology. Environmental epigenetics is how the organism responds and epigenetic transgenerational inheritance is how environmental factors such as toxicants promote pathologies in future generations even when the exposures are removed. Exposures to DDT in the 1950's and 1960's have been shown to have had dramatic effects transgenerationally on pathologies such as obesity (Ben Maamar *et al.,* 2019). Recently, the compounded impacts of different types of exposures at each generation have also been observed through epigenetic transgenerational inheritance (Nilsson *et al.,* 2023).

References

Anway, M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K., 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308, 1466–1469.
Anway, M.D., Leathers, C., Skinner, M.K., 2006. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology 147, 5515–5523.
Davie, J.R., 1998. Covalent modifications of histones: Expression from chromatin templates. Current Opinion in Genetics & Development 8, 173–178.
Holliday, R., Pugh, J.E., 1975. DNA modification mechanisms and gene activity during development. Science 187, 226–232.
Jirtle, R.L., Skinner, M.K., 2007. Environmental epigenomics and disease susceptibility. Nature Reviews. Genetics 8, 253–262.
Kornfeld, J.W., Bruning, J.C., 2014. Regulation of metabolism by long, non-coding RNAs. Frontiers in Genetics 5, 57.
Liu, M.Y., Denizio, J.E., Schutsky, E.K., Kohli, R.M., 2016. The expanding scope and impact of epigenetic cytosine modifications. Current Opinion in Chemical Biology 33, 67–73.
Loidl, P., 1994. Histone acetylation: Facts and questions. Chromosoma 103, 441–449.
Ben Maamar, M., Nilsson, E., Sadler-Riggleman, I., *et al.,* 2019. Developmental origins of transgenerational sperm DNA methylation epimutations following ancestral DDT exposure. Developmental Biology 445, 280–293.

Manikkam, M., Haque, M.M., Guerrero-Bosagna, C., Nilsson, E., Skinner, M.K., 2014. Pesticide methoxychlor promotes the epigenetic transgenerational inheritance of adult onset disease through the female germline. PLoS One 9 (7), 1–19 e102091.

McCarrey, J.R., 2012. The epigenome as a target for heritable environmental disruptions of cellular function. Molecular and Cellular Endocrinology 354, 9–15.

Nilsson, E., Ben Maamar, M., Skinner, M.K., 2022. Role of Epigenetic Transgenerational Inheritance in Generational Toxicology. Environmental Epigenetics 8 (1),1–9, dvac001.

Nilsson, E., McBirney, M., De Santos, S., *et al.*, 2023. Multiple generation distinct toxicant exposures induce epigenetic-transgenerational-inheritance of enhanced pathology and obesity. Environmental Epigenetics 9 (1), 1–19 dvad006.

Singer, J., Roberts-Ems, J., Riggs, A.D., 1979. Methylation of mouse liver DNA studied by means of the restriction enzymes msp I and hpa II. Science 203, 1019–1021.

Skinner, M.K., 2008. What is an epigenetic transgenerational phenotype? F3 or F2. Reproductive Toxicology 25, 2–6.

Skinner, M.K., 2011. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. Epigenetics 6, 838–842.

Skinner, M.K., 2014. Endocrine disruptor induction of epigenetic transgenerational inheritance of disease. Molecular and Cellular Endocrinology 398, 4–12.

Skinner, M.K., 2015. Environmental epigenetics and a unified theory of the molecular aspects of evolution: A neo-Lamarckian concept that facilitates neo-Darwinian evolution. Genome Biology and Evolution 7, 1296–1302.

Skinner, M.K., Manikkam, M., Guerrero-Bosagna, C., 2010. Epigenetic transgenerational actions of environmental factors in disease etiology. Trends in Endocrinology and Metabolism 21, 214–222.

Skinner, M.K., Nilsson, E.E., 2021. Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environmental Epigenetics 7 (1), 1–12, dvab012.

Waddington, C.H., 1942. The epigenotype. Endeavour 1, 18–20.

Yaniv, M., 2014. Chromatin remodeling: From transcription to cancer. Cancer Genetics 207, 352–357.