

REVIEW ARTICLES



Environmentally induced epigenetic transgenerational inheritance of disease susceptibility

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Environmental insults, such as exposure to toxicants or nutritional abnormalities, can lead to epigenetic changes that are in turn related to increased susceptibility to disease. The focus of this review is on the transgenerational inheritance of such epigenetic abnormalities (epimutations), and how it is that these inherited epigenetic abnormalities can lead to increased disease susceptibility, even in the absence of continued environmental insult. Observations of environmental toxicant specificity and exposure-specific disease susceptibility are discussed. How epimutations are transmitted across generations and how epigenetic changes in the germline are translated into an increased disease susceptibility in the adult is reviewed with regard to disease etiology. (Translational Research 2015;165:12–17)

Abbreviation: DMR = DNA methylation region

The definition of epigenetic transgenerational inheritance is germline mediated inheritance of epigenetic information between generations that leads to phenotypic variation in the *absence* of direct environmental influences.¹ One of the initial reports of environmental epigenetic transgenerational inheritance involved toxicants used agriculturally.² In these studies, pregnant rats were exposed to the agricultural fungicide vinclozolin and the pesticide methoxychlor with the goal of examining the effects these environmental toxicants had on gonadal development and function in the offspring (F1 generation). A serendipitous observation was made when F1-generation animals were bred mistakenly to generate the F2-generation offspring. The vast majority of the testes in the F2 generation car-

ried a spermatogenic cell defect of increased apoptosis. This increased apoptosis persisted into the transgenerational F3 and F4 generations, and in outcrossed offspring, exhibiting non-Mendelian genetic inheritance and affecting 90% of the male population. Because the gestating female F0-generation rats were exposed to the toxicants at the time their embryos were undergoing sex determination, the F1-generation animals were exposed directly as a fetus (Fig 1). In addition, the germ cells present in the developing fetus were exposed directly. These exposed germ cells created the F2 generation (grand-offspring). Therefore, the first generation without direct environmental exposure is the F3 generation (great-grand-offspring), and this is the first generation said to exhibit *transgenerational*

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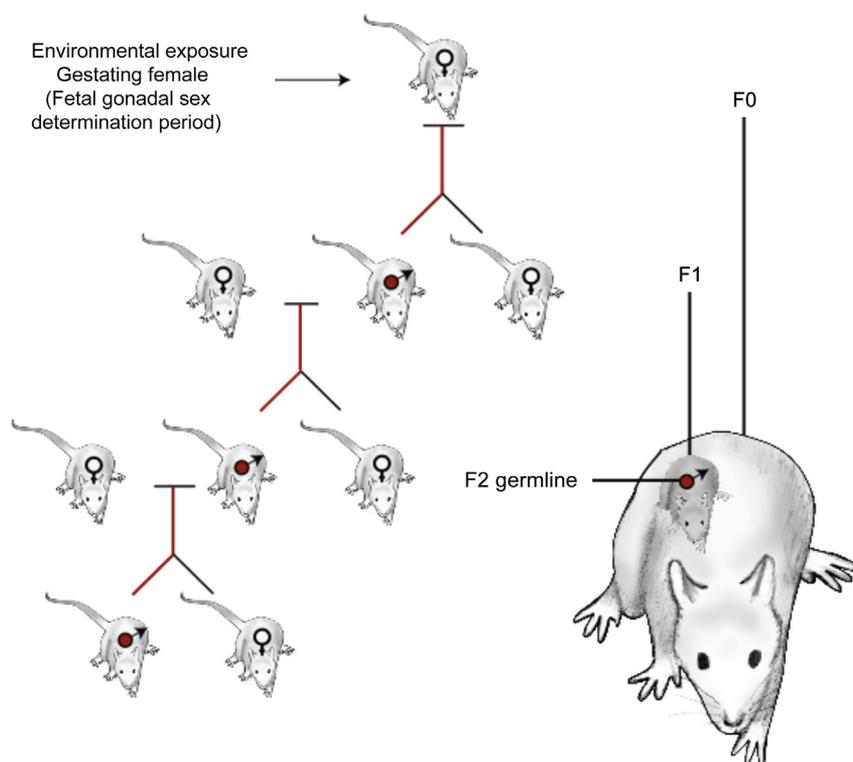


Fig 1. Schematic of environmentally induced epigenetic transgenerational inheritance in the F3 generation. Direct exposure is shown in the F0, F1, and F2 generations.

inheritance of disease susceptibility. In these studies, ancestral exposure to vinclozolin resulted in epigenetic changes in sperm DNA methylation at specific sites.²

In contrast, when an F0-generation male is exposed to an environmental insult, his sperm is exposed directly. These sperm will generate the F1 generation. Therefore, the first unexposed generation is the F2 (grand-offspring; Fig 1). Transgenerational effects in humans have been documented as passing through the male line after men were exposed to famine conditions early in life. These dietary exposures were correlated with longevity and disease in the grandchildren (ie, the transgenerational F2 generation) of these men.³ More recently, similar observations in rodents with effects on behavior and brain development have been observed.⁴

There are many examples in the literature of epigenetically mediated multigenerational inheritance that is not transgenerational, but the result of direct exposure.⁵⁻¹⁶ A well-characterized model of this uses the Agouti mouse. Pregnant Agouti mice, when exposed to the presence of a methyl donor in their diet, have increased DNA methylation of an allele of the Agouti gene, leading to a change in coat color in offspring.¹⁷ However, this DNA methylation change is not passed successively

to subsequent generations.¹⁸ Rather, the normal processes of DNA demethylation and remethylation that occur during germ cell specification and fertilization reset the DNA methylation state of these alleles.¹⁹ A human example of epigenetic multigenerational inheritance is the fetal actions of diethylstilbestrol. The children and grandchildren of women treated with diethylstilbestrol during pregnancy show abnormalities or increased risk of disease. In animal model systems, these abnormalities are associated with epigenetic changes.²⁰⁻²² However, negligible abnormalities have been shown for the F3 (great-grandchildren) generation in humans.²³

GERMLINE EPIMUTATIONS AND TOXICANT SPECIFICITY

Environmentally induced epigenetic transgenerational inheritance requires epimutations to be present in the germline, because only the germ cells (sperm and egg) are passed on to form the next generation. The best-characterized molecular mechanism for epigenetic changes to be transmitted through the germ cells involve changes in DNA methylation. These differential DNA methylation regions (DMRs) appear to become “imprinted-like,”¹⁹ such that they are not reset during

germ cell specification and fertilization.^{2,19,24-30} True imprinted genes have programmed epigenetic marks and are defined as genes with “parent-of-origin allelic transmission with monoallelic gene expression.” Although the differential DMRs associated with transgenerational inheritance of disease susceptibility do often exhibit parent-of-origin allelic transmission,^{2,19} monoallelic gene expression has not been investigated and may in fact not be a salient feature of these differential DMRs. Therefore, the abnormally methylated DNA sites found in germ cells transgenerationally are termed “imprinted-like.”³⁰ Although other epigenetic marks such as histone modifications³¹ and noncoding RNA³² will likely have important roles in transgenerational phenomena, their mechanisms remain to be elucidated.

The effects of exposure to several environmental toxicants have now been investigated to assess exposure specificity. Increased rates of disease and sperm epimutations have been demonstrated transgenerationally after exposure of the F0-generation gestating female to vinclozolin,^{2,24,33-35} dioxin,^{25,36,37} a pesticide and insect repellent mix (permethrin and *N,N*-diethyl-m-toluamide, or DEET),²⁷ plastics (bisphenol A and phthalates),³⁸ and hydrocarbons (jet fuel JP8).³⁹ Interestingly, each toxicant induced a unique set of epimutations in sperm, with negligible overlap in the sperm epimutations between the different ancestral exposures⁴⁰ (Fig 2). This raises the possibility that there are epigenetic signatures of specific ancestral exposures. In the future, epigenetic testing may uncover what the toxicant exposures and associated disease risks are in a person’s ancestry.⁴⁰ Other laboratories have also shown transgenerational inheritance of disease susceptibility to a variety of exposures, including nutrition,⁴¹ stress,⁴² and other toxicants.^{43,44}

DISEASES INHERITED TRANSGENERATIONALLY AND PHENOTYPIC VARIATION

The initial observations of epigenetic transgenerational inheritance of disease susceptibility documented an increase in spermatogenic cell apoptosis after ancestral exposure to vinclozolin.^{2,34} Other diseases and pathologies seen transgenerationally at increased rates after ancestral exposure to various toxicants include prostate disease,^{25,27,33,35,38-40} kidney disease,^{25,27,33,35,38-40} mammary tumor development,³³ immune abnormalities,^{33,39} behavioral effects related to anxiety,⁴⁵ effects on reproduction,^{46,47} stress response,⁴⁸ and obesity.^{39,43,49} Therefore, increased incidence of a wide variety of health abnormalities has been reported to occur transgenerationally after toxicant exposure. A number of these disease states were shown to occur in rats at high rates after

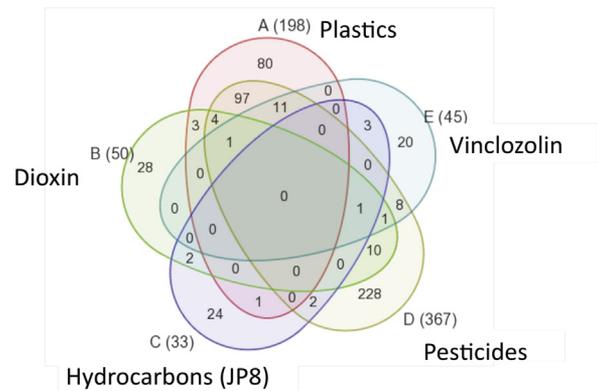


Fig 2. Venn diagram of transgenerational sperm epimutations associated with different exposure groups showing a number of common epimutations in the F3 generation of rats resulting from ancestral exposure of F0-generation gestating females to vinclozolin, dioxin, pesticide, plastics, or hydrocarbons. Modified from Manikkam et al.⁴⁰

ancestral exposure to any of several different environmental toxicants.⁴⁰ For example, certain ovarian diseases, including polycystic ovaries and reduction of the primordial follicle pool size, were found at high rates transgenerationally in females from all the toxicant exposure groups examined.²⁸ The speculation is that some physiological processes such as ovarian follicle development are more susceptible to alterations in gene expression than others. Exposure-induced germ cell epimutations lead to changes in gene expression, in all cells and tissues, such that those tissues most susceptible will develop disease states more often.

Interestingly, some of the environmentally induced epigenetic transgenerational inherited disease susceptibilities appear to be exposure specific. For example, gestating rats exposed to jet fuel hydrocarbons transmit transgenerationally to the F3-generation females an increased rate of luteal ovarian cyst formation.^{39,40} This was not seen after exposure to plastics compounds, dioxin, or other environmental toxicants.^{25,27,38} Similarly, increased risk of obesity is inherited transgenerationally after ancestral exposure to dichlorodiphenyltrichloroethane and plastic compounds, but not vinclozolin.^{38,49} The role of environmentally induced epigenetic transgenerational inheritance in the etiology of disease requires further investigation.

In addition to disease etiology, epigenetic transgenerational inheritance likely plays a role in generating the phenotypic variation that is necessary for natural selection to act on during evolution. Environmental factors that induce epigenetic changes that are passed in the germline can result in inherited changes in gene expression—in all tissues.⁵⁰ This can lead to alterations

in an animal's phenotype that can then be acted on by natural selection. This is a mechanism by which environmental exposures, as well as the induction of classic gene sequence mutations, can lead to increased phenotypic variation in future generations. A study in rats found that ancestral vinclozolin exposure caused marked changes in mate preference transgenerationally.⁵¹ Because sexual selection is a major determinant in evolutionary biology, the epigenetic transgenerational inheritance of this altered mate preference behavior phenotype suggests that transgenerational epigenetics may have an important role in evolution.^{52,53} For example, the ability of environmental exposures to promote phenotypic variation (eg, mate preference) in a population through epigenetic transgenerational inheritance will influence the natural selection process in that population.^{19,51}

ETIOLOGY OF TRANSGENERATIONAL DISEASE

The environmentally induced epigenetic transgenerational inheritance of disease susceptibility requires epimutations to be transmitted through the germ cells from generation to generation. Disease states such as cancer, obesity, or prostate disease involve abnormal regulation of gene expression in the relevant somatic cells. The hypothesis is that epimutations in germ cells lead to epimutations in the somatic cells that develop from those germ cells, and that the epimutations cause aberrant gene expression in somatic cells to increase disease susceptibility.^{19,54} There is ample evidence that ancestral toxicant exposure can cause a change in the transcriptome of a tissue (ie differences in gene expression) transgenerationally.^{1,19,35,45,55-57} However, it does not appear to be the case that exactly the same changes in gene expression are seen in different somatic cells of the same animal.⁵⁸ What is observed is cell- and tissue-specific transgenerational transcriptomes. The epigenetic profile (epigenome) of each cell type in the body is very different from that of every other type. In a study of rats exposed ancestrally to vinclozolin, examination of the transcriptomes of 11 different adult tissues demonstrated that each tissue had genes expressed differentially between control and vinclozolin lineages, with negligible overlap in the differentially expressed genes between tissues.⁵⁸ Consideration of how a relatively small number of sperm epimutations can promote such a large number of specific transcriptome changes led to an evaluation of the genomic locations of the epimutations and differentially expressed genes involved. Gene clusters were identified and termed "epigenetic control regions." These regions are 2–5 megabases in size, with statistically significant overrepresentation of regulated genes within the vicinity of both

epimutations and long noncoding RNA. The long noncoding RNA is proposed to mediate the regional gene regulation, affecting those genes in that region that would normally be expressed in that particular cell type.⁵⁸ Further research is needed to uncover the unique molecular mechanisms that may be involved in epigenetic regulation of these regions and gene expression.

Several studies have helped clarify how an environmentally induced transgenerational inheritance of disease susceptibility within a specific tissue may develop. The ovarian diseases polycystic ovary disease and primary ovarian insufficiency, premature reduction of the primordial follicle pool, were both induced transgenerationally by several environmental toxicants.^{28,40} In 1 study, granulosa cells from ovarian follicles were isolated from younger animals before disease onset, and their epigenomes and transcriptomes were characterized.²⁸ The granulosa cells from vinclozolin-lineage rats were found to have an altered epigenome and transcriptome that suggested specific signaling pathways were affected. A number of the genes identified that were expressed differentially were shown previously to be involved in the development of polycystic ovary disease and primary ovarian insufficiency.²⁸ Similarly, studies have examined the molecular etiology of male infertility associated with testis disease that can be induced by ancestral exposure to vinclozolin. The somatic Sertoli cells in the testis were also found to have transgenerational alterations in their epigenomes and transcriptomes.⁵⁷ A number of the cellular processes and differentially regulated genes identified also have been shown previously to be involved in male infertility.⁵⁷ Therefore, changes in the transcriptome of somatic cells that were induced transgenerationally by ancestral exposure to toxicants appear to be linked to increased susceptibility to specific diseases.

CONCLUSIONS

Research in this field has shown that a nongenetic (ie, epigenetic) form of transgenerational inheritance of disease susceptibility exists that complements the well-known genetic inheritance of gene variants that predispose disease.^{1,19,30} Epigenetic transgenerational inheritance of disease susceptibility can occur after exposure to a number of environmental toxicants and nutritional abnormalities. The epigenetic changes induced in the germline after ancestral exposure to environmental toxicants appear to be specific to the toxicant. The possibility that epigenetic testing could inform people of potential risks of disease susceptibility needs to be investigated further. Increased incidences of many different disease states have been linked to transgenerational epigenetic

inheritance after exposure to toxicants. One mechanism for transgenerational epigenetic inheritance is for an environmental exposure to induce alterations in DNA methylation in the developing germ cells that become fixed or imprinted-like, which are then transmitted transgenerationally. These epigenetic changes in germ cells will produce epigenetic changes in the resulting somatic cells that will lead to aberrant gene expression and the development of disease. Clearly, additional studies are needed to clarify the role of epigenetics and transgenerational inheritance in disease etiology, evolutionary biology, and other areas of cell and developmental biology. Increased knowledge in these areas will have a significant impact on our understanding of normal biology and disease etiology.

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