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Review

Environmentally induced epigenetic transgenerational inheritance of phenotype and disease

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ABSTRACT

Environmental epigenetics has an important role in regulating phenotype formation or disease etiology. The ability of environmental factors and exposures early in life to alter somatic cell epigenomes and subsequent development is a critical factor in how environment affects biology. Environmental epigenetics provides a molecular mechanism to explain long term effects of environment on the development of altered phenotypes and "emergent" properties, which the "genetic determinism" paradigm cannot. When environmental factors permanently alter the germ line epigenome, then epigenetic transgenerational inheritance of these environmentally altered phenotypes and diseases can occur. This environmental epigenetic transgenerational inheritance of phenotype and disease is reviewed with a systems biology perspective.

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1. Introduction

Aristotle introduced the question if the embryo contain all its parts in little from the beginning, or is there a true formation of new structures as it develops (Peck, 1943). Since the emergence of neo-Darwinism the paradigm has been that genes are responsible for the formation of phenotypes and that they control development, with environmental or epigenetic actions being minimally important (Wake and Larson, 1987). According to this view, the environment is assumed to have only a permissive role in development (Gilbert, 2005). However, systemic or integrative biologists have recognized the importance of the role of environment in the developmental process and its importance in shaping phenotypes (Oster and Alberch, 1982; Nijhout et al., 1986). Although the role of genetics is crucial for the developmental process, an exclusively genetic approach ignores important environmentally dependent events that occur during development. In contrast, consideration of epigenetic processes provides the opportunity to understand how environmental signals regulate genome activity or interfere with developmental processes involved in the formation of the adult phenotype (Jaenisch and Bird, 2003; Jirtle and Skinner, 2007). The establishment of epigenetic patterns during development is a crucial process that links how environmental conditions influence development. The action of these environmental compounds induces the establishment of specific epigenetic patterns during key developmental periods that influence phenotypic variation, which in some cases lead to disease states (Jirtle and Skinner, 2007; Skinner et al., 2010).

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The influence of environmental factors on biological processes has been appreciated and investigated for hundreds of years; however, the basic molecular mechanism of how the environment can influence long term gene regulation has only recently been addressed through epigenetic studies. Even in the early days of genetic knowledge, scientists such as Richard Goldschmidt, an integrative biologist, highlighted the fact that early developmental events could have as much importance as genetics in the origin of the adult phenotype (Goldschmidt, 1933). This message is still valid today when even after years of important discoveries in the field of genetics, the phenotypic states cannot be explained solely by observed changes in DNA sequence. Epidemiological studies have for decades suggested significant environmental impacts on biology that could not be explained solely by genetic features. Examples of such observations follow:

1. The association of disease states with single nucleotide polymorphisms (SNPs) in the "Genome-Wide Association Studies" (GWAS) has revealed that genetic components usually explain less than 20% of the phenotypic variance (Wallace, 2010). The importance of moving beyond studying SNPs to examine more complex chromosomal regulation and epigenetic changes is paramount (Yuan and Ferguson, 2011).
2. The premise that a detailed genetic knowledge would allow the causes of the majority of diseases to be determined, which was based on a reductionist view of genotype–phenotype correlations, is now proven to be false when the evidence suggests that the majority of diseases are complex traits (Dipple et al., 2001).
3. The importance of the developmental origins of disease is now well accepted, which has also been recently recognized by the World Health Organization (Godfrey et al., 2007).
4. It is known that the risk for common metabolic diseases varies by geography and ethnicity, therefore making regional environmental influences an important component in disease incidence (Wallace, 2010). Several disease mechanisms are now known to have an important epigenetic component, such as in allergy (Kuriakose and Miller, 2010), hepatic cancer (Pogribny et al., 2006), gastric cancer (Nan et al., 2005), asthma (Martino and Prescott, 2011), colorectal cancer (Choong and Tsafnat, 2011), prostate cancer (Perry et al., 2010), HIV latency (Hakre et al., 2011) or brain disorders (Kaminsky and Tsafnat, 2010).
5. Studies in monozygotic twins (same genetic composition) have revealed striking discordances in the prevalence of many diseases that so far have been thought to have a genetic association (Bell and Spector, 2011). Association of these diseases with epigenetic mechanisms is evident.
6. Several common diseases have had a dramatic increase in incidence in the past decade, with exposure to environmental factors accounting for 40% of deaths worldwide and with the majority of cancer being linked to environmental exposures (Pimentel et al., 2007).
7. Among all environmental compounds or toxicants that are associated with the onset of diseases very few have the ability to alter DNA sequence or promote mutations. For example, carcinogenic metals are weak mutagens (Martinez-Zamudio and Ha, 2011) and few endocrine disruptors have been found to have a mutagenic effect (Skinner et al., 2010; Guerrero-Bosagna and Valladares, 2007).
8. In regards to evolutionary biology, the random mutation hypothesis is not sufficient to explain the origin of phenotypes (Brisson, 2003; Lenski and Mittler, 1993). However, epigenetically induced genomic changes may play an important role in promoting specific types of mutation (Skinner et al., 2010; Guerrero-Bosagna et al., 2005), as for example CG to TG transitions (Sved and Bird, 1990).

These are just a few of the biological observations that suggest a significant impact of the environment on disease etiology, which cannot be easily explained through classic genetic mechanisms. The gaps in knowledge have been partially addressed due to the advent of epigenetics, a phenomenon described by Waddington in the 1940's. His initial definition of epigenetics had a developmental basis, defining it as "*the branch of biology which studies the causal interactions between genes and their products which bring phenotypes into being*" (Jablonka et al., 2002). However, the specific molecular mechanisms involved in epigenetic modification of genome activity were not elucidated until more recently (1970's through today). Currently, the study of epigenetics focuses on "*molecular factors and processes around DNA that regulate genome activity independent of DNA sequence and that are mitotically stable*" (Skinner et al., 2010). Epigenetic systems have been described in several organisms and include histone modifications, chromatin structure, non-coding RNA and DNA methylation and hydroxymethylation (Chen and Riggs, 2005; Craig, 2005; Iqbal et al., 2011; Kim, 2006; Margueron et al., 2005; Skinner and Guerrero-Bosagna, 2009; Wallace and Orr-Weaver, 2005). Epigenetics is a critical element in the regulation of genome activity, which cooperates with genetic factors in regulating physiological responses (Gilbert, 2005). Epigenetics also provides a mechanism that allows environmental factors to influence long-term regulation of gene expression later in life that underlies the process of phenotype formation. Environmentally induced epigenetic changes may have a wide range of phenotypic consequences leading to disease conditions such as cancer, reproductive defects and obesity (Anway et al., 2005, 2006; Cheng et al., 2004; Guerrero-Bosagna et al., 2008; Howdeshell et al., 1999; Newbold et al., 2006, 2008; Waterland et al., 2008; Yamasaki et al., 1992). Focus on these observations have lead to the defining of the area of *environmental epigenetics*, which has had a major role in the elucidating disease etiology.

2. Environmental epigenetic influences on meiosis and mitosis

Cell replication requires the conservation of epigenetic patterns to daughter cells. Environmental exposures can act on both somatic and germ cell replication, influencing the establishment or maintenance of specific epigenetic patterns. These epigenetic processes and programming are influenced by environmental factors. For example, dietary compounds have been implicated in the modulation of histone modifications (Delage and Dashwood, 2008) and even trace elements have been shown to alter DNA methylation during early development (Vahter, 2007; Waalkes et al., 2004). Since DNA and histone methylation are enzymatic reactions that requires methyl donors to proceed (Singal and Ginder, 1999), the environment can influence DNA methylation through modifying the activity of methyltransferases or through altering the availability of methyl donors, which are the substrate for the methylation reaction on histones or CpG dinucleotides. Two different classes of DNA methyltransferases (Dnmts) exist: maintenance and *de novo* methyltransferases. One important aspect of epigenetic mechanisms is their ability to be maintained even after mitotic cell divisions (Skinner, 2011a,b). The mechanism by which DNA methylation states are mitotically maintained is through the action of DNMT1, a methyltransferase that only acts upon hemi-methylated strands of DNA (Yoder et al., 1997). After each cell division, DNMT1 activity will generate newly synthesized DNA strands that are methylated according to the DNA methylation pattern of the paternal strand. In contrast, other methyltransferases such as DNMT3A or DNMT3B act upon unmethylated strands of DNA (Yokochi and Robertson, 2002), which is why they are called *de novo* methyltransferases. Each DNA methyltransferase acts at a different