13.06 Epigenetic Transgenerational Inheritance and Generational Toxicology

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Abstract

The ability of an environmental toxicant to promote a phenotype or disease state not only in the individual exposed, but also in subsequent progeny for multiple generations is termed epigenetic transgenerational inheritance. The majority of environmental factors or toxicants do not promote genetic mutations or alterations in DNA sequence, but do have the capacity to alter the epigenome. This article will review the mechanisms and biology of this epigenetic transgenerational toxicology.

13.06.1 Introduction

The majority of environmental factors and toxicants do not have the ability to alter DNA sequence or promote genetic mutations (Anway *et al.*, 2005; Jirtle and Skinner, 2007; Szyf, 2007). This is due in large part to the stability of the genome. However, most will promote abnormal phenotypes or disease. Early life exposures often lead to later life adult onset disease (Hanson and Gluckman, 2008). This toxicity is not mediated through genetic mechanisms, but instead is mediated through altered molecular processes such as epigenetics (Anway *et al.*, 2005; Jirtle and Skinner, 2007; Mohajer *et al.*, 2021; Morgan and Whitelaw, 2009; Nilsson and Skinner, 2015; Skinner, 2014; Waterland, 2009; Weidman *et al.*, 2007; Zhu *et al.*, 2023). Therefore, in the event that these environmental factors promote a heritable, or familial, transmission of the disease phenotype, it often involves non-Mendelian epigenetic inheritance.

The heritable transmission of environmentally induced phenotypes across generations is referred to as an epigenetic transgenerational inheritance (Anway *et al.*, 2005; Jirtle and Skinner, 2007; Nilsson *et al.*, 2022; Skinner, 2014; Whitelaw and Whitelaw, 2008). The vast majority of environmental exposures will affect somatic cells that cannot promote a transgenerational phenotype, but may be critical for the individual exposed in regard to potential adult onset disease (Anway *et al.*, 2005; Jirtle and Skinner, 2007; Skinner, 2011, 2014). In the event germ-line alterations are involved, then the exposure has the potential to promote a transgenerational phenotype (**Table 1**). Therefore, transgenerational toxicology can be considered as a subset of toxicology involving direct actions of environmental factors on the germ line.

Toxicology studies often involve a correlation between exposure and the development of an abnormal phenotype or disease. The future of the field of toxicology lies in the elucidation of the molecular and cellular mechanisms involved in the actions of the environmental factors or toxicants. A basic understanding of the molecular mechanisms involved in toxicology will dramatically facilitate risk assessment and provide diagnostic tools for exposure analysis and help develop potential treatments for exposures. Although susceptibility to exposure and genetics are important molecular factors, an additional mechanism such as epigenetics is critical to consider in future toxicology research (Nilsson *et al.*, 2022).

13.06.2 Transgenerational Phenotypes

As discussed, the majority of toxicology involves direct exposures of somatic tissues. In contrast, transgenerational phenotypes and toxicology exclude direct exposure and must be transmitted through multiple generations and the germline (**Table 2**) (Jirtle and Skinner, 2007; McCarrey, 2014; Nilsson *et al.*, 2022; Skinner, 2008, 2014). For example, exposure of a gestating female provides direct exposure of the F0 generation female, the F1 generation embryo, and the germ line within that embryo that will generate the F2 generation (Skinner, 2008). Therefore, a phenotype in the F3 generation that derives from the exposed lineage has an obligate transgenerational phenotype. The toxicity observed in the F0 and F1 generations, as well as that in the F2 generation germ line, was due to direct exposures (Jirtle and Skinner, 2007; Nilsson *et al.*, 2022; Skinner, 2008, 2014). Importantly, the ability of a direct

Table 1 Sites of action and phenotypes of environmental factors and toxicants.

Site action	*Biological response and toxicology*
Somatic cells	Allows tissue-specific toxicology and critical for adult onset disease in the individual exposed, but not capable of transmitting a transgenerational phenotype
Germ cells	Allows transmission between generations and in the absence of direct exposure promotes a transgenerational phenotype

Table 2 Transgenerational versus multigenerational phenotypes and toxicology.

Phenotype	*Exposure*	*Definition*
Multigenerational	Direct	Coincident direct exposure of multiple generations to an environmental factor or toxicant promoting alterations in the multiple generations exposed
Transgenerational	None, except the initial generation	After the initial exposure the transgenerational phenotype is transmitted through the germ line in the absence of direct exposure

exposure to influence multiple generations is defined as a multiple generation phenotype rather than a transgenerational phenotype. A transgenerational phenotype requires the absence of a direct exposure and toxicity (Nilsson *et al.*, 2022; Skinner, 2008) (**Table 2**).

One class of environmental compounds or toxicants involved in such phenotypes are endocrine disruptors that interfere with normal hormone signaling. A classic example of a multigenerational exposure involves a pharmaceutical agent with estrogen agonist activity, namely diethylstilbestrol (DES) (Newbold, 2008). Exposure of a gestating female to DES was found to promote an abnormal reproductive tract and gonadal dysfunction in the F1 generation males and females, as well as abnormal female reproductive tract function and male genitourinary tract abnormalities in the F2 generation (Brouwers *et al.*, 2006; Newbold *et al.*, 2006; Titus, 2021). This was accompanied by changes in DNA methylation (Bromer *et al.*, 2009). Interestingly, the phenotype of the F1 and F2 generations differs. Limited information exists on the F3 generation in humans, but only a delay in age of first estrus was observed in F3 generation rodent models (Brouwers *et al.*, 2006; Newbold *et al.*, 2006; Newbold, 2008; Ziv-Gal *et al.*, 2015). It is possible that DES promotes a transgenerational phenotype in humans, but extended generations need to be investigated (Newbold *et al.*, 2006; Titus, 2021). Another example of a multigenerational toxicology is a study with flutamide (Anway *et al.*, 2008a). Exposure of a gestating female to this anti-androgenic endocrine disruptor promoted abnormalities in the testis of the F1 generation and affected skeletal development in the F2 generation, but had no effects on the F3 generation (Anway *et al.*, 2008a). Again, the F1 and F2 generation phenotypes were distinct. In contrast, another endocrine disruptor, vinclozolin, did promote a transgenerational phenotype in the F3 generation (Anway *et al.*, 2008a). There are many environmental factors and toxicants that promote altered phenotypes for multiple generations involving direct exposure of the different factors (Albert and Jegou, 2014; Chen *et al.*, 2015; Clapp and Jaspers, 2017; Corrales *et al.*, 2014; Faroon and Ruiz, 2015; Fullston *et al.*, 2015; Hanson and Gluckman, 2008; Jirtle and Skinner, 2007; Klaver *et al.*, 2015; Milesi *et al.*, 2021; Nilsson *et al.*, 2022; Viluksela and Pohjanvirta, 2019). These multigenerational exposures and phenotypes are not transgenerational, although critical to consider in assessing the toxicology of an environmental agent.

Transgenerational phenotypes and toxicology require transmission between generations to involve the germ line. These transgenerational phenotypes occur in the absence of direct exposure (**Table 2**). Somatic cell targets are critical and common in toxicology to promote adult onset disease and phenotypes, but are not able to transmit the phenotype transgenerationally without continued direct exposure. Therefore, the critical target cell for transgenerational phenotypes and toxicology is the sperm and egg germ cells.

13.06.3 Epigenetics

Epigenetics is defined as molecular factors and processes around DNA that regulate genome activity independent of DNA sequence and are mitotically stable (Skinner, 2011). Epigenetic regulation of genome activity is critical in the development and maintenance of cellular function and differentiation. The term epigenetics was originally coined by Conrad Waddington in his discussion of gene–environment interactions (Waddington, 1940). The first molecular factor identified was DNA methylation in the 1970s (Holliday and Pugh, 1975) followed by histone modifications and chromatin structure in the 1990s and noncoding RNA in 2000s (Jirtle and Skinner, 2007). Therefore, the majority of the molecular elements of epigenetic regulatory processes have only been recently elucidated (Jirtle and Skinner, 2007; Nilsson *et al.*, 2022; Skinner, 2014). Epigenetic processes are known to involve a number of molecular processes including DNA methylation, histone modifications, chromatin structural change, and noncoding RNAs (**Table 3**). These processes do not directly involve DNA sequence and hence are considered epigenetic and are as equally important in regulating genome activity (i.e., gene expression) as the primary DNA sequence (i.e., genetics).

Table 3 Examples of epigenetic processes.

DNA methylations	*Methyl cytosine at CpG sites*
Histone modifications	Methylation and Acetylation at lysine residues
Chromatin structure	Loop and bend structures and nuclear matrix associations
Noncoding RNA	Small RNA influencing RNA stability and gene expression
RNA methylation	Methylation that impacts translation and mRNA stability

The ability of environmental factors or toxicants to influence epigenetic processes associated with altered phenotypes has been demonstrated in different model systems. The first observations of how the environment could influence epigenetics and phenotype was made in rats with the antiandrogenic toxicant vinclozolin (Anway *et al.*, 2005). Early observations of non-genetic phenotypes in plants have also been made (Cuzin *et al.*, 2008). A classic mouse model is the Agouti model (Dolinoy, 2008; Rakyan *et al.*, 2003). An epigenetic modification of the Agouti locus alters coat color and metabolic function (Dolinoy, 2008; Waterland, 2009). Environmental factors, such as nutrition, and toxicants, such as the estrogenic endocrine active substance bisphenol A (BPA) that is a common plasticizer compound to which humans are exposed, can modulate the DNA methylation state in the murine Agouti locus to alter phenotypes (Dolinoy *et al.*, 2007). There are many other environmental factors that promote phenotypic changes through epigenetic processes (Clapp and Jaspers, 2017; Dominguez-Salas *et al.*, 2012; Hanson and Gluckman, 2008; Jirtle and Skinner, 2007; Leung *et al.*, 2021; Ma *et al.*, 2022; Morgan and Whitelaw, 2009; Nava-Rivera *et al.*, 2021; Tobi *et al.*, 2014; Veenendaal *et al.*, 2013).

As discussed, the majority of toxicology and actions of environmental factors are on somatic cells (**Table 2**). Examples of specific toxicants acting on a given tissue to promote a disease state in many cases involve epigenetic processes. An example is the action of BPA on the pubertal prostate to promote an epigenetic effect on DNA methylation that is associated with adult onset prostate disease (Ho *et al.*, 2006). Similar effects on prostate disease have also been observed with the fungicide vinclozolin (Cowin *et al.*, 2008). The majority of environmental factors influencing adult onset disease will likely involve direct or indirect epigenetic modifications in the tissue or affected somatic cells (Bhatia-Dey *et al.*, 2023; Clapp and Jaspers, 2017; Hanson *et al.*, 2011; Jirtle and Skinner, 2007; Skinner, 2014). These somatic cell effects will be critical in the etiology of disease in the individual exposed, but the toxicology will not become transgenerational without a persistent phenotype continued in the absence of exposure of subsequent generations.

Since the germ line is required for the transmission of genetic information between generations, in the event a permanent epigenetic modification of the germ line occurrs then an epigenetic transgenerational phenomenon develops (Nilsson *et al.*, 2022). In the germ-line there are critical periods of development where epigenetic modifications could be introduced. During embryonic development in mammalian species, the primordial germ cells (PGCs) migrate to the developing gonad prior to sex determination as a pluripotent stem cell (Allegrucci *et al.*, 2005; Durcova-Hills *et al.*, 2006; Hanson *et al.*, 2011; Svingen and Koopman, 2013; Trasler, 1998). Upon gonadal sex determination, the germ cells develop into male or female germ lines. The female germ line then enters meiosis in the developing embryonic ovary. The male germ line continues to proliferate until immediately prior to birth and then suspends proliferation after birth until puberty. In the adult, the female germ line undergoes oogenesis during follicle development to generate oocytes. The male germ line develops from spermatogonial stem cells and undergoes spermatogenesis for the production of spermatozoa in the testis.

Epigenetic programming of the germ line occurs during the migration of the PGCs to the gonad in the embryo. The migrating PGCs undergo an erasure, or "demethylation," of portions of their DNA during migration and colonize the early bipotential gonad prior to gonadal sex determination (Allegrucci *et al.*, 2005; Durcova-Hills *et al.*, 2006; Trasler, 1998). Then, when gonadal sex determination is initiated, the PGCs develop female or male germ cell lineage and initiate the DNA remethylation in a male- or female-specific manner. Recent evidence suggests that these demethylation and remethylation events are not universal across the genome, and that genomic regions that are not CpG islands (i.e., that have a low density of CpG nucleotides) are subjected to a mix of demethylation and remethylation (Ben Maamar *et al.*, 2022; Ben Maamar *et al.*, 2023). However, the germ-cell DNA has extensive methylation changes during gonadal sex determination, and is potentially sensitive to perturbations from environmental factors and toxicants at these times (Allegrucci *et al.*, 2005; Ben Maamar *et al.*, 2023; Durcova-Hills *et al.*, 2006; Seisenberger *et al.*, 2013; Trasler, 1998).

Although there are alterations in the male and female germ-line epigenomes (i.e., DNA methylation) during gametogenesis in the adult gonads (Zamudio *et al.*, 2008), the embryonic period of gonadal sex determination is the most sensitive to environmental insults that influence the epigenome. The female germ cell can allow the transmission of numerous types of epigenetic processes. The male germ cell during spermatogenesis replaces the majority of histones with protamines, induces DNA condensation to affect chromatin structure, and then silences the genome for expression of noncoding RNAs (Godmann *et al.*, 2009; Skinner, 2014). However, recent evidence suggests that DNA methylation, the retention of histones, modification of these retained histones, and actions of non-coding RNAs can all transmit epigenetic information in sperm to the subsequent progeny (Beck *et al.*, 2021).

The best studied example of epigenetic inheritance is that of imprinted genes that have a specific pattern of DNA methylation that is transmitted through a parent of origin allele to subsequent progeny. These imprinted sites regulate gene expression in an allele-specific manner. Therefore, DNA methylation has been established as an epigenetic inheritance mechanism (Ideraabdullah

et al., 2008). In addition, studies have suggested that the few histone nucleosome complexes retained in sperm may epigenetically regulate subsequent fetal development (Carone *et al.*, 2014; Carrell, 2012; Karam and Molaro, 2023; Meyer *et al.*, 2017; Samans *et al.*, 2014), although further investigations are needed (Gaspa-Toneu and Peters, 2023). Non-coding RNAs present in sperm can also epigenetically regulate development in subsequent generations (Cheuqueman and Maldonado, 2021; Larriba and del Mazo, 2016; Yan, 2014). Due to the reprogramming of the germ line, gonadal sex determination is one of the most sensitive periods for environmental exposures to influence the germ line and create a transgenerational phenotype.

13.06.4 Epigenetic Transgenerational Phenomena

The initial observations of epigenetic transgenerational phenotypes were made in mammals when transient exposure to the agricultural fungicide vinclozolin during gonadal sex determination was found to promote adult onset diseases in the F1 generation of rats, as well as in subsequent generations (i.e., F1–F4) (Anway *et al.*, 2005). Early observations made in plants involved DNA methylation and paramutation mechanisms (Cuzin *et al.*, 2008; Mathieu *et al.*, 2007). This was partially attributed to DNA methylation changes in the male germ line (i.e., sperm) that were associated with transgenerational changes in the transcriptome for a number of tissues (Anway and Skinner, 2008; Anway *et al.*, 2008b; Skinner *et al.*, 2008; Skinner *et al.*, 2012; Skinner, 2014). The adult onset diseases observed included testis abnormalities, prostate disease, kidney disease, immune abnormalities, and tumor development (Anway *et al.*, 2006). Therefore, the environmental exposure of a gestating female to vinclozolin during the critical period of gonadal sex determination appears to have modified the male sperm epigenome to allow the transgenerational transmission of adult onset disease (Anway *et al.*, 2005; Brieno-Enriquez *et al.*, 2015; Jirtle and Skinner, 2007) . These studies provide one of the first examples of an epigenetic transgenerational phenomenon (Anway *et al.*, 2005; Nilsson *et al.*, 2022).

Several other environmental toxicants and models are now being used to further describe these epigenetic transgenerational phenomena (Katz *et al.*, 2009; Nilsson *et al.*, 2022; Skinner, 2014; Xing *et al.*, 2007) (**Table 4**). The Agouti mouse model has been used to document a transgenerational adult onset obesity phenotype (Waterland *et al.*, 2008). Modification of the DNA methylation pattern of the Agouti locus with environmental toxicants such as BPA modified this phenotype (Dolinoy *et al.*, 2007). Another example involves the ability of BPA to promote testis abnormalities for three (F1–F3) generations (Salian *et al.*, 2009). BPA has also been shown to transgenerationally promote pubertal abnormalities, ovarian disease, obesity, and behavioral changes (Manikkam *et al.*, 2013; Wolstenholme *et al.*, 2012; Ziv-Gal *et al.*, 2015). Exposure to phthalates, another class of plastic toxicants, increased the incidence of ovarian disease and testis function abnormalities (Doyle *et al.*, 2013; Manikkam *et al.*, 2013). Transgenerational increases in the incidence of disease have been reported in model species or humans after exposures to the pesticides methoxychlor (Manikkam *et al.*, 2014), permethrin (Blanc *et al.*, 2021; Manikkam *et al.*, 2012a), and DDT (King *et al.*, 2019; Maggio *et al.*, 2022; Skinner *et al.*, 2013). Similarly, the incidence of reproductive abnormalities, asthma or obesity was shown to increase transgenerationally after exposure to the industrial contaminants dioxin (Baker *et al.*, 2014; Bruner-Tran *et al.*, 2014; Gaspari *et al.*, 2021; Manikkam *et al.*, 2014), hydrocarbons such as jet fuel or diesel (Gregory *et al.*, 2017; Tracey *et al.*, 2013), and tributyltin (Chamorro-Garcia *et al.*, 2013; Mohajer *et al.*, 2021), among others (King and Skinner, 2020; King *et al.*, 2019). Many of the toxicants listed above might be considered endocrine disruptors. However, there is evidence that the transgenerational effects of the fungicide vinclozolin are not due to vinclozolin's anti-androgenic properties (Anway *et al.*, 2008a). Smoking can have deleterious effects transgenerationally in humans and rodents (Golding *et al.*, 2014; McCarthy *et al.*, 2018; Rehan *et al.*, 2013; Zhu *et al.*, 2014), and transgenerational effects have been reported after alcohol exposure (Gangisetty *et al.*, 2022; Govorko *et al.*, 2012), and exposure to other recreational drugs (Baratta *et al.*, 2021; Goldberg and Gould, 2019; Yohn *et al.*, 2015). Nutritional defects can also promote a transgenerational response (Franzago *et al.*, 2020; Kaati *et al.*, 2007; Kaspar *et al.*, 2020) and influence

Table 4 Toxicant exposure induced epigenetic transgenerational inheritance and generational toxicology.

Vinclozolin (agricultural fungicide)	(Anway *et al.*, 2005; Anway *et al.*, 2006; Nilsson *et al.*, 2022)
Methoxychlor (agricultural pesticide)	(Anway *et al.*, 2005; Manikkam *et al.*, 2014)
TCDD/dioxin (industrial contaminant)	(Baker *et al.*, 2014; Bruner-Tran and Osteen, 2011; Gaspari *et al.*, 2021; Manikkam *et al.*, 2012b)
Plastics (BPA, phthalate-DEHP and DBP)	(Manikkam *et al.*, 2012; Manikkam *et al.*, 2013; Ziv-Gal *et al.*, 2015)
Jet fuel [JP8] (hydrocarbon mixture)	(Gregory *et al.*, 2017; Tracey *et al.*, 2013)
Permethrin and DEET (pesticide and insect repellent)	(Blanc *et al.*, 2021; Manikkam *et al.*, 2012a)
DDT (pesticide)	(King *et al.*, 2019; Maggio *et al.*, 2022; Skinner *et al.*, 2013)
BPA (plastic toxicant)	(Salian *et al.*, 2009; Wolstenholme *et al.*, 2012)
Phthalates (plastic toxicant)	(Doyle *et al.*, 2013)
Tributyltin (industrial toxicant)	(Chamorro-Garcia *et al.*, 2013)
Glyphosate	(Ben Maamar *et al.*, 2021; Kubsad *et al.*, 2019)
Smoking	(Golding *et al.*, 2014; McCarthy *et al.*, 2018; Rehan *et al.*, 2013; Zhu *et al.*, 2014)
Alcohol	(Gangisetty *et al.*, 2022; Govorko *et al.*, 2012)

transgenerational genetic defects (Arai *et al.*, 2009). Therefore, further analysis of the actions of environmental factors and toxicants when exposure could affect the germ line needs to be performed to elucidate the extent the epigenetic transgenerational phenomena are involved in adult onset disease and environmental toxicology. All the studies and examples demonstrate a need to consider the role of environmentally induced epigenetic transgenerational inheritance in generational toxicology.

13.06.5 Summary and Future Directions

Epigenetic transgenerational inheritance and generational toxicology will require the involvement of the germ line to allow the transmission of an epigenetic abnormality between multiple generations. The ability of environmental factors or toxicants to promote an alteration in the epigenome will be common for somatic tissues, but less common for the germ line due to the limited developmental period that the germ line is sensitive to reprogramming. In the event an altered germ-line epigenome becomes permanently programmed, an epigenetic transgenerational phenotype would be possible. The phenomenon of the fetal basis of adult onset disease has been established (Hanson and Gluckman, 2008; Jirtle and Skinner, 2007) and evidence suggests epigenetics plays a critical role in this process (Ryznar *et al.*, 2021). In consideration of the toxicology of an environmental agent, the transient early life exposures in the individual exposed and the transgenerational transmission in the germ line both need to be considered causal factors for adult onset disease. Further investigation into the role of epigenetics in disease etiology is now needed to determine whether early life toxicity may be a significant factor in disease. Elucidation of the epigenetics involved in generational toxicology would provide insights into the diagnosis of exposure and potential therapeutic targets for disease. Although the prevalence of epigenetic transgenerational toxicity needs to be assessed in various disease states, the role of epigenetics will likely be a major factor to consider in toxicology and medicine in the future (Nilsson *et al.*, 2022).

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