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Epigenetic underpinnings of developmental immunotoxicity and autoimmune disease

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Abstract

The concordance rate for developing autoimmune disease in identical twins is around 50% demonstrating that gene and environmental interactions contribute to disease etiology. The environmental contribution to autoimmune disease is a wide-ranging concept including exposure to immunotoxic environmental chemicals. Because the immune system is immature during development suggests that adult-onset autoimmunity may originate when the immune system is particularly sensitive. Among the pollutants most closely associated with inflammation and/or autoimmunity include Bisphenol-A, mercury, TCDD, and trichloroethylene. These toxicants have been shown to impart epigenetic changes (e.g., DNA methylation) that may alter immune function and promote autoreactivity. Here we review these autoimmune-promoting toxicants and their relation to immune cell epigenetics both in terms of adult and developmental exposure.

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1. Introduction

The immune system is designed to recognize and eliminate foreign antigens. If the immune system instead attacks self-antigens, autoimmune diseases may occur. Approximately 24 million Americans have one or more autoimmune disease. These chronic, incurable disorders disproportionately affect females, and are among the leading causes of death for young and middle-age women [1]. Twin studies have shown that although an individual's genome may increase susceptibility, environmental triggers are required to initiate disease. Defining how the environment promotes autoimmunity will enhance understanding of so-called idiopathic autoimmune disease. The elevated prevalence and incidence rates of autoimmune disease parallel the documented increase in environmental pollutants leading to an appreciation of environmental toxicants common to industrialized nations as important riggers for autoimmunity [2].

Enhanced sensitivity of the immune system to environmental perturbations during key developmental events occurring prenatally and/or postnatally are critical for later life function [3–6]. The cells of the innate immune system (i.e. neutrophils, dendritic cells, NK cells, and macrophages) provide the first line of defense against pathogens. Their relative functional immaturity at birth means that innate immunity is weak in the newborn compared to an adult. The second line of defense is mediated by the cells of the adaptive immune system. T cells derived in the thymus are abundant at birth, and they need to undergo further maturation in the periphery to become fully functional. Peripheral B cells in the newborn are similarly immature, and require further maturation to respond to antigens. Thus, due to the vulnerability of the developing immune system, developmental exposures may influence adult autoimmunity [7].

When contemplating how developmental toxicant exposure "programs" the host for autoimmunity, one likely scenario involves epigenetic alterations such as aberrant DNA methylation. The epigenome consists of modifications of the genome that do not alter DNA base sequences, but can regulate gene expression and phenotype. While it is understood that the epigenome is regulated by several epigenetic mechanisms other than DNA methylation (e.g., histone acetylation and microRNA expression), of the various forms of epigenetic modifications, DNA methylation is the most thoroughly investigated. Maturation of immune cells are largely controlled by DNA methylation events that occur most often in early life that are functionally evident in later life and potentially to additional generations [8]. Autoimmune diseases [(lupus, rheumatoid arthritis, type 1 diabetes (T1D), and multiple sclerosis)] associated with environmental toxicants are also linked to abnormal methylation [9] and may represent a mechanism by which environmental triggers promote autoimmunity. Thus, the review will focus on toxicant-induced effects on DNA methylation in autoimmune disease.

2. DNA methylation changes at various stages of immune development

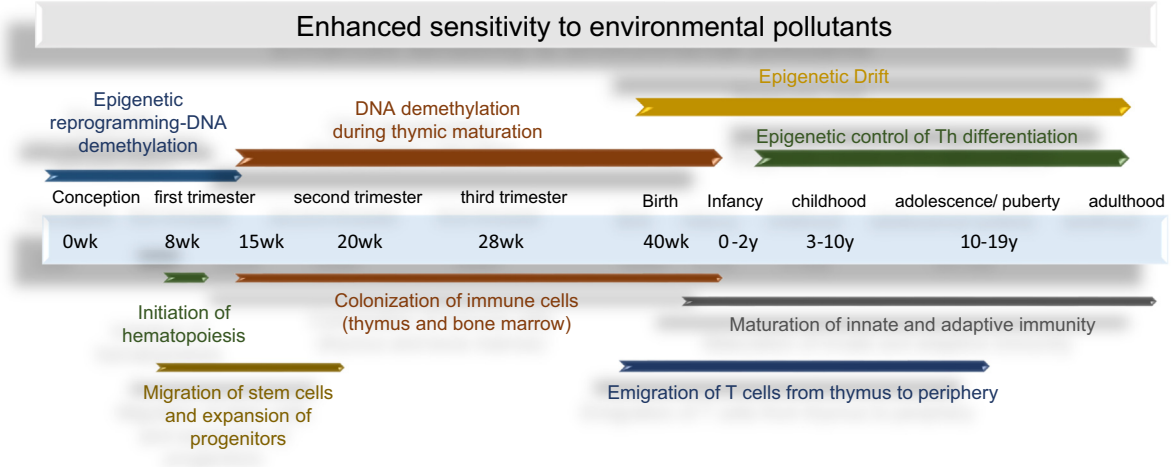
Autoimmune disease, whether antibody-or T cell-mediated is largely driven by $CD4^+$ T cells. As shown in Fig. 1, epigenetic events play an important role in immune cell development and correspond to several key cellular maturational events. Prior to immune system development, genome-wide global epigenetic reprogramming in early embryonic development occurs immediately after fertilization to ensure loss of DNA methylation allowing for global repression and gene expression in all cells [10]. In later stages, CpG methylation coincides with general developmental life stages with a reported global trend of demethylation during T cell development in the thymus closely related to the development of TCR function [11].

Another DNA methylation mechanism identified as an emerging concept in toxicology is epigenetic drift (i.e., drift) [12]. Drift is the divergence of the epigenome as a function of age due to stochastic changes in methylation. Under normal circumstances drift occurs because the fidelity of maintaining CpG methylation in mammalian cells (about 97–99% per cell division) is not absolute [13]. The small but significant error rate creates opportunity for changes in the methylome to occur and accumulate in constantly dividing cells, such as self-renewing effector/memory $CD4^+$ T cells [14]. Drift involves both involves both hypo- and hyper-methylation events, and can encompass as much as 2.2% of total CpG sites, and 5–25% of specific genes over time [15,16]. Drift can impact promoter methylation status and gene expression, and has been used to explain the subset heterogeneity of memory $CD4^+$ T cells that occurs during aging. In terms of autoimmune disease (e.g., T1D) results from twin studies suggest that drift causes heterogeneity in disease onset, severity, and predisposition to secondary complications [17]. The events that dysregulate drift are unclear, but appear to involve environmental exposures [18,19]. Importantly, although drift appears soon after birth, it occurs at a higher rate of change in children compared with adults [20]. Thus, although drift is still an understudied area of epigenetics, environmental influences may perturb this process in early life to promote autoimmunity.

One stage of vulnerability mediated by epigenetic changes is $CD4^+$ T cell differentiation. Beginning in early life, the phenotype of differentiated $CD4^+$ T cell subsets are normally controlled by carefully maintained levels of DNA methylation in the promoters of pertinent regulatory genes [21,22] (Fig. 2). The development of autoimmune disease can disrupt the methylation patterns of differentiated $CD4^+$ T cells, resulting in the demethylation of genes that encode immunomodulatory factors as reported in juvenile arthritis [23]. Subsets of differentiated $CD4^+$ T cells (i.e., Th1/Th17) have been shown to promote autoimmune disease in part to their persistence as effector/memory $CD4^+$ T cells. The dysregulated methylome in autoimmune disease is associated with increased heterogeneity or plasticity in these subsets [24,25].

While several key maturational and differentiation events in T cells are regulated by DNA methylation, it is not known whether these events promote autoreactivity. While studies have shown that the function of autoreactive $CD4^+$ T cells can be mediated by epigenetic processes, most of this work has been done in lupus

Fig. 1



Key human immune system developmental checkpoints that correspond with important changes in DNA methylation. General steps of human immune system development spans from gestation to early postnatal life. These events in particular are epigenetically regulated via DNA methylation and represent a sensitive window for perturbation due to environmental insults that may later manifest in later life autoimmune disease in certain individuals with genetic susceptibility or lifestyle factors.