Progress in Biophysics and Molecular Biology xxx (2015) 1–11

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

# Elusive inheritance: Transgenerational effects and epigenetic inheritance in human environmental disease

Suzanne N. Martos*, Wan-yee Tang, Zhibin Wang*

*Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, USA*

ARTICLE INFO

*Article history:*
Available online xxx

*Keywords:*
Transgenerational
Epigenetic
Mammals
Environment

ABSTRACT

Epigenetic mechanisms involving DNA methylation, histone modification, histone variants and nucleosome positioning, and noncoding RNAs regulate cell-, tissue-, and developmental stage-specific gene expression by influencing chromatin structure and modulating interactions between proteins and DNA. Epigenetic marks are mitotically inherited in somatic cells and may be altered in response to internal and external stimuli. The idea that environment-induced epigenetic changes in mammals could be inherited through the germline, independent of genetic mechanisms, has stimulated much debate. Many experimental models have been designed to interrogate the possibility of transgenerational epigenetic inheritance and provide insight into how environmental exposures influence phenotypes over multiple generations in the absence of any apparent genetic mutation. Unexpected molecular evidence has forced us to reevaluate not only our understanding of the plasticity and heritability of epigenetic factors, but of the stability of the genome as well. Recent reviews have described the difference between transgenerational and intergenerational effects; the two major epigenetic reprogramming events in the mammalian lifecycle; these two events making transgenerational epigenetic inheritance of environment-induced perturbations rare, if at all possible, in mammals; and mechanisms of transgenerational epigenetic inheritance in non-mammalian eukaryotic organisms. This paper briefly introduces these topics and mainly focuses on (1) transgenerational phenotypes and epigenetic effects in mammals, (2) environment-induced intergenerational epigenetic effects, and (3) the inherent difficulties in establishing a role for epigenetic inheritance in human environmental disease.



**Contents**

1. Introduction ..... 00
 1.1. Transgenerational versus intergenerational epigenetic effects ..... 00
 1.2. Epigenetic reprogramming in mammals ..... 00
 1.3. Transgenerational epigenetic inheritance in eukaryotic organisms ..... 00
2. Transgenerational phenotypes in mammals ..... 00
 2.1. Transgenerational effects of environmental exposures ..... 00
 2.2. Mutation-induced epigenetic instability and transgenerational phenotypes ..... 00
 2.3. RNA-mediated paramutation-like effects ..... 00
 2.4. Transgenes and metastable epialleles ..... 00
3. Environment-induced intergenerational epigenetic effects ..... 00
4. Establishing a role for epigenetic inheritance in human environmental disease ..... 00
 4.1. Transgenerational human disease ..... 00
5. Establishing a role for epigenetic inheritance in human environmental disease ..... 00
 Transgenerational human disease ..... 00
 Limitations of human epidemiology studies ..... 00

* Corresponding authors. 615 N. Wolfe Street, Room E7618, Baltimore, MD 21205, USA. Tel.: +1 410 955 7840.
*E-mail addresses:* smartos1@jhu.edu (S.N. Martos), zwang47@jhu.edu (Z. Wang).

http://dx.doi.org/10.1016/j.pbiomolbio.2015.02.011
0079-6107/

Limitations of interspecies extrapolation of phenotypes ..... 00
Genome–epigenome dynamics ..... 00
6. Potential implications for human environmental health and disease ..... 00
Conclusions ..... 00
Acknowledgments ..... 00
References ..... 00

## 1. Introduction

Barker et al. postulated that organs undergo developmental programming in utero that predetermines subsequent physiological and metabolic adaptations during adult life (Barker et al., 1993; Hales and Barker, 2001). Classic examples include association between low birth weight and a greater risk of coronary heart disease, hypertension, stroke, depression, type 2 diabetes, and osteoporosis in later life (Barker et al., 1993; Fernandez-Twinn and Ozanne, 2006; Gluckman and Hanson, 2004). The observation from the Dutch famine studies also provided a proof of this concept. The paradigm is rooted in the process of developmental plasticity (Bateson et al., 2004) that argues that most human organs, prior to full maturation, are capable of re-directing their course of development based on early life clues that forecast later-life demands. It is thought that a fetal environment can alter various organ systems, rendering the individual more susceptible to disease in later life when there is a chance to encounter a second, disease-promoting stimulus (Burdge et al., 2009). Epigenetics now underpins the developmental reprogramming by demonstrating the molecular relationship between the environment and gene expression (Jirtle and Skinner, 2007; Tang and Ho, 2007).

Within the last decade, studies have been published, suggesting the possibility of transgenerational epigenetic effects in mammals (Anway et al., 2005; Padmanabhan et al., 2013; Rassoulzadegan et al., 2006). These observations force us to question whether environment-altered epigenetic marks can be inherited over generations to contribute to human disease. We now present the possible epigenetic mechanisms underlying the developmental plasticity (adaptive epigenetic variations) and epigenetic inheritance towards exogenous environmental factors and whether these epigenetic effects persist in subsequent generations. We briefly define transgenerational, discuss how mammalian epigenetic reprogramming should prevent most epigenetic marks from persisting across multiple generations, and summarize established mechanisms of transgenerational epigenetic inheritance in non-mammalian eukaryotic organisms. Then we review mammalian models demonstrating transgenerational phenotypes and environment-induced intergenerational epigenetic effects. Finally, we discuss the difficulties in establishing a role for epigenetic inheritance in human environmental disease and why this necessitates an understanding of the molecular basis underlying transgenerational phenotypes to determine potential implications for human health.

### 1.1. Transgenerational versus intergenerational epigenetic effects

Many studies have described intergenerational effects as evidence for transgenerational inheritance. However, correcting the misconception that these two terms are interchangeable is necessary for progress to be made in the study of epigenetic inheritance in human disease. Clarifying these definitions will allow researchers to develop and choose appropriate model systems for examining environmental influences on intergenerational and transgenerational phenotypes and associated mechanisms. In mammals, pregnant females exposed to environmental factors, such as nutrition, hormones, toxicants, or stress can affect fetal development. Such in utero exposures can also affect developing germ cells within the fetus (Skinner, 2008). Environment-induced epigenetic changes are referred to as ***intergenerational*** when they occur in the adult female organism (F0), the first generation of offspring (F1), or the second generation of offspring (F2), because the adult, the fetus, and the primordial germ cells (PGCs) would be directly exposed to the inducing agent. Effects may be ***transgenerational*** only when observed in subsequent generations (F3 or later) in the absence of exposure to the inducing agent or environmental factor that initiated the change. Effects observed in the male germline during the second-generation offspring (F2) may be transgenerational when induced during exposure to the adult male (F0) and his germline (F1). Importantly, this does not imply that all epigenetic effects in F3 after gestational female exposure or F2 after male exposure are necessarily epigenetic inheritance. Parental effects (Daxinger and Whitelaw, 2012; Whitelaw and Whitelaw, 2008), recapitulation (Waterland, 2014) and DNA sequence changes (Heard and Martienssen, 2014) should be excluded. For example, that seminal fluid can affect the uterine environment (Bromfield, 2014; Robertson, 2005) and impact offspring phenotype (Bromfield et al., 2014) implies that paternal effects could also influence developing PGCs (F2), independent of germline-transmitted effects. Examples of non-germline maternal effects are described later in Sections 2.2 and 2.4. Several reviews have previously described distinguishing between intergenerational and transgenerational effects in greater detail (Daxinger and Whitelaw, 2012; Heard and Martienssen, 2014; McCarrey, 2014; Schmidt, 2013; Skinner, 2013). Up to date, the majority of environmental toxicants are shown to influence somatic cells (in F0 and/or F1 germ cell) via epigenetic mechanisms and induce disease phenotypes in mammals but not transmit those epigenetic effects into F3 (mother exposed) or F2 (father exposed). Transgenerational inheritance of epigenetic changes is commonly shown in plants only. Limited studies have demonstrated that environmental toxicants are able to promote transgenerational inheritance of phenotypes and diseases states in mammals. Findings from either aspect can help us to define the exposure window to the nutritional, hormonal, or stress/toxin environments that may induce the adaptive and/or heritable epigenetic changes on the developing embryo and its germline, and cause disease phenotypes in subsequent generations.

### 1.2. Epigenetic reprogramming in mammals

An understanding of the resetting of epigenetic marks during development is needed to investigate the role of epigenetic inheritance in human disease. Within the mammalian life-cycle, the genome undergoes two global epigenetic reprogramming events, once in the zygote and second in the developing PGCs, reviewed in Cowley and Oakey (2012), Hackett and Surani (2013), Heard and Martienssen (2014) and McCarrey (2014). For zygote reprogramming after fertilization, the paternal genome is rapidly demethylated, and the maternal genome is passively demethylated; after implantation, genome-wide de novo methylation occurs and is

Please cite this article in press as: Martos, S.N., et al., Elusive inheritance: Transgenerational effects and epigenetic inheritance in human environmental disease, Progress in Biophysics and Molecular Biology (2015), http://dx.doi.org/10.1016/j.pbiomolbio.2015.02.011