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Review

Endocrine disruptor induction of epigenetic transgenerational inheritance of disease

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ABSTRACT

Environmental exposures such as toxicants, nutrition and stress have been shown to promote the epigenetic transgenerational inheritance of disease susceptibility. Endocrine disruptors are one of the largest groups of specific toxicants shown to promote this form of epigenetic inheritance. These environmental compounds that interfere with normal endocrine signaling are one of the largest classes of toxicants we are exposed to on a daily level. The ability of ancestral exposures to promote disease susceptibility significantly increases the potential biohazards of these toxicants. Therefore, what your great-grandmother was exposed to during pregnancy may influence your disease development, even in the absence of any exposure, and you are going to pass this on to your grandchildren. This non-genetic form of inheritance significantly impacts our understanding of biology from the origins of disease to evolutionary biology. The current review will describe the previous studies and endocrine disruptors shown to promote the epigenetic transgenerational inheritance of disease.

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1. Introduction

If genetic (DNA sequence) mutations are the cause of disease susceptibility, how come identical twins generally have different disease conditions? How come if someone moves early in life from one region of the world to another they generally develop the prominent disease conditions of the place they move rather than from where they were born? How come hundreds of environmental toxicants that are associated with disease do not induce DNA sequence mutations? These and other observations suggest that the environment has a significant impact on disease development (Jirtle and Skinner, 2007) (Table 1), and classic genetic mechanisms have difficulty explaining these observations.

One of the most predominant paradigms in the biological sciences today is "genetic determinism". The concept is that the DNA sequence alone is the building block for biology and that mutations in this sequence are the primary causal factors for most biological phenomena from disease development to evolutionary biology. This paradigm is the basis for most of our current education programs and theories in biology. The problem is that many phenomena (Table 1) cannot be easily explained with classic genetics or DNA sequence mutation mechanisms alone. An example is the numerous genome wide association studies (GWAS) that have generally shown less than 1% of a specific disease population have a correlated DNA sequence mutation (Visscher et al., 2012; Zhao and Chen, 2013). Could it be that an additional mechanism may be

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Table 1
Environmental epigenetic impacts on biology and disease.

- Worldwide regional disease frequencies
- Low frequency of genetic component of disease as determined with genome wide association studies (GWAS)
- Dramatic increases in disease frequencies over past decades
- Identical twins with variable disease frequency
- Environmental exposures associated with disease
- Regional differences and rapid induction events in evolution

involved that we have not seriously considered in the past? It is not that genetics and the DNA sequence are not absolutely critical for biology, it is simply not the whole story.

The additional molecular factor to be considered is "epigenetics". Although more traditional definitions exist (Skinner, 2011; Skinner et al., 2010), in considering the new science regarding mechanism "epigenetics" is defined as:

> "Molecular factors/processes around the DNA that regulate genome activity independent of DNA sequence, and these processes 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) (Table 2). In the 1970s the first epigenetic molecular mark was identified as DNA methylation in which a small (methyl) chemical group is attached to DNA at primarily the cytosine base in animals (Holliday and Pugh, 1975; Singer et al., 1979). In the 1990s the histone proteins DNA is wrapped around were found to also be chemically modified to alter gene expression. 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). Therefore, the currently known epigenetic molecular processes are DNA methylation, histone modifications, functional non-coding RNA and chromatin structure (Jirtle and Skinner, 2007) (Table 2). 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 ultimate control of genome activity (i.e. gene expression) will be the combined and cooperative actions of both epigenetic and genetic mechanisms. Two of the most studied epigenetic processes are X-chromosome inactivation and imprinted genes (Henckel et al., 2012; Lee and Bartolomei, 2013) (Table 2). The female has two X-chromosomes and requires one to be inactivated for normal biology and this has been shown to involve DNA methylation and non-coding RNA. Imprinted genes are a small set of genes that are expressed from either the mother's (maternal) or father's (paternal) contributed DNA (allele), but not both. Imprinting has also has been shown to involve DNA methylation and non-coding RNA to control this parent of origin gene expression (Henckel et al., 2012; Lee and Bartolomei, 2013). These are good examples of how epigenetics and genetics cooperate to control genome activity and normal biology.

Table 2
History of epigenetics.

1940s	Conrad Waddington coined the term epigenetics as an environment–gene interaction induced phenotype
1975	Holliday and Pugh/Riggs identify DNA methylation
1988	X-Chromosome inactivation and DNA methylation
1990s	Imprinted genes, allelic expression and DNA methylation
1995	Histone modifications and chromatin structure
2000s	Functional non-coding RNAs
2005	Epigenome mapping

2. Environmental epigenetics

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). "Environmental epigenetics" is defined as the ability of an environmental factor to directly act and alter epigenetic processes to promote gene expression and phenotype (physiological characteristics) alterations. The altered epigenetic mark(s) at a specific DNA site in response to an environmental factor to influence gene expression 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 (Skinner et al., 2010).

There are a number of environmental epigenetic models where direct exposures to environmental factors promote disease development or altered physiological characteristics (i.e. phenotypes). One of the best examples of an animal model is the Agouti mouse where a gestating female is exposed to abnormal nutrition or toxicants that influence a specific DNA methylation site to alter the coat/hair color of the offspring from yellow to brown (Bernal and Jirtle, 2010; Blewitt and Whitelaw, 2013). One of the best examples of a human model is in the late 1950s and early 1960s when women in the late stages of pregnancy were exposed to the pharmaceutical diethylstilbesterol (DES) which was shown to promote abnormal uterine and cervical development in the female offspring and grand-offspring (Kalfa et al., 2011; Newbold, 2004). Subsequently the phenotypes were found to be due to abnormal epigenetic programming of these organs and critical genes (Bromer et al., 2009; Pistek et al., 2013). A large number of more recent studies have demonstrated direct exposure to toxicants or abnormal nutrition (caloric restriction or high fat diets) promotes specific epigenetic alterations to influence disease development or physiological phenotypes (Albert and Jegou, 2014) (Table 3).

These direct exposures to environmental factors include nutrition, stress, temperatures, pharmaceuticals, synthetic chemicals and environmental toxicants. Epigenetic effects have been observed in nearly all organisms studied from plants to humans. Generally exposures at critical windows of early development (fetal, birth, puberty) have the most dramatic impact on later life disease development or abnormal physiology. This developmental concept is referred to as the developmental origins of health and disease (Barker, 2004). Since epigenetics and genetics cooperate in regulating genome activity (gene expression), a cascade of genetic and epigenetic events is required to achieve normal adult development (differentiation) (Skinner, 2011) (Fig. 1). The direct environmental exposure at a critical window of early development can alter the epigenetic programming that subsequently influences genetic programming and gene expression. The result is an environmentally modified versus normal adult differentiated (mature) state that has an altered epigenome and transcriptome which later in life promotes the susceptibility to develop disease or abnormal physiology (Fig. 1). Epigenetics provides a molecular process to allow the environment to cooperate with genetic processes to influence the phenotypes and biology of the individual. This is a normal component of biology that can be altered by abnormal environmental conditions during development.

Table 3
Direct (multigenerational) exposure epigenetic phenotypes.

Exposure	Model	Generation	Phenotype
Flutamide (anti-androgenic pharmaceutical)	Rat	F1, F2	Testis defect
Diethylstilbesterol (DES) (pharmaceutical estrogen)	Mouse	F1, F2	Female reproductive tract abnormalities
High fat diet (nutrition)	Mouse	F1	Metabolic disease
Caloric restriction (nutrition)	Human	F1, F2	Metabolic disease
Alcohol (toxicant)	Mouse	F1	Skull and facial abnormalities
Bisphenol A (BPA) (toxicant)	Agouti mouse	F1	Coat color change
Genistein (estrogenic plant compound)	Agouti mouse	F1	Coat color change and obesity

3. Epigenetic transgenerational inheritance

During an investigation of the actions of two environmental toxicants, endocrine disruptors, on the process of gonadal (testis and ovary) development in the fetus, effects on the adult following this fetal exposure were identified (Anway et al., 2005). The F1 generation adult males developed a testis abnormality. When the F1 generation offspring was 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 fourth generation 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., 2006a). The frequency of the abnormality did not decline at each generation, but stayed high suggesting a non-Mendelian phenomenon not following classic genetics. 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 found to be transmitted through the male germline (sperm) (Fig. 2). Later experiments with other toxicant exposures have shown transmission through the female germline predominantly (McCarrey, 2012), such that the transgenerational phenotype is transmitted in a parent of origin allelic manner, similar to imprinted genes.

In considering transgenerational phenomenon it is essential to distinguish between direct exposure effects versus germline (sperm or egg) mediated transgenerational events. When a gestating female is exposed the F0 generation female, the F1 generation fetus and the germ cell (sperm or egg) that is inside the fetus that will produce the F2 generation are directly exposed (Fig. 2). Any effects in the F0, F1 and F2 generations are primarily due to direct exposure toxicity or environmental epigenetics as discussed above. The F3 generation (great grand-offspring) is minimally needed to assess transgenerational phenomenon, since direct exposure effects are not involved (Skinner, 2008) (Fig. 2). In contrast, in the event an adult male or non-pregnant female is exposed the F0 generation adult and germ cell that will generate the F1 generation is directly exposed, such that examination of the F2 generation (grand-offspring) is required to demonstrate a transgenerational phenomenon (Skinner, 2008). When multiple generations are directly exposed (Fig. 2), this is referred to as a multigenerational exposure which has been shown with a variety of exposures (Skinner, 2008; Skinner et al., 2010) (Table 3). The ability to transmit information from one generation to the next requires the sperm or egg such that transgenerational events are germ cell mediated (Skinner et al., 2010).

In considering the development of the germ cell (sperm or egg) there are several critical stages of development where dramatic epigenetic programming occurs (Feng et al., 2010; Messerschmidt et al., 2014). The first is when the stem cells (precursor cells) for the germ cells called primordial germ cells develop during fetal development prior to and during the time of testis and ovary development. The DNA methylation of these cells is predominantly erased and then re-methylation occurs during testis and ovary maturation. The second is when the sperm and egg come together at fertilization and the DNA contributed by the sperm and egg again is demethylated to create the embryonic stem cells (Feng et al., 2010; Messerschmidt et al., 2014). This epigenetic programming allows a cell to develop pluripotency. Interestingly, when the exposures to toxicants or abnormal nutrition occurs during fetal testis or ovary development the epigenetic programming or DNA methylation of the germ cell can become reprogrammed and transmit the altered epigenetic information to the next generation (Anway et al., 2005; Skinner et al., 2010). A set of imprinted gene sites has been shown to be protected from DNA methylation erasure at fertilization in a sex specific manner (Seisenberger et al., 2013) such that they transmit the epigenetic information to all subsequent generations (Skinner et al., 2010). When these normal sperm and egg epigenetic programming events are altered (Skinner et al., 2013a) they have the ability to transmit this epigenetic information transgenerationally.

If the germ cell (sperm or egg) is transmitting epigenetic information transgenerationally then altered epigenetic marks (epimutations) should be observed. Analysis of the F3 generation

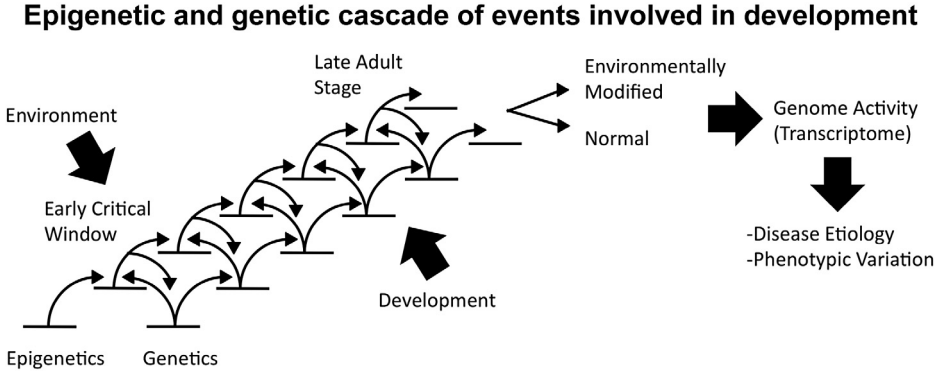

Fig. 1. Epigenetic and genetic cascade of events involved in development. (Modified from Skinner, 2011).

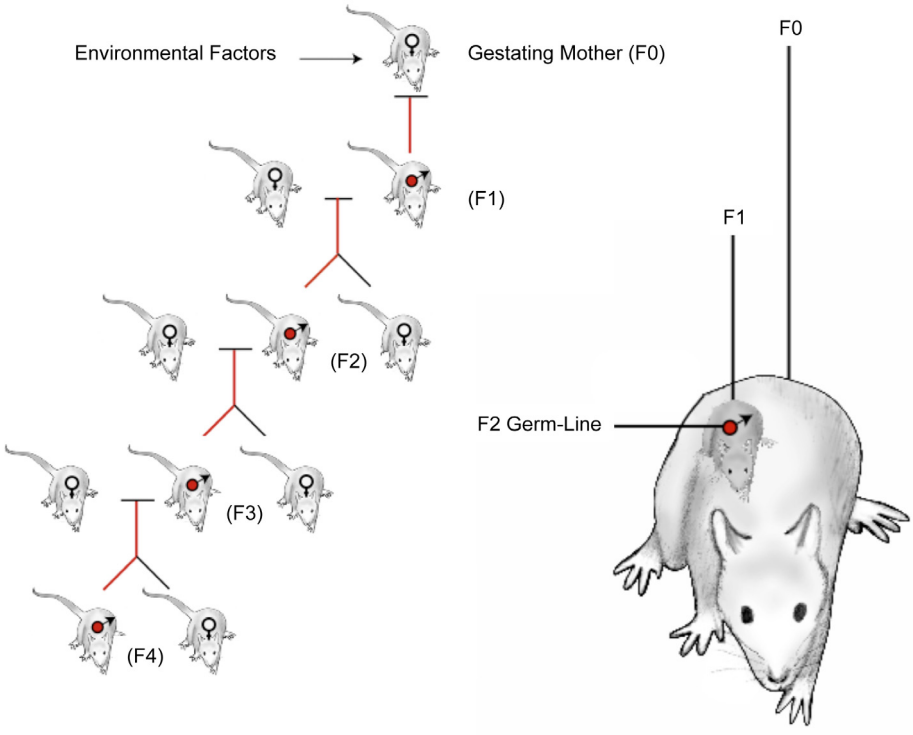

Fig. 2. Environmentally induced epigenetic transgenerational inheritance through male germline. Exposure of the F0 generation gestating female, F1 generation fetus, and germline within the F1 generation fetus that will generate the F2 generation. Therefore, the F3 generation is the first transgenerational generation not directly exposed. (Modified from Skinner, 2008).

(great-grand-offspring) sperm from environmental toxicant lineage versus control lineage males was found to have epimutations with altered DNA methylation (Guerrero-Bosagna et al., 2010; Manikkam et al., 2012a). Interestingly, a variety of different environmental toxicants shown to promote transgenerational disease were each found to promote a unique signature or pattern of epimutations in the F3 generation sperm (Manikkam et al., 2012a) (Fig. 3). This figure shows a fungicide vinclozolin with 45 epimutations, plastics (BPA and phthalate) derived compounds with 198 epimutations, pesticides with 367 epimutations, hydrocarbons (jet fuel) with 33 epimutations, and dioxin with 50 epimutations. The inner circle shows 0 overlap between these epimutations and the outer portion of each exposure circle has the majority of epimutations unique to the exposure (Manikkam et al., 2012a) (Fig. 3). Therefore, these various environmental toxicants promote the epigenetic transgenerational inheritance of exposure specific sperm epimutations. These exposure specific epimutation signatures may be used in the future as biomarkers/diagnostics for your ancestral exposure and future disease susceptibility.

The "epigenetic transgenerational inheritance" is defined as (Skinner et al., 2010):

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

A number of different environmental toxicants (e.g. endocrine disruptors) have been shown to promote the epigenetic transgenerational inheritance of disease or abnormal phenotypes (Skinner et al., 2011) (Table 4). These toxicants range from fungicides (Anway et al., 2005, 2006), pesticides (Manikkam et al., 2012b, 2014), industrial contaminants (Manikkam et al., 2012c), plastics (Doyle et al., 2013; Manikkam et al., 2013; Salian et al., 2009; Wolstenholme et al., 2012, 2013), to hydrocarbons (Tracey et al., 2013). In addition to environmental toxicants, nutrition also can promote the epigenetic transgenerational inheritance of disease and abnormal physiologies (Burdge et al., 2007; Dunn et al., 2011; Waterland, 2014). This can include high fat diets and caloric restriction. Good examples are famine human populations in Sweden

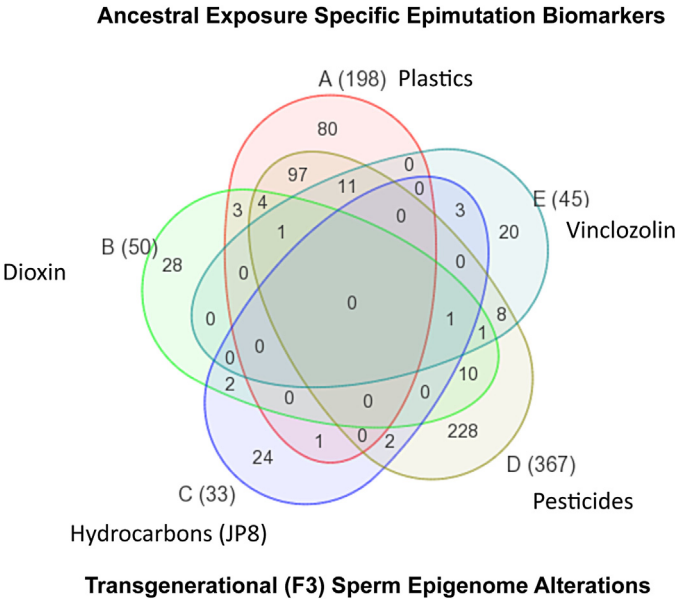

Fig. 3. Ancestral exposure specific epimutation biomarkers. Transgenerational F3 generation sperm differential DNA methylation regions (epimutations) with the total listed next to exposure in brackets and Venn diagram showing overlap between the exposure epimutation. (Modified from Manikkam et al., 2012a).

Table 4
Exposure induced epigenetic transgenerational inheritance.

Endocrine disruptor exposures	
Vinclozolin (agricultural fungicide)	Anway et al., 2005, 2006a
Methoxychlor (agricultural pesticide)	Anway et al., 2005; Manikkam et al., 2014
TCDD/dioxin (industrial contaminant)	Bruner-Tran and Osteen, 2011; Manikkam et al., 2012c
Plastics (bisphenol-A, phthalate-DEHP and DBP)	Manikkam et al., 2012a, 2013
Jet fuel [JP8] (hydrocarbon mixture)	Tracey et al., 2013
Permethrin and DEET pesticide and insect repellent	Manikkam et al., 2012b
DDT (pesticide)	Skinner et al., 2013b
Bisphenol A (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
Other types exposures	
Folate (nutrition)	Padmanabhan and Watson, 2013
High fat diet (nutrition)	Burdge et al., 2011; Dunn et al., 2011
Caloric restriction (nutrition)	Burdge et al., 2007; Painter et al., 2008; Pembrey et al., 2006; Veenendaal et al., 2013
Temperature and drought (plant flowering and health)	Norouzitallab et al., 2014; Song et al., 2013; Suter and Widmer, 2013; Zheng et al., 2013
Stress (behavioral)	Dias and Ressler, 2014; Gapp et al., 2014
Smoking (health)	Pembrey, 2010; Rehan et al., 2013
Alcohol (health)	Govorko et al., 2012

(Pembrey et al., 2006) and Holland (Veenendaal et al., 2013) that have been shown to have generational disease phenotypes. Another environmental factor shown to promote transgenerational inheritance is stress (Dias and Ressler, 2014; Gapp et al., 2014; Matthews and Phillips, 2012). In addition, individuals' stress responses can be altered by ancestral exposures in the transgenerational generations (Crews et al., 2012). In plants, cold temperature and drought have been shown to promote epigenetic transgenerational inheritance of flowering and growth characteristics (Norouzitallab et al., 2014; Song et al., 2013). A wide variety of environmental factors have been shown to induce the phenomenon (Table 4). Epigenetic transgenerational inheritance phenomenon has been shown in plants (Hauser et al., 2011; Norouzitallab et al., 2014; Song et al., 2013), worms (Benayoun and Brunet, 2012; Kelly, 2014), flies (Buescher et al., 2013; Grentzinger et al., 2012), fish (Baker et al., 2014), rodents (Anway et al., 2005; Guerrero-Bosagna et al., 2012), pigs (Braunschweig et al., 2012) and humans (Pembrey et al., 2006; Veenendaal et al., 2013).

A variety of different disease and abnormal physiological conditions can be induced transgenerationally (Anway and Skinner, 2008; Anway et al., 2005, 2006a; Manikkam et al., 2012a; Nilsson et al., 2008; Skinner et al., 2008, 2013b), (Table 5). The frequency of these phenotypes range from 10% to greater than 90% depending on the disease, environmental factor involved, and male or female sex. Interestingly, with many of the exposures the vast majority of females develop ovarian disease such as polycystic ovaries (Nilsson et al., 2012), which is one of the most common female reproductive diseases in women (Barthelmess and Naz, 2014). Testis abnormalities and sperm cell defects are also very common among the different exposures (Anway et al., 2006b). The primary tumors developed in either male or female are mammary gland/breast tumors (Anway et al., 2006a; Nilsson et al., 2008). Behavioral effects in regard to anxiety or social recognition are also observed (Crews et al., 2007; Skinner et al., 2008). Recently we found the pesticide DDT promotes the susceptibility to develop obesity in the transgenerational F3 generation in greater than 50% of the males and females, but had no effect on the F1 generation obesity frequency (Skinner et al., 2013b). The environmentally induced epigenetic transgenerational inheritance of disease and abnormal physiologies suggests ancestral exposures may have an important role in why the majority of disease conditions in our population have dramatically increased over the past several decades.

Table 5
Transgenerational disease and abnormality examples.

Disease and abnormalities	Frequency
• Spermatogenic defect	(>90%)
• Male infertility	(~10%, 20%)
• Kidney disease	(~30–40%)
• Prostate disease	(~50%)
• Increase in mammary tumor formation	(~10–20%)
• Behavior (mate preference, anxiety and stress)	(>90%)
• Pre-eclampsia-like during late pregnancy	(~10%)
• Premature ovarian failure (POF/POI)	(>90%)
• Polycystic ovarian disease	(>90%)
• Female premature pubertal onset	(>30%)
• Obesity	(~10–50%)

The basic mechanism involved in environmentally induced epigenetic transgenerational inheritance of disease or abnormal physiologies is presented in Fig. 4 (Skinner et al., 2010). The exposure of a gestating female at the critical window of gonadal (testis or ovary) sex determination modifies the epigenetic (e.g. DNA methylation) programming of the germ cell that the F1 generation adult animal will transmit to the F2 generation. All cell types and tissues derived from the developing embryo will have an altered epigenome and transcriptome such that those tissues sensitive to an altered gene expression profile will develop disease or abnormalities as the individual ages. This adult F2 generation individual will then transmit the same germ cell epimutations to the next F3 generation (great-offspring) and the same mechanism and process occur in all subsequent generations (Fig. 4). The transgenerational germ cell (sperm) epigenome changes (Guerrero-Bosagna et al., 2010; Manikkam et al., 2012a) and altered transgenerational tissue and cell transcriptomes (Guerrero-Bosagna et al., 2013; Nilsson et al., 2012; Skinner et al., 2012) have been confirmed. Therefore, environmental exposures can promote this form of non-genetic inheritance through this epigenetic transgenerational inheritance mechanism to promote disease and altered phenotypes. The potential role of this mechanism in our understanding of disease etiology needs to be considered.

4. Endocrine disruptors

As discussed above, a number of environmental toxicants can promote the epigenetic transgenerational inheritance of disease (Table 4). Many of these chemicals act as endocrine disruptors. Endocrine disruptors are defined as environmental chemicals that can interfere with endocrine hormone signaling (e.g. hormone receptor actions) to alter cellular function and health (Bergman et al., 2013; Brevik et al., 2012; Fowler et al., 2012; Jurisicova et al., 2007; Zama

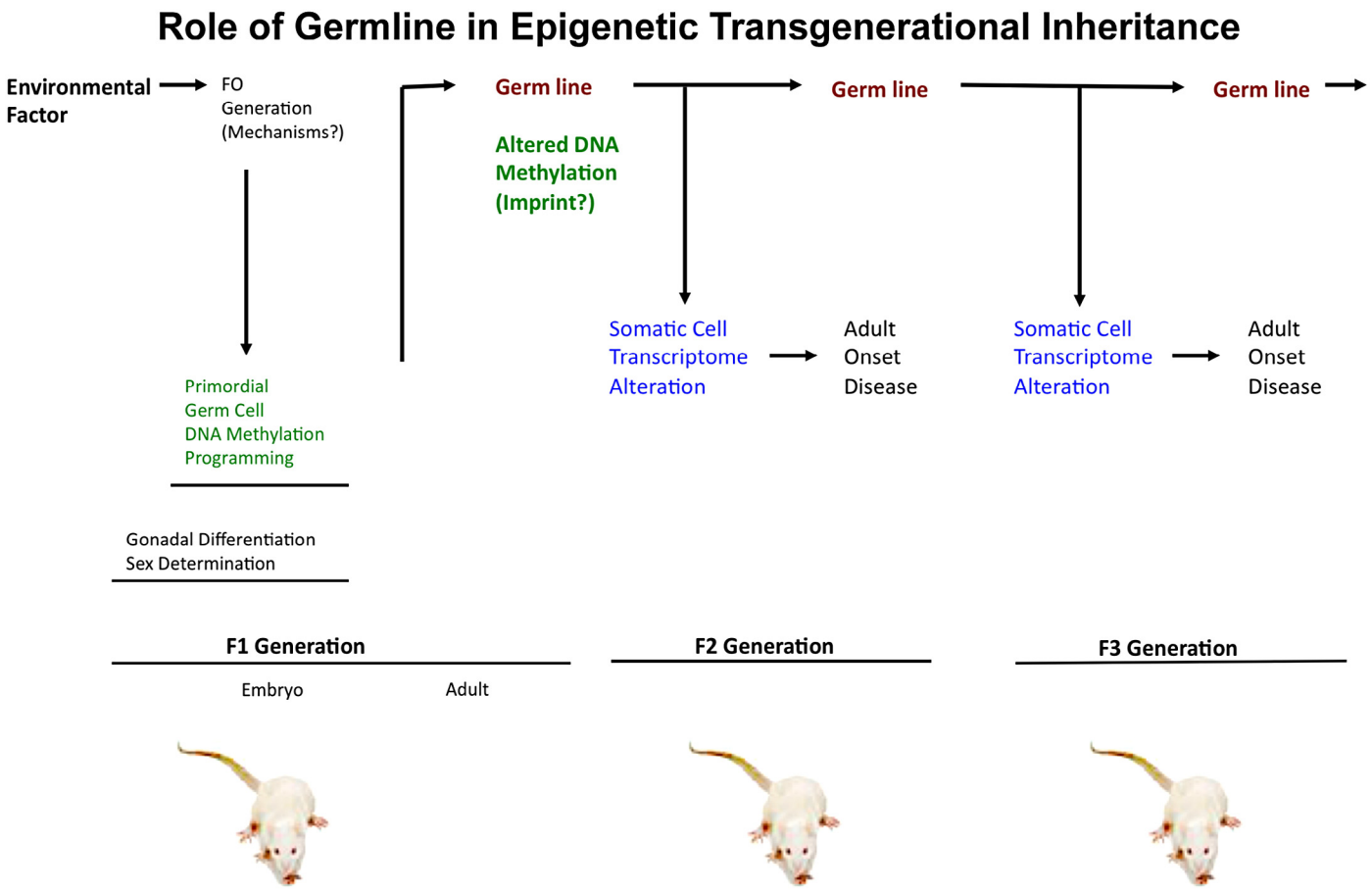

Fig. 4. Role of germline in epigenetic transgenerational inheritance. Summary of environmentally induced epigenetic reprogramming of primordial germ cells that leads to the germline transmission of epimutations resulting in all somatic cells having an altered transcriptome that results in disease susceptibility. (Modified from Skinner et al., 2010).

and Uzumcu, 2010). When a chemical can bind to a hormone receptor and act as an agonist or antagonist, or alter the downstream signaling transduction of the hormone, the compound is considered an endocrine disruptor. Some of these compounds are natural substances obtained from our diet. A good example of this is genestein, which is a compound found in soy that has estrogenic activity and is a strong estrogen signaling agonist (Jefferson et al., 2007). However, the majority of the endocrine disruptors studied are man-made chemicals used in the environment. Nearly all known signal transduction systems are linked to hormone signaling so can be altered by endocrine disruptors. The categorizing of endocrine disruptors often is associated with the specific class of hormones. For example, many compounds have estrogenic activity or block estrogenic hormone action, such as bisphenol A (BPA), DES, and genestein. Others bind to broader spectrum receptors such as the aryl hydrocarbon receptor (AhR) and PPAR/RXR receptors that bind a variety of organic compounds such as dioxin, organophosphates and hydrocarbons. The major endocrine disruptors that have been shown to promote the epigenetic transgenerational inheritance of disease are presented in Table 4.

The initial endocrine disruptor found to promote the epigenetic transgenerational inheritance of disease was the anti-androgenic compound vinclozolin, which is one of the most commonly used agricultural fungicides worldwide (Anway et al., 2005, 2006a; Paoloni-Giacobino, 2014). The pesticide methoxychlor is a mixed estrogenic, anti-estrogenic and anti-androgenic endocrine disruptor shown to promote transgenerational disease (Anway et al., 2005; Manikkam et al., 2014; Paoloni-Giacobino, 2014). The industrial contaminant dioxin binds the AhR receptor and promotes transgenerational disease (Bruner-Tran and Osteen, 2011; Manikkam et al., 2012c). The plastic derived estrogenic compound BPA has been shown to promote transgenerational disease (Manikkam et al., 2012a, 2013; Salian et al., 2009) and behavioral abnormalities (Jang et al., 2012; Wolstenholme et al., 2012, 2013). The plastic derived phthalates also promote transgenerational disease (Doyle et al., 2013; Manikkam et al., 2012a, 2013). The hydrocarbon mixture of jet fuel (JP8) which can associate with AhR also promotes transgenerational disease (Tracey et al., 2013). A common pesticide and insect repellent (permethrin and DEET) also promotes transgenerational disease (Manikkam et al., 2012b). The pesticide DDT is an estrogenic endocrine disruptor and promotes transgenerational disease such as obesity (Skinner et al., 2013b). The industrial biocide tributylin that influences the PPAR/RXR receptors was found to promote transgenerational obesity and metabolic disorder (Chamorro-Garcia et al., 2013). The studies discussed above (Table 4) are transgenerational studies that demonstrate the germline transmission of phenotypes in absence of direct exposure or genetic manipulation. A number of studies reported in the literature are incorrectly referred to as transgenerational and instead are due to direct environmental exposures (Skinner, 2008). It is anticipated that a variety of different endocrine disruptors and other exposures will also promote transgenerational phenotypes when sufficient generations are considered.

Interestingly, the majority of the endocrine disruptors found to promote the epigenetic transgenerational inheritance of disease listed in Table 4 generally promoted similar diseases or abnormalities. Testis

and ovary diseases were the most common, along with kidney and prostate diseases (Anway et al., 2005, 2006a; Manikkam et al., 2012c, 2014; Skinner et al., 2013b). Those diseases listed in Table 5 have more similarities than differences between the various endocrine disruptor exposures. Although some disease differences occur, such as DDT, jet fuel, and plastics promoting obesity, but not vinclozolin or dioxin, the transgenerational disease phenotypes were often similar. Therefore, exposure specific or signal transduction specific effects were not generally observed.

As shown in Fig. 4, since the germline is transmitting an altered epigenome to the embryonic stem cell, all adult cell types that develop will have an altered epigenome and transcriptome (Guerrero-Bosagna et al., 2013; Skinner et al., 2008, 2012). Although there are exposure specific germline epimutation signatures (Manikkam et al., 2012a), and tissue and cell specific transgenerational transcriptomes (Skinner et al., 2012), the disease etiology and biology are generally similar between the various exposures. The hypothesis is proposed that in the event a large number of epimutation and gene expression changes are present in tissues that are sensitive to disease, the tissues will develop the disease independent of the specific environmental exposure and transgenerational epigenetic signature. Therefore, if you effect the expression of hundreds of genes in certain cell types, independent of the specific set of genes, a disease susceptibility will exist. This is a more system biology consideration versus a reductionist view involving specific genes or epimutations. Understanding this phenomenon and molecular mechanisms involved will significantly enhance our future ability to therapeutically treat, prevent and improve health.

5. Epigenetics and evolution

The current molecular mechanism considered in evolutionary biology involves random DNA sequence mutations and other genetic mechanisms such as genetic drift to facilitate neo-Darwinian natural selection events. Nearly all the current models for evolution involve genetic mechanisms. The environment is considered important for the natural selection process, but has not been considered to alter the molecular processes of evolution. The problem with this theory is that the frequency of genetic mutations is extremely rare such that the speed of evolution is difficult to explain. In fact the probability of a random mutation is over 1000 times less than the anticipated frequency of an epigenetic change (Schmitz et al., 2013). Environmental epigenetics and particularly environmentally induced epigenetic transgenerational inheritance may provide a molecular mechanism to enhance the genetic mechanisms currently considered. As discussed, environmental induction of epigenetic change can dramatically increase phenotypic variation that can facilitate natural selection, and epigenetic transgenerational inheritance can allow the continued presence of adapted phenotypes. Therefore, several recent reviews have suggested a role for epigenetics in evolution (Day and Bonduriansky, 2011; Geoghegan and Spencer, 2013; Guerrero-Bosagna et al., 2005; Klironomos et al., 2013).

A previous example provided was that the F3 generation toxicant exposure lineage animals when compared to control lineage animals had different mate preference characteristics (Crews et al., 2007). Recently the gene bionetworks in specific regions of the brain have been identified and correlated to the epigenetic transgenerational inheritance of mate preference differences (Skinner et al., 2014a). Mate preference involving biological parameters such as bird feather color and song is a critical component of sexual selection, which Charles Darwin proposed as a major determinant in evolutionary biology (Darwin, 1871). More recently we examined the epimutations and genetic mutations in a number of different species of Darwin's finches and found a large number of epimutations that significantly correlated with the phenotypic

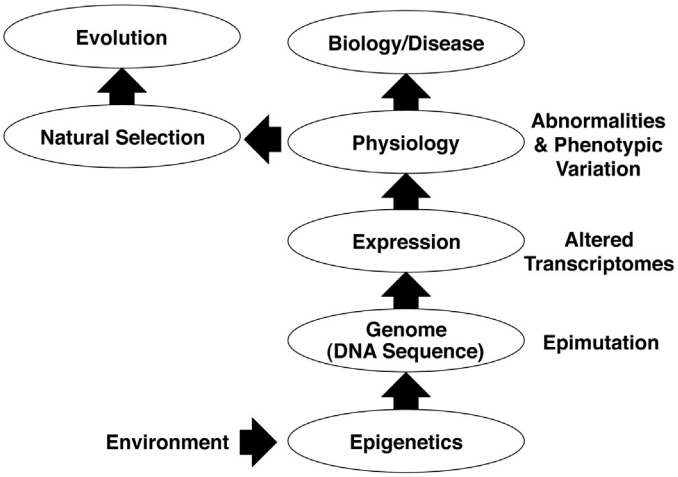

Fig. 5. Schematic of environmental effects of epigenetics promoting disease etiology or phenotypic variation to influence evolution.

relatedness (family tree) of the finches (Skinner et al., 2014b). Therefore, data are starting to be obtained that support an important role for environmental epigenetics and epigenetic transgenerational inheritance in facilitating natural selection and evolution. In addition to a role in disease development, epigenetics will have a role in other areas of biology such as evolution (Fig. 5).

6. Conclusions

Scientific observations over the past 200 years have demonstrated a significant impact of environmental exposures on all aspects of biology, but genetics alone cannot easily explain many of these observations. Although "genetic determinism" has helped elucidate many aspects of biology, such that the DNA sequence and genetics are critical for all of biology, genetics has limitations in its ability to explain major factors such as disease development and evolution (Table 1). Epigenetics provides solutions for these failures of genetic determinism (Fig. 5). The current concept for inheritance involves primarily genetics in that your DNA sequence is considered your destiny. The environmentally induced epigenetic transgenerational inheritance discussed provides a form of non-genetic inheritance which we previously did not appreciate (Daxinger and Whitelaw, 2012; Schmidt, 2013; Skinner et al., 2010). This significantly impacts how we think about who we are and how our environment may be a significant factor in our health and evolution.

The current concept in science today for disease etiology involves DNA sequence mutations and abnormalities as the primary causal factor. However, environmentally induced epigenetic inheritance of disease will likely be an equally important consideration. Although the concept that our ancestors' exposures and the epimutations inherited affects our health has an element of doom and gloom, the simple realization that this mechanism exists and epimutations are present can be used to address the issue. The epimutations can potentially be used to develop diagnostics to assess what your ancestral exposures potentially were and what disease you may be susceptible to develop. These diagnostics could be used to predict a disease development, before the disease develops. Therapeutics could then be potentially created to prevent the disease from developing, which may be more efficient than trying to treat the disease after it has developed. This is termed "preventative medicine" and we have not been able to do this well because we did not have these early stage diagnostics. These epimutations may act

as diagnostics to provide the ability to facilitate preventative medicine in the future.

The current concept in evolutionary biology is that random DNA sequence mutations and classic genetic mechanisms promote phenotypic variation that natural selection acts upon to facilitate Darwinian evolution. Although environment is a critical component for natural selection, the ability of environmental factors to promote directly phenotypic variation through epigenetic transgenerational inheritance is a novel concept for evolution. Lamarck proposed in 1800 the ability of environment to promote phenotypic change (Lamarck, 1802). Therefore, environmentally induced epigenetic transgenerational inheritance provides a neo-Lamarckian concept that facilitates Darwinian evolution. Epigenetics now needs to be seriously considered as an additional molecular component of evolution.

Consideration of environmentally induced epigenetic transgenerational inheritance is anticipated to have a significant role in all areas of biology. This phenomenon significantly extends our current genetic determinism focus. Environmental epigenetics and epigenetic inheritance will help to better understand how environment (e.g. endocrine disruptors) influences our health and disease.

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Glossary

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

Genetic determinism: The concept is that the DNA sequence alone is the building block for biology and that mutations in this sequence are the primary causal factors for most biological phenomena from disease development to evolutionary biology.

Environmental epigenetics: The ability of an environmental factor to directly act and alter epigenetic processes to promote gene expression and phenotypic change (physiological characteristics).

Epimutation: The altered epigenetic mark at a specific DNA site in response to an environmental factor that influences gene expression.

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