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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.