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Early life environment and developmental immunotoxicity in inflammatory dysfunction and disease

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Abstract

Components of the innate immune system such as macrophages and dendritic cells are instrumental in determining the fate of immune responses and are, also, among the most sensitive targets of early life environmental alterations including developmental immunotoxicity (DIT). DIT can impede innate immune cell maturation, disrupt tissue microenvironment, alter immune responses to infectious challenges, and disrupt regulatory responses. Dysregulation of inflammation, such as that observed with DIT, has been linked with an increased risk of chronic inflammatory diseases in both children and adults. In this review, we discuss the relationship between early-life risk factors for innate immune modulation and promotion of dysregulated inflammation associated with chronic inflammatory disease. The health risks from DIT-associated inflammation may extend beyond primary immune dysfunction to include an elevated risk of several later-life, inflammatory-mediated diseases that target a wide range of physiological systems and organs. For this reason, determination of innate immune status should be an integral part of drug and chemical safety evaluation.

Keywords

developmental immunotoxicity; inflammation; TLRs; risk factors; macrophages; dendritic cells; innate immunity

Introduction

The developing immune system is extremely sensitive to alteration through exposure to environmental toxicants (Bunn et al. 2001a, 2001b; Luebke et al. 2006). These alterations lead to inappropriate inflammatory responses, and since there are critical windows of immune development during which key, often one-time, maturational processes occur, the alterations can persist throughout life. Although environmental risk for disease is usually compartmentalized into prenatal versus neonatal exposure and/or by the different categories of environmental factors (environmental chemicals, drugs, maternal and childhood diet, infections, and stress), these risks do not occur in isolation and often act in combination (Chen et al. 2004; Wigle et al. 2008). For example, certain prenatal environmental exposures including maternal dietary factors can either enhance (Fujiwara et al. 2010) or alternatively,

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reduce (Grandjean et al. 2010) the normally beneficial impact of breastfeeding on neonatal immune regulation. Interactions between genetic and environmental factors during these critical immune windows also determine later-life, immune-based health risks. As a result, timing, genetics, and combinations of exposure to environmental risk factors, all determine the eventual immunological outcome and later-life disease risk (Bunn et al. 2001a, 2001b). Such later-life sequelae include allergy, autoimmune disease, metabolic syndrome, inflammatory diseases, and cancer (Dietert 2011).

Environmental factors can affect almost any aspect of the immune system. But when environmentally-induced immune insult occurs developmentally, it has the potential to result in a dysfunctional immune response pattern that may persist across a lifetime. Concern for the ramifications of developmental immunotoxicity (DIT) extends beyond humans (Dietert 2009) to include both agricultural (Bunn, Marsh, and Dietert 2000; Lavoie and Grasman 2007; Peden-Adams et al. 2009) and wildlife species (Grasman and Fox 2001). In a prior review, the ramifications of developmental immunotoxicity (DIT) on the risk of pediatric asthma and allergy were discussed (Dietert and Zelikoff 2008). In this review, we discuss another major outcome associated with early life environment and DIT: misregulated innate immune responses, inflammatory dysfunction, and the risk of chronic inflammatory disease. We discuss examples of how environmental exposures change the phenotype and function of innate immune cells, and describe in detail one example, lead (Pb), and its effect on a critical innate immune cell, the macrophage. We illustrate an integrative model for metal-induced immunotoxicity of dendritic cells and macrophages using lead (shown in Figure 1) and suggest that changes in the early immune system through environmental exposures can alter both the repertoire of immune responses and the capacity for effective inflammatory regulation. Lastly, we suggest that in response to the recent findings on the sensitivity of the innate immune system during development and the importance of appropriate innate immune function for health of humans. DIT testing of environmental toxicants must incorporate measures of: (1) innate immune cell function, (2) the expression and function of the innate immune cell receptors, and (3) newly discovered regulatory mechanisms that control inflammation.

Innate immunity and the developing immune system

Environmental interference during development of the innate immune system has the potential to limit the normal expansion of immune function and result in Th2-biased immunity or inappropriate/chronic inflammatory responses (Gao, Mondal, and Lawrence 2007; Kasten-Jolly, Heo, and Lawrence, 2010) and is, therefore, an important consideration for childhood vaccine development (Philbin and Levy 2009). Newborns have an inherently immature immune system (Zhao et al. 2008), and the default profile of immune responses during pregnancy and at birth is Th2-biased (Kollmann et al. 2009; Lee et al. 2008; White et al. 2010). Early life microbial exposures facilitate the maturation of dendritic cells (DCs) (Hoeman, Dhakal, and Zaghouani 2010; Troy and Kasper 2010) and expand the repertoire of immune functions to include Th1, Th17, and other immune response patterns. Prenatal and/or early postnatal exposure to toxicants (e.g., alcohol, heavy metals, tobacco smoke), certain infectious agents (e.g., gram-negative bacteria), and dietary factors (e.g., prenatal overnutrition, postnatal formula feeding) can alter the normal trajectory of innate immune

maturation contributing to tissue pathology rather than adequate host resistance and tissue homeostasis (Auten et al. 2009; Beloosesky et al. 2010; Bry, Hogmalm, and Backstrom 2010; Caicedo et al. 2008; Calderon-Garciduenas et al. 2009; Ding et al. 2010; Fry et al. 2007; Sharkey et al. 2009; Tomat, Costa Mde, and Arranz 2011). These alterations in immune function have the potential to change the trajectory of subsequent pathogen-stimulated innate immune responses throughout life (Perrone et al. 2010; Strunk et al. 2011). Failure to appropriately clear infection or to regulate inflammatory responses can lead to long-lasting inflammation. Chronic inflammation has been correlated with many different diseases and syndromes such as chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, rheumatoid arthritis, psoriasis, and the metabolic syndrome-related conditions of childhood obesity, hepatic steatosis, and atherosclerotic vascular diseases (Konner and Bruning 2011; Monteiro and Azevedo 2010; Sacheck 2008). We suggest that environmental insults during critical windows of innate immune cell maturation are likely to elevate the risk of adult inflammatory-related diseases many of which will arise in non-lymphoid tissues.

Direct effects of DIT on innate immune cells

Innate immune cells such as DCs and macrophages, seed tissues, and organs early in prenatal development, and have an increased likelihood of encountering the full range of environmental factors in the neonate due to their residence in the portals of environmental exposure (e.g., lung, skin, gut) (Maeda et al. 2010; Novak et al. 2010). Furthermore, the function of these innate immune cells is directly impacted by exposure to environmental toxicants (Bahri, Saidane-Mosbahi, and Rouabhia 2010; Gupta et al. 2010; Myrtek et al. 2008). Since these cells participate in homeostasis, respond to infectious challenge, and promote tissue remodeling, alterations in their function can change the outcome of responses in tissues such as the lung, skin, liver, and brain (Kramer et al. 2009; Verney et al. 2010; Zhao et al. 2009). Some of the developmental risk factors that directly impact innate immune cells include maternal smoking and environmental tobacco smoke (ETS), polychlorinated biphenyls (PCBs), heavy metals such as lead (Pb), air and traffic pollution, ozone, prenatal and postnatal dietary fatty acid intake, lack of animal-microbial exposure in early life, inadequate vitamin D intake, lack of breastfeeding, birth delivery mode, and paracetamol use (Tables 1 and 2).

Exposure of DCs to environmental insults during their maturation *in vitro* or *in vivo* changes their functional properties in many different ways. Bone-marrow DCs differentiated in the presence of nicotine are functional but express increased surface costimulatory molecules and major histocompatibility antigens (Nouri-Shirazi, Tinajero, and Guinet 2007). Therefore, these cells will have a lower threshold for inducing T cell responses. However, these cells are deficient in Th1 promoting cytokines and, therefore, promote a Th2-biased T cell repertoire characterized by increased interleukin (IL) 4 and reduced interferon gamma (IFN-γ). Similar effects were observed with exposure to organic dust associated with agriculture (Poole et al. 2009). Urban aerosols also enhanced costimulatory molecule expression on dendritic cells, but unlike nicotine and organic dust, proinflammatory cytokines such as IL-1 and IL-6 were increased. This suggests that these DCs will induce a dysregulated and more robust inflammatory response. Increased production of

proinflammatory cytokines correlated with higher antigen specific immunoglobulin (Ig) G and IgE following intranasal ovalbumin challenge in a mouse model (Yoshida et al. 2010). Together, these studies demonstrate that environmental exposures directly alter DC function in a way that promotes excessive and/or Th2-biased chronic inflammatory responses.

Exposure to environmental toxins also alters the function of specialized tissue resident macrophages such as alveolar macrophages in the lung and microglial cells in the brain (Campbell 2004; Moreno et al. 2009a, 2009b). Manganese exposure in juvenille mice led to increased activation of microglia cells and upregulation of nitric oxide (NO) synthase, an enzyme critical for the production of reactive nitrogen intermediates (Campbell 2004; Moreno et al. 2009a, 2009b). These early effects resulted in alterations in glial cell function in adult mice. Pesticides such as lindane and dieldrin accumulate in the brain and enhance production of reactive oxygen by microglial cells (Mao and Liu 2008). Microglial-produced reactive oxygen has been linked to neurodegeneration (Lull and Block 2010), suggesting that pesticide exposure may increase the risk for neuroinflammatory diseases such as Parkinson's disease (Mao and Liu 2008).

Alveolar macrophages are located at the interface between the host and the environment and are, therefore, constantly bombarded with a myriad of different environmental insults that can alter their function (Bateson and Schwartz 2008; Bhalla et al. 2009). Ambient particulate matter and diesel exhaust act directly on human alveolar macrophages to suppress inflammatory cytokine production (Sawyer et al. 2010). While this seems counterintuitive to the initiation of chronic inflammation, these responses are critical for host defense and may lead to failure to eliminate pathogens and result in chronic inflammation. This study also showed that some particulates reduced inflammatory cytokines, but actually increased the neutrophil chemotactic factor IL-8. Since neutrophils are a major mediator of tissue damage in response to inflammatory and infectious stimuli, these changes could lead to increased immune-mediated inflammatory tissue damage. Human blood-derived macrophages treated with arsenic displayed marked alterations in morphology, surface marker expression, phagocytic uptake, and cytokine secretion (Lemarie et al. 2006). In a mouse model, cigarette smoke reduced macrophage-mediated bacterial phagocytosis and clearance (Phipps et al. 2010). Lastly, exposure of a mouse macrophage cell line to synthetic pyrethroid insecticides resulted in dramatically increased reactive oxygen response (Zhang et al. 2010) reinforcing the observations that a broad array of chemically-driven effects on inflammatory cell function are possible depending upon the specific toxicants and concentration involved.

A specific example: lead exposure, macrophage function, and disease susceptibility

To emphasize the linkage of DIT to innate immune dysfunction, a more detailed example involving the heavy metal lead (Pb) is shown in Figure 1. Multiple genetic, life-stage, gender, nutritional, and environmental factors influence the sensitivity to Pb exposure (Bishayi and Sengupta 2006; Bunn et al. 2001a, 2001b; Miller et al. 1998; Snyder et al. 2000). Following Pb exposure, multiple cell types exhibit altered function including macrophages and DCs (Gao, Mondal, and Lawrence 2007; Guo, Mudzinski, and Lawrence 1996; Sengupta and Bishayi 2002). Pb exposure of dendritic cells reduces phagocytosis and

limits bactericidal activities of lysosomes necessary for bacterial killing (Bishayi, Sengupta, and Ghosh 2004). This leads to increased sensitivity to bacterial infection. Similarly, macrophages are primary targets for Pb-induced immunotoxicity resulting in the overproduction of inflammatory mediators such as TNF-α (Cheng, Yang, and Liu 2006), prostaglandin-E2 (Grizzo and Cordellini 2008), and reactive oxygen species (ROS) (Pineda-Zavaleta et al. 2004; Shabani and Rabbani 2000). The elevated risk of innate immune-mediated oxidative damage in tissues is further exacerbated by a Pb-induced reduction in cellular glutathione and defenses against oxidative damage (Chetty et al. 2005). Alterations in innate immune cell function lead to a significant bias toward Th2 responses by effector T cells, which can also have their function directly affected by Pb exposure (Gao and Lawrence 2010; Gao, Mondal, and Lawrence 2007; Heo, Lee, and Lawrence 1998). Together, these alterations largely define the hallmarks of Pb-induced immunotoxicity (Dietert and Piepenbrink 2006).

Interactive immune effects among environmental risk factors

Although the vast majority of studies have examined the impact of single environmental risk factors on the developing immune system, it is important to recognize that synergistic or antagonistic interactions between categories of environmental risk factors (both positive and negative) can alter the relative likelihood for DIT and inflammation-promoted disease. Exposure to more than one environmental risk factor for DIT can arise either through exposure to mixtures (e.g., metal mixtures in water, air or soil) or via the exposure to multiple sources of immunomodulatory factors (e.g., environmental tobacco smoke and breastfeeding). In the latter case of multiple sources, the exposures could occur simultaneously during development or during different life stages.

For example, prenatal exposure of rats to Pb when the dams were fed a 20% protein diet resulted in a significant elevation of TNF-α production *ex vivo* in the offspring. However, if instead the dams were fed a 10% protein isocaloric diet, the effect of Pb exposure on the production of this proinflammatory cytokine was not significantly different from controls (Chen et al. 2004). This suggests the possibility that maternal diet might affect the risk of Pb-induced inflammatory dysfunction. But there is evidence suggesting that the reverse is also likely where exposure to an immunotoxicant can overcome the beneficial effects of other immunomodulatory factors. Early-life farming environments protect against the risk of childhood asthma and atopy, which may be associated with changes among innate immune cell receptors and innate immune responses (Ege et al. 2006; von Mutius 2010). But other agriculturally-related exposures appear to undermine the benefit of a microbial-rich early-life environment. Hoppin et al. (2008) reported that pesticide use among women growing up on a farm elevated their risk of asthma versus women raised on a farm who were not involved with pesticides (Hoppin et al. 2008). So, direct exposure to some pesticides during childhood may blunt the benefits of immune maturation in a diverse microbial environment.

Similar interactive effects among risk factors were seen in a recent study from the Faroe Islands. Evidence suggests that prolonged breastfeeding can benefit innate immunity and effective immune balance when compared versus formula feeding (Andersson et al. 2009). It also helps to reduce the risk of childhood asthma possibly via the innate immune

modulating, soluble CD14 molecule (Rothenbacher et al. 2005). But exposure to environmental toxicants such as PCBs in the Faroe Island diet can undermine the normal benefit of breastfeeding. Grandjean et al. (2010) reported that PCB contamination of breast milk above a certain threshold concentration increased the risk of allergic sensitization in children (Grandjean et al. 2010). Therefore, it is important to consider the interactive effects of multiple or mixed exposures across all of innate immune development and not only the effects of a single environmental risk factor during a narrow period of immune development (e.g., neonatal microbial environment).

Lifetime health risks associated with DIT mediated innate immune dysfunction

Defects in fetal-neonatal innate immune development can lead to imbalanced and inappropriate responses that persist throughout a lifetime (Bellinger, Lubahn, and Lorton 2008; Selgrade et al. 2008; Thornton 2010). These uncontrolled or inappropriate responses increase risk for later-life inflammatory disease. However, it is important to note that such later-life adverse outcomes are components of much broader immune-based disease patterns, which include depression, sleep disorders, sensory impairment, and cancer (Dietert, Dietert, and Gavalchin 2010).

Psychiatric disturbances such as depression and mood disorders correlate with developmentally-associated inflammatory dysfunction and resulting inflammatory disease (Ahola et al. 2010; Fang et al. 2010; Gershon et al. 2010; Leonard 2010; Wilson et al. 2010). For example, chronic overproduction of proinflammatory cytokines and disruption of the pro- and anti-inflammatory cytokine balance can contribute to an increased risk of depression, mood disturbances, suicidal behavior, and sleep disturbances (Ferini-Strambi 2011; Janelidze et al. 2011; Reeves et al. 2007; Song and Wang 2010). Beside the chronic nature of these conditions, it is clear that the underlying innate immune dysfunction and the dysregulated inflammation pattern act beyond the lung or gut to affect other major health parameters that negatively impact the quality of life and may require medical intervention. Table 3 illustrates the extent to which inflammation-associated chronic diseases with putative early life risk factors affect most systems and organs of the body. Many of these diseases (e.g., asthma, coronary heart disease, COPD, diabetes, Alzhemier’s disease) have a significant prevalence among present adult populations, represent significant public health concerns, and are a focus of risk reduction strategies.

Chronic disease outcomes of inflammatory dysfunction are not restricted to non-cancerous conditions. When innate immune dysfunction and chronic inflammation persist across decades of life, two types of cancers are commonly observed: tissue-specific cancers and leukemic cancers (Dietert 2011). Although chronic inflammatory diseases are often negatively correlated with the risk of cancer, the risk is often elevated for the tissue that is a target of persistent inflammatory insult (Dietert, DeWitt, et al. 2010). This can include both the risk of tissue-specific cancer itself (Ji et al. 2009) as well as the association of inflammation with the recruitment of circulating tumor cells to the target tissue (Taranova et al. 2008). Additionally, leukemic cancers are commonly associated with some forms of immune dysfunction-based patterns (e.g., celiac disease, psoriasis) suggesting that

dysfunctional immunoregulation established early in life can promote both childhood- and adult-onset cancer (Dietert 2011).

The mechanistic connection between chronic inflammation and cancer is linked to the high production of growth factors needed to repair tissue damage and an abundance of inflammatory cytokines (Coussens and Werb 2002; Karin and Greten 2005; Terzic et al. 2010). Although low levels of inflammation promote tissue homeostasis, tumors take advantage of proinflammatory cytokines to promote their own survival and growth (e.g. TNF, IL-1, IL-6, IL-8) (Chen et al. 2007; Rakoff-Nahoum, Hao, and Medzhitov 2006; Rakoff-Nahoum and Medzhitov 2007).

Given the importance of inflammatory-based diseases across a lifetime (Dietert and Zelikoff 2010), increased attention to other health risks linked with innate immune dysfunction is needed. Effective management of innate immune maturation requires both avoidance of hazardous environmental chemicals, drugs, and physical factors, as well as promotion of positive factors such as prolonged breastfeeding, adequate vitamin D levels, and useful balances of dietary fatty acids (Dietert, DeWitt, et al. 2010). DIT-induced dysfunctional innate immunity can impact the risk of adult leukemic and/or tissue-specific cancer that is linked to several chronic inflammation-associated diseases (Dietert 2011).

Identification of innate immune and inflammatory dysfunction in safety evaluation

This review highlights one of the major problems in the preclinical safety screening of drugs and in the safety screening of environmental chemicals for immunotoxicity. To date, the primary focus of immune safety assessment has been on histopathology combined with a limited number of adaptive immune responses usually directed against protein or xenogeneic cell antigens (Dietert 2009, 2011). Comprehensive innate immune analysis and assessment of inflammatory regulation in response to infectious agent challenge is rarely required in adult safety assessment (FDA S8 guidelines), although such protocols are available (Burleson and Burleson 2007, 2008; Neff-LaFord et al. 2007). This is a significant problem if protocols utilized for immune assessment lack the capacity for evaluating the regulation of inflammation. Adult immunotoxicity assessment is not routine (FDA S8 guidelines) and, when performed, usually lacks measures of inflammatory responses. Relevant innate immune assessment of the developing immune system is even less common.

The list of chronic inflammatory diseases shown in Table 3 and their relative importance to public health underscores the need for such immune safety information. Given the immature status of the innate immune system in the neonate and the risk for drug and chemical exposures to cause inflammatory dysfunction in later life, a priority should be given for ensuring that drug and chemical safety screening is designed to detect developmentally-induced inflammatory dysfunction.

Focus on pattern recognition receptors

A promising focus for the evaluation of innate immune-directed immunotoxicity in neonates and adults is the family of pattern recognition receptors (PRRs) including the Toll-like receptors (TLRs). The TLRs are expressed on innate immune cells and bind directly to microbial structures such as lipopolysaccharide and components of Gram+ bacterial cell walls (Takeda, Kaisho, and Akira 2003). TLR stimulation initiates inflammatory cytokine secretion and leads to maturation of dendritic cells (Medzhitov, Preston-Hurlburt, and Janeway 1997), which is critical to induce effector T cell responses. Depending on the cues that dendritic cells receive during this maturational process, different types of effector T cell responses can occur (Mazzoni et al. 2001, 2003; Mazzoni and Segal 2004, 2006). The importance of appropriate regulation of these responses initiated through TLRs is highlighted in inflammation-mediated autoimmune disease, such as systemic lupus erythematosus. In mouse models of lupus, inappropriate and uncontrolled responses through TLRs result in overproduction of cytokines, and type I interferons, which results in inflammatory damage (Leadbetter et al. 2002). Therefore, it is critical to understand the molecular mechanisms regulating these receptors and consider the effects of environmental exposures on their expression and regulation.

Recent studies suggest that traditional mRNA profiles of innate immune genes, such as TLRs, are insufficient to correlate receptor expression with inflammatory responses. Instead, modifications of TLRs after protein synthesis determine the magnitude of cellular responses. For example, mRNA levels do not necessarily correlate with protein function, since intracellular localization and proteolytic processing control cellular response to TLR9 ligands (Barton, Kagan, and Medzhitov 2006; Chockalingam et al. 2009, 2011; Leifer et al. 2004, 2006). Therefore, to determine the effects of environmental exposure on innate immune function, new targets and assays are desperately needed. We propose that new targets to evaluate innate immune function are (1) to examine the effect of prenatal exposure to toxicants on TLR signaling in neonatal and adult macrophages and dendritic cells and (2) to determine whether processes such as bacterial killing by adult macrophages, which depends in part on recognition of the bacterium through TLRs, is reduced by prenatal exposure to toxicants. Since these types of evaluations are lacking in current safety testing, we may be underestimating the effect that prenatal and early life exposures have on immune cell function.

Conclusions

The newborn emerges with an immune system that favors Th2 adaptive responses and lacks the innate immune maturity that will be needed to effectively protect the child. Prenatal or postnatal environmental conditions that impair the continued and effective maturation of the innate immune system create a hyperinflammatory state. Dysfunctional innate immunity alters host responses to infections. This in turn causes tissue damage and promotes chronic inflammation. DIT has the potential to affect the ability of resident innate immune cells in their seeding of organs, expansion-repopulation of cells in the organ, acquisition of specialized phenotypes, interaction with other resident cells in the tissue, response to environmental stimuli, and recruitment of additional immune cells to the tissue. Yet, to date,

the functional status of these cells following early-life exposure to drugs or environmental chemicals is usually only known retrospectively and is rarely, if ever, evaluated in required safety testing (Dietert 2009, 2011). We argue that it is not possible to evaluate the risk that a chemical or drug poses without determining its effect on the functional status of resident innate immune cells and its potential to elevate the risk of later-life inflammatory disease.

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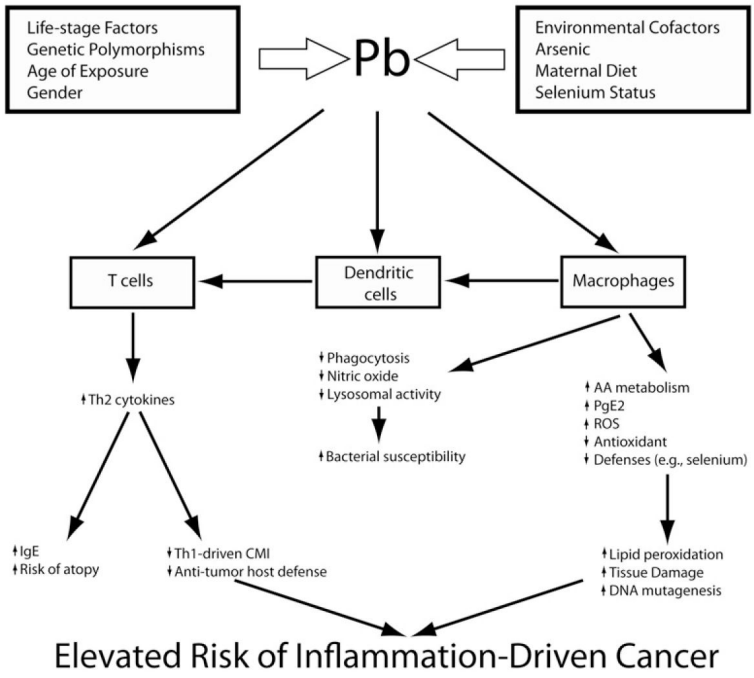

Figure 1.

Lead as a specific example of effects on innate immune function. During early development, a single immunotoxicant, the heavy metal, Pb, can target macrophages, dendritic cells and T cells producing innate immune dysfunction, hyperinflammation and Th2 bias. The elevated health risks from developmental exposure to Pb extend beyond the risk of allergic disease to include a variety of innate immune cell-influenced conditions.

Table 1

Developmental risk factors for innate immunity and inflammation: environmental chemicals and drugs.

Developmental risk factors	Innate immune effects(s)	Altered inflammatory conditions	References
Maternal smoking and ETS	Altered expression of TLRs; increased numbers of lung mast cells and eosinophils; decreased phagocytosis but elevated production of ROS by macrophages	Dyslipidemia, hyper-inflammation; higher infant oxidative stress	Blacquiere et al. (2009) Ishida et al. (2009) Ng et al. (2009) Noakes et al. (2006, 2007) Pfefferle, Pinkenburg, and Renz (2010) Yu et al. (2009)
Air and/or traffic pollution	Variant TLR-2 and 4 alleles affect pollutant impact	Increased eosinophilic inflammation and airway remodeling	Clark et al. (2010) Herr et al. (2010, 2011) Kerkhof et al. (2010) Morgenstern et al. (2008)
Ozone	Disrupted epithelial barrier; altered macrophage function	Interaction with maternal PM exposure to produce childhood airway hyperreactivity	Auten et al. (2009) Hollingsworth, Kleeberger, and Foster (2007) Lin et al. (2008)
Pb and synergistic effects with other metals	Altered dendritic cell maturation (promotion of Th2); excessive TNF-alpha and ROS by macrophages	Inflammatory dysfunction; promotion of tissue damage, apoptosis and DNA mutagenesis	Bishayi and Sengupta (2006) Kasten-Jolly, Heo, and Lawrence (2010) Snyder et al. (2000)
Polychlorinated biphenyls	Macrophage apoptosis; disrupted epithelial barrier function	Upregulation of ICAM-1, MCP-1; Notch3, CCLs and IL-8; enhanced vascular adhesion and inflammation	Choi et al. (2010) Eum et al. (2009) Felty, Yoo, and Kennedy (2010) Grandjean et al. (2010) Majkova et al. (2009) Shin et al. (2000
Maternal and early childhood paracetamol use	Decreased gluthathione, TNF-alpha and IL-6 production by pulmonary macrophages	Glutathione depletion; increased oxidant-induced inflammation	Bakkeheim et al. (2010) Beasley et al. (2008) Dimova et al. (2005) Etminan et al. (2009) Farquhar et al. (2010) Gonzalez-Diaz et al. (2010) Shaheen, Newson, Ring, et al. (2010)

Table 2

Developmental risk factors for innate immunity and inflammation: physical, microbial and dietary factors.

Developmental risk factors	Innate immune effects (s)	Altered inflammatory conditions	References
Caesarian delivery	Increased levels of IL-13; reduced IFN-gamma	Restricted diversity of gut microbiota	Biasucci et al. (2008) Ly et al. (2006) Pistiner et al. (2008) Protonotariou et al. (2010) Tollanes et al. (2008)
Low maternal infant dietary n – 3 fatty acid and high n – 6 fatty acid-trans fat	Receptor-dependent functional alterations in macrophages	Increased risk of inflammatory disorders; elevated neonatal oxidative damage and LTB4 production	Dunstan et al. (2007) Furuhjelm et al. (2009) Innis (2007) Oh da et al. (2010) Prescott et al. (2007) Thijs et al. (2011)
Low prenatal-neonatal animal bacterial exposures	Depressed MyD88 (myeloid) driven recruitment of T regs to the airways	Shifts in the types of inflammatory response observed	Cao et al. (2010) Pfefferle, Pinkenburg, and Renz (2010) von Mutius and Radon (2008)
Absence of prolonged breast feeding (e.g., formula feeding)	Delayed development of innate immune cells	Increased later life risk of inflammatory disease (e.g., metabolic syndrome)	Andersson et al. (2009) Codispoti et al. (2010) Nobili et al. (2009)
Vitamin D deficiency	Neonatal innate immune misregulation; suppressed autophagy in human macrophages; reduced IL-10 by dendritic cells and Tregs; suppressed cathelicidins; reduced metabolism of 25-OHD	Chronic low grade inflammation and increased risk of tissue-localized inflammatory damage	Erkkola et al. (2009) Hewison (2010) Kamen and Tangpricha (2010) Lee et al. (2008) Litonjua (2009) Misawa et al. (2009) Rochat et al. (2010) Sandhu and Casale (2010) Yuk et al. (2009)

Table 3

Inflammatory diseases and reported developmental risk factors.

Inflammatory disease or condition	Target system or organ	Putative environmental risk factor(s)	Reference(s)
Atherosclerosis	Cardiovascular	Air pollution	Brook and Rajagopolan (2010)
Coronary heart disease	Cardiovascular	Traffic-associated pollution	Gan et al. (2010)
Psoriasis	Dermal	Environmental tobacco smoke (women)	Jankovic et al. (2009)
Dental caries/ Periodontal disease	Dental	Maternal smoking; Environmental tobacco smoke; Dietary fatty acid intake	Erdemir et al. (2010), Julihn, Ekbom, and Modeer (2009) and Naqvi et al. (2010)
Celiac disease	Gastrointestinal	Neonatal infections	Sandberg-Bennich, Dahlquist, and Kallen (2002)
Colon cancer	Gastrointestinal	Microbial depletion in early environment; Early life diet	Davis and Milner (2009), Roberfroid et al. (2010) and Xiao et al. (2007)
Inflammatory bowel disease	Gastrointestinal	Early antibiotic use	Hviid, Svanstrom, and Frisch (2011) and Shaw, Blanchard, and Bernstein (2010)
Nonalcohol fatty liver disease	Hepatic	Heavy metals	Cave et al. (2010)
Chronic kidney disease	Nephrotic	Heavy metals	Fadrowski et al. (2010), Gobe and Crane (2010) and Soderland et al. (2010)
Alzheimer's disease	Neurological	Metals	Duce and Bush (2010)
Multiple sclerosis	Neurological	Vitamin D and/or ultraviolet radiation deficiency; smoking exposure	Handel et al. (2011), Sloka et al. (2011) and Staples, Ponsonby, and Lim (2010)
Parkinson's disease	Neurological	Certain pesticide exposures	Elbaz et al. (2009) and Gatto et al. (2009)
Otitis media	Otological	PCB/PCDF exposure	Dallaire et al. (2006) and Guo et al. (2004)
Type 1 diabetes	Pancreatic	Prenatal nutrient over-load and/or Reduced neonatal microbial environment	D'Angeli et al. (2010)
Type 2 diabetes	Pancreatic	Prenatal nutrient energy overload or Prenatal nutrient-insufficiency	Kanaka-Gantenbein (2010)
Childhood asthma	Respiratory	Traffic pollution; Environmental tobacco smoke; Paracetamol	Baena-Cagnani et al. (2009), Carlsten et al. (2011) and McConnell et al. (2010)
			Shaheen, Newson, Smith, et al. (2010) Sly (2011)
COPD	Respiratory	Tobacco smoke; Biomass smoke exposure	Beyer, Mitfessel, and Gillissen (2009), Grigg (2009) and Taylor (2010)
Juvenile idiopathic arthritis	Skeletal	Maternal smoking	Berkun and Padeh (2010) and Jaakkola and Gissler (2005)
Osteoporosis/Risk of bone fractures	Skeletal	Cadmium exposure; Vitamin D deficiency	Nawrot et al. (2010), Papandreou et al. (2010) and Shin, Paek, and Yoon (2011)

Inflammatory disease or condition	Target system or organ	Putative environmental risk factor(s)	Reference(s)
Systemic sclerosis	Systemic: connective tissue disease	Vitamin D deficiency	Caramaschi et al. (2010) and Vacca et al. (2009)