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Epigenetic transgenerational inheritance

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Abstract

Endocrine disruptors are critical environmental exposures that influence health and can promote epigenetic transgenerational inheritance of disease and abnormal physiology. Advances in 2015 included analyses of the effects of endocrine disruptors on human disease, further examples of endocrine disruptors promoting transgenerational behavioural effects, insights into effects of endocrine disruptors on epigenetic programming of primordial germ cells and the finding that endocrine disruptors can transgenerationally promote genetic mutations.

Environmental compounds that alter and/or disrupt normal endocrine hormone signalling at the receptor or signal transduction level are termed endocrine disruptors. The first endo crine disruptors studied and shown to promote abnormal physiology and disease were diethyl stilbestrol (DES) and dichlorodiphenyltrichloroethane (DDT)[1]. The number of known endocrine disruptors has since expanded dramatically to include compounds such as bisphenol A (BPA) and phthalates; natural compounds, such as genistein from plants, can also act as endocrine disruptors[1]. Over the past several decades, research on endocrine disruptors has improved our under standing of the molecular and physiological actions of these agents on human health[1]. In addition to the direct effects of exposure on an individual, molecular alterations to the germ line can promote effects on subsequent generations. As most exposures to endocrine disruptors do not promote genetic mutations, these generational effects are mediated via epigenetic mech anisms. When the effects of an endocrine disruptor alters the epigenetic programming of the germ line, these changes are transmitted between generations in the absence of direct exposure (FIG. 1), an effect termed epigenetic transgenerational inheritance[1].

The initial observation of epigenetic transgenerational inheritance involved the endocrine disruptor vinclozolin, an antiandrogenic agricultural fungicide[2]. Vinclozolin and the pesticide methoxychlor promote the epi genetic transgenerational inheritance of reduced male fertility[2]. A large number of other endocrine disruptors and environ mental exposures have now also been shown to promote epigenetic transgenerational inheritance of disease and abnormal physiology in a wide variety of species from plants to humans[1]. This process involves epigenetic alterations of the germ line that can include DNA methylation, non-coding RNAs, histone modifications and alterations in chromatin structure. The effects range

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from reproductive and behavioural effects to obesity[1]. This nongenetic form of inheritance has altered our understanding of the molecular control of disease aetiology and evolution. Here, I focus on advances in 2015 involving endocrine disruptors and epigenetic transgenerational inheritance.

A large epidemiology study published in 2015 by Kalfa *et al.*[3] extended the findings of a previous study reporting the effects of phthalates on humans[4] by demonstrating the associ ation of human hypospadias with prenatal exposure to a variety of endocrine disruptors. This French study examined a cohort of 300 consecutive children without a genetic defect and found that after control for genetic mutation, parental occupational and environ mental exposure to chemical products increased the risk of hypospadias in children[3]. Although Kalfa and colleagues focused on exposure in children, a future consideration is if such effects might influence epigenetic transgenerational inheritance mechanisms.

Another advance in 2015 further documented the generational effect of endocrine disruptors on brain development and behaviour. Quinnies and colleagues demonstrated the transgenerational actions of the phthalate di-(2-ethylhexyl)phthalate (DEHP) on levels of stress hormones and behaviour[5]. Gestating mice were exposed to DEHP during fetal gonadal sex determination and the subsequent third generation (F3) had altered stress hormone levels (corticosterone), pitui tary gene expression and behaviour in both male and female mice[5]. A number of previous studies have demonstrated the trans generational actions of endocrine disruptors on behaviour[1], and a recent review[6] focusing on the neuro science of the phenomena supports the concept that epigenetic mechanisms might inform us about the transgenerational inheritance of behavioural traits that are increasingly being reported.

In considering the molecular mechanisms underlying endocrine-disruptor-induced epigenetic transgenerational inheritance of disease and phenotypic variation, the germ line transmission of epigenetic information between generations in the absence of continued exposure is critical[1] (FIG. 1). The original observations suggested that DNA methylation alterations in the sperm were crucial[2]; noncoding RNAs and histone modifications have, subsequently, also been shown to be involved[1]. Epigenetic reprogramming of the germ line primarily involves the primordial germ cell (PGC) development period and later stages of gametogenesis. Brieno-Enriquez and colleagues exposed gestating female mice to vinclozolin to produce epigenetic transgenerational inheritance of testicular cell apoptosis and abnormalities[7]. This study confirmed the observations and transgenerational phenotypes previously observed in a rat model[2]. Brieno-Enriquez *et al.* extended the previous observations with an analysis of PGCs and identified alterations in epigenetic programming and gene expression that are critical to PGC development (such as those in *Blimp1*). Although the global DNA methylation analysis used was insufficient to assess specific DNA methylation sites, this study[7] demonstrated interesting alterations in noncoding RNAs such as miR-23b and miR-21. Brieno-Enriquez and colleagues also showed that vinclozolin promotes epigenetic transgenerational inheritance of abnormalities in male testes and alters PGC noncoding RNA programming. A supporting study provided a major resource for epigenetic alterations during development of the human germ line epigenome[8]. This study identified a critical role for the Blimp-1 pathway, DNA methylation reprogramming and gene expression alterations that occur during normal develop ment of PGCs and the

subsequent germ line[8]. Specific DNA methylation sites that escaped DNA methylation erasure, termed ‘escapees’, were also identified and support a role for altered germ line DNA methylation in epigenetic transgenerational inheritance[8]. This supporting study provides additional mechanistic insights into the study of Brieno-Enriquez and colleagues[7]. Although science today has a strong reductionist view that tends to choose one process over another, the epigenetic control of transgenerational inheritance involves the integrated actions of DNA methylation, noncoding RNAs and histone modifications. These epigenetic processes are so interlinked that they must be viewed as integrated rather than disconnected. The observation that PGCs and the developing germ line undergo major epigenetic programming, which can be transgenerationally altered by endocrine disruptors[7], was a significant advance in 2015.

Endocrine-disruptor-induced epigenetic transgenerational inheritance of germ line epimutations has a critical role in this form of nongenetic inheritance[1]. Previous studies have shown that susceptibility to genetic mutations is increased by epigenetic alterations such as CpG methylation that promotes C to T conversions (point mutations), DNA methylation that influences repeat element copy number variation (CNV) and transposable element movement, and histone modifications and DNA methylation that alter chromosome translocation breakpoints. The role of genetics in epigenetic transgenerational inheritance is, thus, important. In 2015, my colleagues and I showed that vinclozolin promotes epigenetic transgenerational inheritance of genetic mutations in sperm (that is, CNV)[9]. In the directly exposed F1 generation, no change in CNV was seen, but in the F3 generation a significant increase in CNV was observed[9]. Transgenerational alterations in the epigenome, therefore, increase genetic instability and promote genetic mutation and variation. Transgenerational mechanisms and phenotypes will probably involve a combination of epigenetics and genetics, as genetics and epigenetics cannot be separated[9]. Further studies are now needed to elucidate this process, which might have a critical role in environmentally influenced disease aetiology and evolution.

The effects of endocrine disruptors on epigenetic programming during development provides a molecular mechanism for the development of disease later in life[1]. In the event that germ line epigenetic programming is altered, this change can lead to environmentally induced epigenetic transgenerational inheritance of disease and phenotypic variation. Although the majority of environmental exposures are not endocrine disruptors, in today's society, endocrine disruptors are an important source of contamination. The advances in 2015 discussed here support critical effects of endocrine disruptors on human health and in inducing epigenetic transgenerational inheritance, and increase our understanding of the molecular processes involved. This form of nongenetic inheritance that is environmentally responsive affects all of biology from disease aetiology to evolution.

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Key advances

- Prenatal exposure to endocrine disruptors is associated with human hypospadias[3]
- Epigenetic transgenerational inheritance of behavioural abnormalities is induced by the phthalate di-(2-ethylhexyl)phthalate[5]
- Vinclozolin induces epigenetic transgenerational inheritance of primordial germ cell epigenetic programming via noncoding RNAs and alterations in gene expression[7]
- Endocrine disruptors induce epigenetic transgenerational inheritance of genetic mutations in sperm[9]

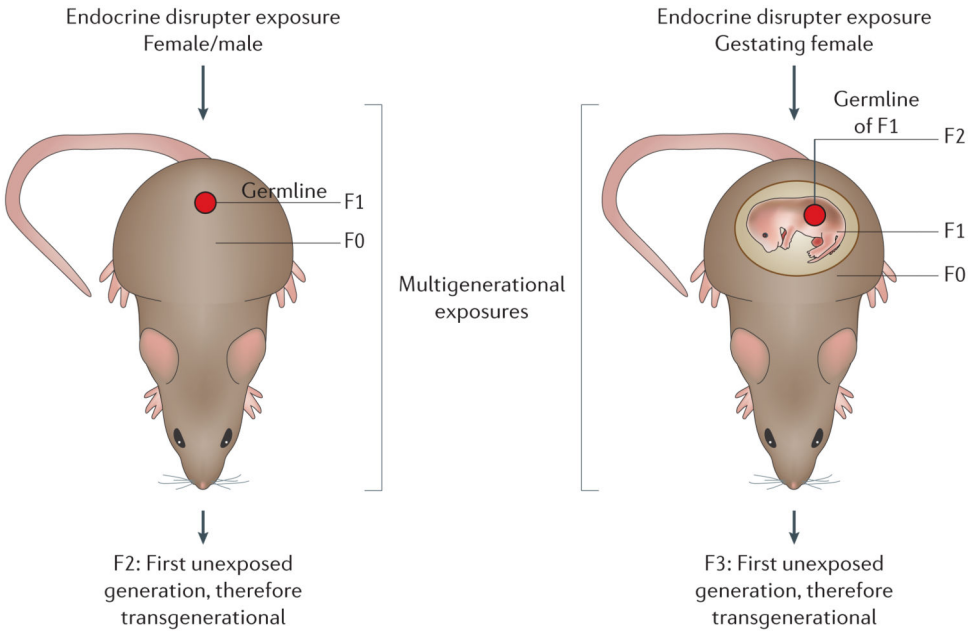

Figure 1. Endocrine-disruptor-induced epigenetic transgenerational inheritance

Schematic representation of environmental exposure and affected generations.