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Review

Multigenerational and transgenerational effects of endocrine disrupting chemicals: A role for altered epigenetic regulation?

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ABSTRACT

Increasing evidence has highlighted the critical role of early life environment in shaping the future health outcomes of an individual. Moreover, recent studies have revealed that early life perturbations can affect the health of subsequent generations. Hypothesized mechanisms of multi- and transgenerational inheritance of abnormal developmental phenotypes include epigenetic misregulation in germ cells. In this review, we will focus on the available data demonstrating the ability of endocrine disrupting chemicals (EDCs), including bisphenol A (BPA), phthalates, and parabens, to alter epigenetic marks in rodents and humans. These epigenetic marks include DNA methylation, histone post-translational modifications, and non-coding RNAs. We also review the current evidence for multi- and transgenerational inheritance of abnormal developmental changes in the offspring following EDC exposure. Based on published results, we conclude that EDC exposure can alter the mouse and human epigenome, with variable tissue susceptibilities. Although increasing data suggest that exposure to EDCs is linked to transgenerational inheritance of reproductive, metabolic, or neurological phenotypes, more studies are needed to validate these observations and to elucidate further whether these developmental changes are directly associated with the relevant epigenetic alterations.

Contents

Abbreviations: AhR, aryl hydrocarbon receptor; BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; DMR, differentially methylated region; DES, diethylstilbestrol; DOHaD, developmental origins of health and disease; DNMT, DNA methyltransferase; EDC, endocrine disrupting chemical; ER, estrogen receptor; F[#], filial generation; ncRNA, non-coding RNA; PTM, post-translational modification; ROS, reactive oxygen species; TDS, testicular dysgenesis syndrome; TET, ten-eleven translocase.

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1. Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that early life experiences can influence health outcomes later in life [1]. David Barker and colleagues were among the first to demonstrate this phenomenon over 25 years ago, correlating low birth weight with an increased risk of cardiovascular and metabolic diseases during adulthood [2]. Various environmental factors can disrupt proper developmental trajectories, and endocrine disrupting chemicals (EDCs) have received considerable attention due to their ubiquity in the environment and the increased incidence of endocrine-related disorders in humans, including pregnancy complications, genital malformations (*i.e.* cryptorchidism and hypospadias in male infants), and cancer (*i.e.* breast, ovarian, prostate, testicular) [3]. EDCs are natural or synthetic compounds capable of interfering with the biosynthesis, storage, release, transport, and/or receptor binding of endogenous hormones, ultimately interfering with the proper functions of these hormones [4]. About 800 commercial chemicals are suspected to interfere with the endocrine system, but only a small fraction of these has been tested for potential adverse effects [3]. Although the precise mechanisms responsible for exposure-induced phenotypes are unknown, epigenetic mechanisms have been proposed to mediate developmental reprogramming and subsequent disease susceptibility that occurs later in life.

The fetus and neonate represent particularly vulnerable populations to EDC exposures. Early development requires precise timing of hormone action to promote proper growth of tissues and organs, and EDCs can interfere with the endogenous activities of these hormones. In addition, the enzymes involved in xenobiotic biotransformation and the processes required to eliminate these compounds are not fully developed in the fetus or neonate [5,6]. Therefore, a toxic compound can persist and accumulate, reaching levels sufficient to cause adverse effects on target organs among these populations. Finally, large-scale epigenetic reprogramming events occur at two critical time points during early development to establish totipotency in the zygote and to specify the germ cell lineage [7]. EDCs could prevent the proper erasure, re-establishment, or maintenance of epigenetic marks during these periods of development, alter the cellular epigenome, and subsequently enhance postnatal disease susceptibility. If germline epigenetic marks are disrupted, this could result in the transmission of adverse phenotypes across multiple generations.

A growing research interest within the DOHaD field is the multi- and transgenerational inheritance of an abnormal phenotype. These two phenomena differ depending on whether the affected generation had direct exposure to the original stimulus. If a pregnant mother (designated as the filial [F] 0) is exposed to an adverse stimulus, her child (designated the F1) may be affected as a consequence of direct exposure to the same stimulus *in utero* (Fig. 1). Moreover, because the germ cells of the F1 offspring are developing throughout gestation, the grandchildren (designated F2) are also directly exposed. Effects seen in the F2 generation would be considered multigenerational. In contrast, effects observed in the F3 generation that had no direct exposure to the original stimulus would be transgenerational. An important note regarding transmission of an abnormal phenotype through exposure from the mother is the presence of maternal effects (*e.g.*, behavior or metabolic milieu), which may confound the associated epigenetic change and observed phenotype [8]. When an exposure occurs through the F0 father, transgenerational effects are observed in the F2 generation, as the only other generation directly exposed to the original stimulus is the future F1 offspring, which is exposed as a germ cell (Fig. 1).

To elicit a transgenerational phenotype, EDCs must affect the germ cell directly or indirectly by altering the function of its

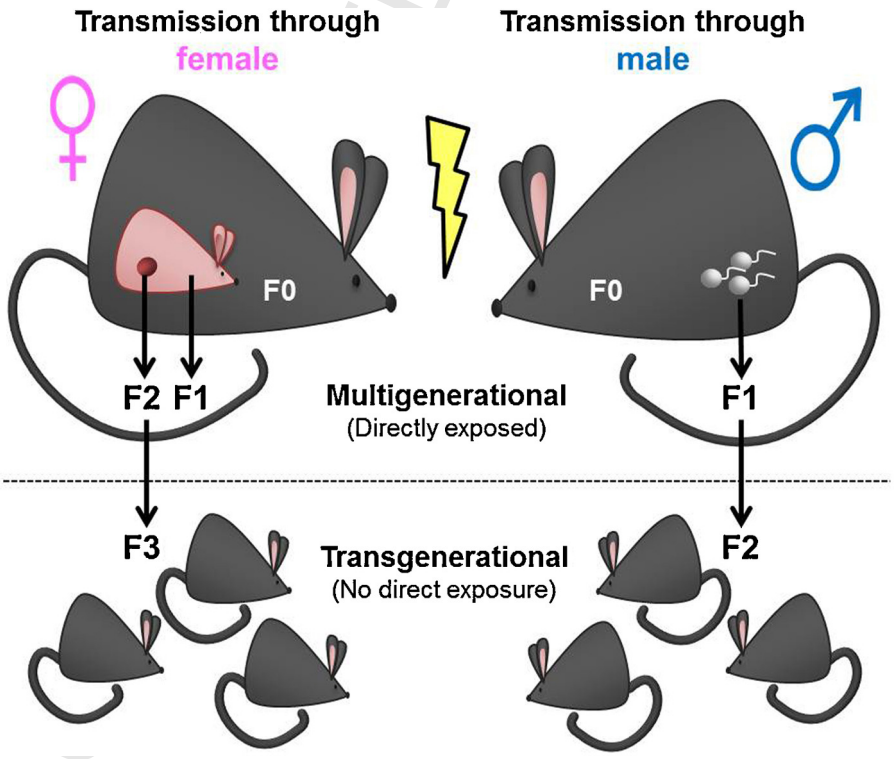

Fig. 1. Multigenerational *vs.* transgenerational effects transmitted through the F0 female *vs.* F0 male. Exposure of a pregnant F0 dam directly exposes both the F1 (exposed as developing fetus) and F2 (exposed as developing germ cells of F1) generations. The first generation to experience no direct exposure to the original stimulus (lightning bolt) from maternal exposure is the F3 generation. Paternal F0 exposure directly exposes the F1 generation only (exposed as germ cells). Effects observed in the F2 generation are, therefore, considered transgenerational.

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