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Review

Epigenetic inheritance and evolution: A paternal perspective on dietary influences

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ABSTRACT

The earliest indications for paternally induced transgenerational effects from the environment to future generations were based on a small number of long-term epidemiological studies and some empirical observations. Only recently have experimental animal models and a few analyses on human data explored the transgenerational nature of phenotypic changes observed in offspring. Changes include multiple metabolic disorders, cancer and other chronic diseases. These phenotypes cannot always be explained by Mendelian inheritance, DNA mutations or genetic damage. Hence, a new compelling theory on epigenetic inheritance is gaining interest, providing new concepts that extend Darwin's evolutionary theory. Epigenetic alterations or "epimutations" are being considered to explain transgenerational inheritance of parentally acquired traits. The responsible mechanisms for these epimutations include DNA methylation, histone modification, and RNA-mediated effects. This review explores the literature on a number of time-dependent environmentally induced epigenetic alterations, specifically those from dietary exposures. We suggest a role for the male germ line as one of nature's tools to capture messages from our continuously changing environment and to transfer this information to subsequent generations. Further, we open the discussion that the paternally inherited epigenetic information may contribute to evolutionary adaptation.

Contents

1. Epigenetic inheritance of environmental exposures through the father: the role of sperm

The idea of heritability of ancestral environmental exposures and their influences on phenotypic characteristics and risk of diseases in the offspring has fascinated many scientists for decades

Abbreviations: ALT, alanine aminotransferase; BMI, Body Mass Index; DMRs, differentially methylated regions; DNMT, DNA methyltransferase; HDAC, histone deacetylase; PGC, primordial germ cells; ROS, reactive oxygen species; SC, spermatocytes; SG, spermatogonia; SZ, spermatozoa.

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(Nelson and Nadeau, 2010; Pembrey, 2010; Soubry et al., 2014). While some observational studies in the 1930s and 70s have led to the suggestion of a paternal role in this transgenerational process (Fabia and Thuy, 1974; Price, 1939), the focus of most research studies in the last decade was on influences from periconceptional or *in vitro* exposures through the mother. Numerous animal and epidemiological data on mothers and their offspring have provided evidence that besides genetic damage also epigenetic features may be affected by environmental changes, leading to heritable phenotypic alterations that persist through multiple generations. The biological mechanism underlying this transgenerational inheritance has been proposed to involve the epigenome. Only in the last few years have some researchers started to invest in a search for potential paternal contributions in epigenetic inheritance of environmental exposures. Some of the controversial literature and theories on paternally inherited phenotypic changes from occupational harmful exposures include paint, industrial solvents, agriculture, war, and ionizing radiation but also effects from paternal diet or life-style and environmental pollution have been reported (Soubry et al., 2014). The physiological consequences in children or even grandchildren have often been attributed to DNA damage or mutations in paternal germ cells but to date this has not always been proven. Increasing evidence supports the idea that at least some epigenetic marks acquired during spermatogenesis may be sustained through embryonic development. Fig. 1 links the effects of several environmental exposures with potential molecular changes during male gametogenesis, causing persistent epigenetic alterations and phenotypic consequences in the next generation(s). The sperm epigenetic machinery includes DNA methylation, histone modifications, and transcription of non-coding RNAs (such as microRNAs) (Jenkins and Carrell, 2011). During gametogenesis, from primordial germ cells (PGCs) to spermatozoa (SZ) (Fig. 1), epigenetic marks are created in a sex-specific way (Marques et al., 2011; Niemitz and Feinberg, 2004). Imprinted genes are perfect candidate genes to capture and keep the environmental messages, since they escape the large-scale DNA methylation erasure after fertilization. However, other yet unidentified genes or gene promoters cannot be excluded from this selective protection. Modification and retention of histones and/or retention of other proteins or enzymes at specific DNA sequences are possible mechanisms to regulate the inheritance of environmentally induced epigenetic changes (Jenkins and Carrell, 2012; Jirtle and Skinner, 2007; Miller et al., 2010). In the fetus (not presented in the figure), after embryonic reprogramming, primordial germ cells lose their epigenetic marks as they migrate to the genital ridge. Complete epigenetic erasure is suspected, including erasure of imprint regulatory regions. Hence, theoretically, a new epigenetic pattern is created in the second generation and DNA methylation is guaranteed in a sex-specific manner (Murphy and Jirtle, 2003). However, some studies indicate that "permanent" epigenetic alterations induced by the environment are possible; germ cells may harbor this ancestral environmental information as epigenetic alterations, and subsequently transfer this to the next generations (Manikkam et al., 2013; Tracey et al., 2013). It should be noted that the terminology used to describe transmission of parental exposures varies. Terms like transgenerational, multigenerational and intergenerational are used interchangeably (Burton and Metcalfe, 2014; Skinner, 2008). The term "transgenerational effect" has generally been used if the effect is (still) present in the generation that was not exposed directly. If it was the germ line that was exposed, the effect can only become "transgenerational" if a permanent reprogramming occurred. This can only be verified if phenotypic consequences are analyzed in the next (non-exposed) generation (Skinner et al., 2014); which is not always feasible in studies on humans. Although we do not exclude any effects through the mother and the female germ line, studies on paternal exposures make it possible to

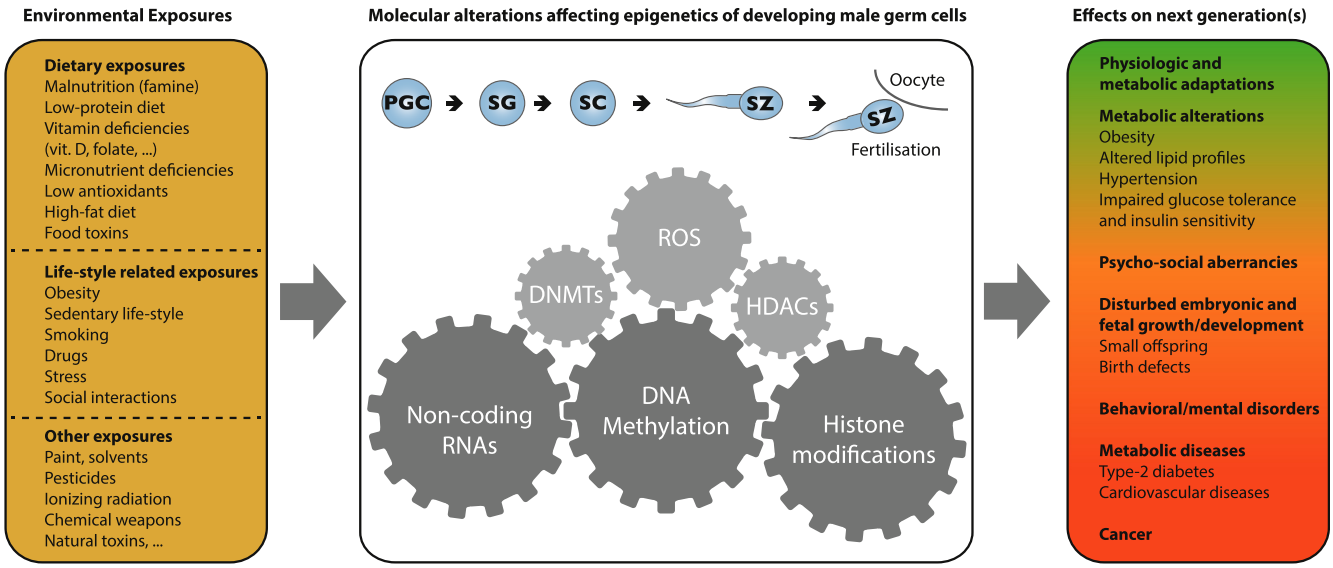

Fig. 1. The sperm epigenome: a messenger of ancestral exposures. Schematic overview of environmentally acquired epigenetic changes and disorders in the offspring through the paternal germ line. Examples of studies on transgenerational inheritance include exposures to malnutrition (such as famine (Heijmans et al., 2008) or overnutrition (Pembrey et al., 2006)), low-protein diet (Carone et al., 2010), vitamin or micronutrient deficiencies (Mejos et al., 2013), high fat diet (Ng et al., 2010; Wei et al., 2014), plastic-derived toxins (Manikkam et al., 2013), obesity (Soubry et al., 2013b), smoking (Northstone et al., 2014), stress (Gapp et al., 2014; Rodgers et al., 2013), paint and solvents (Reid et al., 2011; Wilkins and Sinks, 1984), pesticides (Skinner et al., 2013), ionizing radiation (Gardner et al., 1990; Koturbash et al., 2006), and war (Ngo et al., 2010). Although the molecular components are largely known, it is unclear how they are interlinked and how or when the environment interferes in these processes. Male germ cells develop from primordial germ cells (PGCs) to spermatogonia (SG) before puberty. They further differentiate to spermatocytes (SC) and finally spermatozoa (SZ) during each reproductive cycle. Candidate epigenetic components important in sperm development include DNA methylation, histone modifications, and non-coding RNAs (e.g. microRNAs). Enzymes, such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), often form a link between these components; they are important to fine-tune intermolecular effects. Unbalanced reactive oxygen species (ROS) generation may also to trigger this fine-tuning. Environmental messages are able to alter the epigenetic machinery in male germ cells. If the effects persist, these alterations may be either beneficial (green), they may disturb homeostasis or metabolism (orange), or they may be harmful (red) to the next generations.

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