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Transgenerational epigenetic actions of environmental compounds

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Abstract

Endocrine disrupting chemicals are known for their capacity to alter development and reproduction in mammals. One of the periods most sensitive to endocrine disruptor exposure is embryonic gonadal sex determination, when the germ line is undergoing epigenetic programming and DNA re-methylation. Epigenetic changes derived from exposure to endocrine disruptors have been described in several tissues and organisms. Endocrine disruptor induced epigenetic changes may have a wide range of phenotypic consequences, leading to disease conditions such as cancers, reproductive defects and obesity. Interestingly, the incidence of some diseases resulting from exposure to endocrine disruptors can be transgenerationally transmitted. In particular, exposure to the endocrine disruptor vinclozolin during early development is capable of inducing adult onset disease states that can be perpetuated across multiple generations. Environmental compounds such as endocrine disruptors can produce changes in the genome without altering DNA sequence. These changes are epigenetic in basis and can produce phenotypes that perpetuate transgenerationally. The suggestion that environmental factors can reprogram early development to induce epigenetic transgenerational phenotypes is a new paradigm in biology that will open new avenues for studies in disease etiology, reproduction and evolutionary biology.

Keywords: DNA methylation, endocrine disruptors, epigenetics, germline, inheritance, transgenerational.

Introduction

Endocrine disrupting chemicals are known for their capacity to alter development and reproduction in a variety of organisms, acting as estrogens, antiestrogens or antiandrogens (McLachlan, 2001; Skinner *et al*., 2010). Exposure to environmental compounds during early development have important consequences on adult stages (Danzo, 1998; McLachlan, 2001; Skinner *et al*., 2010). One of the periods most sensitive to endocrine disruptor exposure is embryonic gonadal sex determination, when the germ line is undergoing epigenetic programming and DNA re-methylation (Anway *et al*., 2005; Guerrero-Bosagna and Skinner, 2009; Skinner *et al*., 2010). When exposure to endocrine disruptors occurs during this sensitive period, the effects can be transgenerationally transmitted (Anway *et al*., 2005; Skinner *et al*., 2010). In particular, exposure to the endocrine disruptor vinclozolin early during development is capable of inducing adult onset disease states that can be perpetuated across multiple generations (Anway *et al*., 2005, 2006a, b; Nilsson *et al*., 2008). Recent evidence suggests that this transgenerational transmission may be based on epigenetic modifications (Anway *et al*., 2005). Endocrine disruptor induced epigenetic changes may have a wide range of phenotypic consequences, leading to disease conditions such as cancers, reproductive defects and obesity (Yamasaki *et al*., 1992; Howdeshell *et al*., 1999; Cheng *et al*., 2004; Anway *et al*., 2005, 2006a; Newbold *et al*., 2006, 2008; Guerrero-Bosagna *et al*., 2008; Waterland *et al*., 2008). In the event an environmental factor promoted the permanent reprogramming of the gamete epigenome, the transmission of this altered genome could promote a transgenerational inheritance of corresponding phenotypes to subsequent generations and progeny (Skinner and Guerrero-Bosagna, 2009).

Vinclozolin and transgenerational epigenetics

Recent experiments from our group have examined the possibility that early developmental exposure to endocrine disruptors alters the germ line and produces changes in the adult, which are transmitted to subsequent generations. The model endocrine disruptor tested is vinclozolin, which is a fungicide that acts as an anti-androgenic compound commonly used in agriculture (Wong *et al*., 1995). It has been previously showed that developmental exposure to vinclozolin can effect embryonic testis development to subsequently cause an increase in spermatogenic cell apoptosis in the adult (Uzumcu *et al*., 2004). Interestingly, this spermatogenic defect was found to be transgenerational (F1, F2, F3 and F4 generations; Anway *et al*., 2005, 2006a, b) and hypothesized to be due to a permanent altered DNA methylation of the male germ-line (Anway *et al*., 2005).

Interestingly, the altered sperm epigenome may subsequently have the capacity through the paternal allele to impact the genome activity of a variety of developing tissues and cell types. The pattern of gene expression is found to be altered in the embryonic testis (Clement *et al*., 2007, 2010) and surprisingly this altered transcriptome is similar for all generations (F1-F3; Anway *et al*., 2008). Transgenerational transcriptomes

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were also identified in prostate (Anway and Skinner, 2008) and brain (Skinner *et al*., 2008), with each tissue having a unique set of differentially expressed genes.

Therefore, vinclozolin was found to promote a transgenerational alteration of the sperm epigenome that appears to be correlated to transgenerational alterations in the transcriptomes of somatic cells and tissues. The functional relationships between the differential DNA methylation and transcriptome effects remain to be established.

In addition to detection of the male testis disorder (spermatogenic cell defects), as the animals age transgenerational effects on other disease states were observed including tumor development, prostate disease, kidney disease and immune abnormalities (Anway *et al*., 2006a). Recent observations also suggest transgenerational effects on behaviors such as sexual selection and anxiety (Crews *et al*., 2007; Skinner *et al*., 2008). Therefore, a number of different adult onset disease states were identified and found to transgenerationally develop at high frequencies in an epigenetic manner.

Conclusions

It is becoming increasingly accepted that environmental compounds such as endocrine disruptors can produce changes in the genome that in spite of not altering DNA sequence can produce important and permanent changes in the phenotype. The transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination that alter the epigenetic (i.e. DNA methylation) programming of the germ line. This event then alters the transcriptomes of developing organs, inducing a variety of adult onset disease states transgenerationally. The suggestion that environmental factors can reprogram early development to induce epigenetic transgenerational disease is a new paradigm in disease etiology not previously considered.

Although the actions of most environmental factors will likely involve alterations in the somatic cell epigenome and not promote an intrinsic transgenerational process, the perpetuation of the action of the stimuli across generations could still produce long lasting consequences in a lineage (Guerrero-Bosagna *et al*., 2005; Jirtle and Skinner, 2007; Guerrero-Bosagna and Skinner, 2009; Skinner *et al*., 2010). This opens new avenues for the consideration of environmental epigenetics in disease etiology, reproduction or evolutionary biology.

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