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Developmental immunotoxicity (DIT), postnatal immune dysfunction and childhood leukemia

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ABSTRACT

The developing immune system is a sensitive target for environmentally-induced disruption producing postnatal immune dysfunction. Unique immune maturational events occur during critical windows of prenatal/perinatal development and environmentally-induced disruption of one-time events can have serious health consequences. Additionally, the specialized immunological conditions necessary to bring a semi-allogeneic fetus to term place restrictions on both the maternal and offspring immune systems. These features combine not only to increase the risk of early-life immune insult (ELII), which includes xenobiotically-induced developmental immunotoxicity (DIT), but also to influence the nature of DIT-associated diseases for the child. Exposure to certain toxicants as well as maternal infections and other pregnancy stressors is known to induce postnatal immune dysfunction. Because dysfunctional immune responses to childhood infections have been proposed to play a role in childhood leukemia, DIT is a potential risk factor for this disease. This review details the range of disease susceptibilities impacted by DIT and discusses the importance of effective DIT safety testing for drugs and chemicals as a preventative measure.

Introduction

Development of the immune system pre- and postnatally proceeds through a well-defined sequence of cellular and organ events involving the specialized microenvironments of the bone marrow and thymus, cell selection and apoptotic depletion, seeding of the tissues and establishment of immunologic memory [1,2]. Many of these events are restricted to *in utero* development or, if they occur postnatally, have a different impact after birth. As a result, it is not surprising that early life, developmentally-timed immune maturational events are exquisitely sensitive to environmental disruption [3,4]. Depending upon the nature of the environmental disruptor and the timing of the exposure, different adverse outcomes can result [reviewed in 5]. In fact, even exposure to the same xenobiotic during different periods of prenatal development can result in different postnatal immunotoxic changes [6]. This is not unique to the immune system. For example, *in utero* exposure of humans to the pesticide *p,p′*-dichlorodiphenydichloroethylene (DDE) has different neurobehavioral impacts depending upon the trimester of exposure [7].

Critical windows of immune vulnerability to toxicants have been previously described [5,8]. Among the known targets of xenobiotically-induced developmental immunotoxicity (DIT) are: seeding and homeoregulatory function of macrophages in organs and tissues, seeding of the thymus with lymphocytes, positive and negative selection of thymocytes, generation, activation and seeding of T regulatory cells, development of Th1 cells, maturation of dendritic cells, production of surfactants and modulation of macrophage function [5]. Not surprisingly, different toxicants appear to disrupt events occurring in different immune critical windows, or combinations of windows. For example, heavy metals seem to target macrophage homeoregulatory function, inflammatory responses, and Th1 response maturation involving T lymphocytes and dendritic cells. In contrast 2,3,7,8-tetradichlorobenzo-*p*-dioxin (TCDD) disrupts several events including thymocyte selection in the developing thymus causing not only thymic atrophy [9] but also an elevated risk of autoimmunity [10]. Alcohol has been reported to target late gestational surfactant production [11], to produce severe macrophage impairment [12] and to increase the risk of newborn infections [13].

The specific health risk resulting from DIT is linked to the nature of the prenatal–early postnatal immune insult. However, it should be noted that for a surprising incidence of developmental immunotoxicants, marked sex-based differences in outcome have been observed [reviewed in 14]. Depending upon the specific environmental factor and the doses examined, one sex may show a postnatal immunotoxic effect and the other show little to no change. Alternatively, both sexes may show a similar pattern of immune dysfunction but differ significantly in dose sensitivity.

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Finally, for some environmental factors, a prenatal exposure may produce opposite postnatal immune alterations among the sexes. Clearly, the possibility of sex-based differences in outcome following *in utero* DIT exposure needs to be considered in a determination of specific health risks.

Pregnancy, immune tolerance and unbalanced immune development

Apart from the existence of unique windows of immune development during gestation when specialized maturational events occur, the very nature of the pregnancy itself has an impact on both maternal immune status as well as the timeline for perinatal immune development. The fetus is semi-allogeneic to the mother and under normal circumstances would stimulate a robust Th1-dependent graft rejection type response. But in successful pregnancies brought to term, a T helper 2 (Th2)-biased environment is generated for much of the pregnancy [15–18]. In fact this skewing is sufficiently strong enough that in pregnant women with autoimmune diseases, most Th1-dependent autoimmune conditions lessen in severity during the pregnancy while Th2-dependent conditions increase in severity [19–21]. At the maternal–fetal interface, NK cells [22] and regulatory T cells [23] help to maintain a local environment where inappropriate allogeneic antigen stimulation is minimized. As a result, Th1-dependent cytokine production is suppressed throughout a major portion of the pregnancy [24,25] protecting both mother and fetus.

In fact, the pregnancy is at risk under situations where a Th2 bias cannot be generated and inappropriate Th1/proinflammatory cytokine production occurs [26]. Malamitsi-Pucher et al. [27] have suggested that interferon-gamma-dependent biomakers offer promise as mid-trimester predictors of preterm birth. In women where Th1-suppression is inadequate, reoccurring miscarriage is likely [15,28,29]. Additionally, lack of gestationally-timed Th2 skewing has been linked to the percentage of spontaneous abortion cases [30,31].

Because fetal Th1 development is delayed, there is a risk that the newborn will be deficient in some host defenses and not achieve the needed Th1/Th2 balance unless major shifts in immune balance are promoted after birth [32,33]. The maturation upon birth includes changes in dendritic cells and macrophages resulting in increased IL-12 production [34]. Levy [35] has reviewed the health risk for children under conditions where an imbalance continues. One of the outcomes of DIT seen with some frequency is a “fetal freeze” type of effect where postnatal Th1 increases never occur. This is often combined with aberrant inflammatory responses [14]. Because Th1 responses are critical for host defense against a variety of infectious agents (*e.g.* viruses) as well as tumors, the health implications of DIT can be significant.

Linkage of early-life immune insult, developmental immunotoxicity and increased health risks

Obviously, the increased risk of disease associated with ELII and DIT depends upon the nature of the prenatal insult (type of toxicant, infectious agent, stressor). For xenobiotics, previous adult immunotoxicity safety testing emphasized detection of profound immunosuppression usually involving major immune cell loss. However, that is not the primary concern with DIT. Instead, what has become clear in recent years is that the range of environmental factors causing profound developmental immunotoxicity with extensive loss of immune cells is modest when compared against the number of environmental factors that, with early life-exposures, produce immune dysfunction with minimal-modest cell loss.

Not surprisingly, shifts in juvenile and/or adult immune dysfunction stemming from prenatal/neonatal immune insult impact the risk of several diseases. A common occurrence with DIT is an increased risk of asthma [36–38] and allergic diseases [38–40]. This seems to be associated in part with altered dendritic cell and macrophage function as well as a shift toward Th2-biased responses. Disruption of thymocyte selection during gestation and interference in T regulatory cell seeding can increase the risk of later-life autoimmunity [41–43]. DIT-associated suppression of Th1-dependent functions increases susceptibility to certain infections [44–46] including influenza [47] as well as reduced responses to childhood vaccines [48]. Duramad et al. [49] discuss the relationship between prenatal toxicant exposure, aberrant cytokine production and postnatal disease risk including cancer.

The apparent impact of DIT on later life health risk is not restricted solely to diseases involving the immune system or host resistance to disease. Dietert and Dietert [14] recently reviewed the association of DIT with a variety of diseases impacting the immune as well as other systems. Of note is the recognition that environmentally-induced misdirected inflammation during gestation is responsible for non-immune tissue damage producing a constellation of conditions affecting the neurological and endocrine systems. Early life cytokine dysfunction has been linked to a cadre of postnatal neurobehavioral conditions including learning disabilities [50], autism and autistic spectrum disorders (ASD) [51,52], Parkinson's disease [53] and schizophrenia [54–56]. Additionally, respiratory system [57–59] and reproductive system dysfunction [60] have been associated with early-life misdirected inflammation.

Early-life links to neonatal immune dysfunction and childhood leukemia

One of the landmark concepts surrounding early-life risk factors for some forms of childhood leukemia is that a neonatal dysfunctional immune response against common childhood infectious agents promotes the disease [61–63]. Both maternal and early childhood infections are known to play a role in increased risk of some forms of childhood leukemia. Their association with the risk of childhood acute lymphoblastic leukemia (ALL) has been generally supported [64,65], although with calls for additional research by some investigators [66].

Greaves [63] recently reviewed the data supporting the infectious agent-host dysfunctional immune response tenet of childhood leukemia. More than one early life event is required to produce leukemia including some prenatal changes. For example, *in utero*-initiated chromosomal translocations are associated with many childhood leukemias [67]. Additionally, there is evidence that prenatal or perinatal immune alterations may impair early life host defense. Roman et al. [68], using results from the United Kingdom Childhood Cancer Study, found that children who later developed acute lymphoblastic leukemia had more neonatal infections than control children. The authors attributed this to a dysfunctional immune response capacity among neonates at risk for leukemia.

This supports the idea that prenatal–perinatal immune insult including DIT is likely to play a role in the risk of childhood leukemia. The fact that newborns have an immature immune system at birth compared with that of adults does not explain specific leukemia risk. If newborns at risk for leukemia are more prone to infections than age-matched controls [68] and also respond to infections with dysfunctional immune responses [63], then environmentally-induced alteration of the developing immune system before the critical period of neonatal infections would seem likely. This is supported by Kim et al. [69] who suggested that early life exposures are a critical factor in acute lymphocytic leukemia (ALL) and that critical windows of vulnerability are likely to exist. Hence, DIT and/or other early-life immune insults may help explain the proposed dysfunctional immune responses suspected in the children at greatest risk.