Cytokines and other immunological biomarkers in children's environmental health studies

Paurene Duramad [a,b], Ira B. Tager [a], Nina T. Holland [a,*]

[a] *Children's Environmental Health Center, School of Public Health, University of California, Berkeley, CA 94720-7360, United States*
[b] *Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, CA 02115, United States*

Abstract

Environmental exposures (e.g. pesticides, air pollution, and environmental tobacco smoke) during prenatal and early postnatal development have been linked to a growing number of childhood diseases including allergic disorders and leukemia. Because the immune response plays a critical role in each of these diseases, it is important to study the effects of toxicants on the developing immune system. Children's unique susceptibility to environmental toxicants has become an important focus of the field of immunotoxicology and the use of immune biomarkers in molecular epidemiology of children's environmental health is a rapidly expanding field of research. In this review, we discuss how markers of immune status and immunotoxicity are being applied to pediatric studies, with a specific focus on the various methods used to analyze T-helper-1/2 (Th1/Th2) cytokine profiles. Furthermore, we review recent data on the effects of children's environmental exposures to volatile organic compounds, metals, and pesticides on Th1/Th2 cytokine profiles and the associations of Th1/Th2 profiles with adverse health outcomes such as pediatric respiratory diseases, allergies, cancer and diabetes. Although cytokine profiles are increasingly used in children's studies, there is still a need to acquire distribution data for different ages and ethnic groups of healthy children. These data will contribute to the validation and standardization of cytokine biomarkers for future studies. Application of immunological markers in epidemiological studies will improve the understanding of mechanisms that underlie associations between environmental exposures and immune-mediated disorders.

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1. Importance of using biomarkers to study children's environmental health

More than 33% of diseases in children less than 5 years of age are caused by environmental exposures (WHO, 2006). The main risk factors include pesticides, air and water pollution, lead, environmental tobacco smoke, infections, and inadequate diet (EPA, 2006). A growing number of childhood diseases such as allergic disorders (e.g. allergic rhinitis, atopic dermatitis, asthma), cancer (e.g. acute lymphoid and myeloid leukemias), and others (e.g. type 1 diabetes) have been linked to environmental exposures during prenatal and early postnatal development. Because the immune response plays a critical role in each of these diseases, it is important to consider the effects of toxicants on children's developing immune system. In the recent years, children's susceptibility to environmental exposures has become an important focus of the field of immunotoxicology (Garry, 2004; Holsapple et al., 2004).

Despite the recognition that early childhood represents a critical period of immune development there is a

* Corresponding author at: 733 University Hall, Berkeley, CA 94720-7460, United States. Tel.: +1 510 455 0561; fax: +1 510 643 5426.
E-mail address: ninah@berkeley.edu (N.T. Holland).

dearth of data on the distributions of immune parameters in healthy children. Most of the data available for infants and children have been acquired from pediatric populations afflicted with either acute or chronic health conditions, or they have been extrapolated from adult studies. However, children's immune systems are less developed and, thus potentially more susceptible to environmental exposures (Kovarik and Siegrist, 1998). Moreover, immunological markers and reference values that have been used in adult occupational health studies (Colosio et al., 1999; Vogt, 1991) are being applied in children's studies, a situation that also is not always appropriate since immune function evolves over time after exposures to environmental antigens. Finally, collecting blood from a pediatric population poses an important ethical issue and while most of the current immunological assays require less than 1 ml of blood, given the invasive nature of blood collection, careful planning is required to maximize the use of these samples (Holland et al., 2003; Neri et al., 2006).

Luster et al. (2005) recently summarized current efforts to identify and implement tests of immune function (e.g. cytokine profiles) in children with various diseases of the immune system. However, several issues remain with this relatively new application of cytokine measurements in children's studies: (a) lack of data on the distribution of different cytokine levels in normal, healthy children, (b) lack of standardized methods, (c) the fact that cytokine levels measured in peripheral blood on a single occasion represent only a "snapshot" that may not reflect the response that occurs at the target organ.
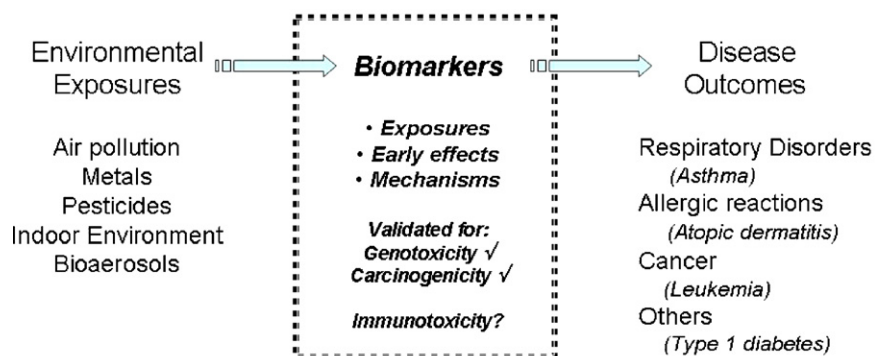
In this review, examples from the literature and recent data from two studies conducted at the University of California, Berkeley, the Northern California study of childhood leukemia (Ma et al., 2002; Buffler et al., 2005)

and the CHAMACOS birth cohort of Latino mothers and children from agricultural community (Eskenazi et al., 2003) are presented to illustrate how cytokine markers have been used to link environmental exposures to cytokine profiles and how these immunological biomarkers can be applied in the study of adverse health outcomes in children.

2. Biomarkers help link environmental exposures to disease outcome

A biological marker (biomarker) is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention" (NIH Biomarkers Definitions Working Group, 2001). Additionally, biological markers are important tools for molecular epidemiology and human biomonitoring studies (NRC, 2006). They have been used in exposure assessment (Metcalf and Orloff, 2004; Aprea et al., 2002; Anwar, 1997) and health risk prediction (Bonassi and Au, 2002). Biological markers of exposure to bioaerosols (e.g. allergens), air pollution, metals, pesticides etc. can provide specific evidence of exposures (Fig. 1) and their relation to outcomes and, thus, aid in the study of how environmental exposures contribute to the development of adverse human health effects.

As has been defined previously for all biomarkers (NIH Biomarkers Definitions Working Group, 2001), a useful immunological biomarker should have the following attributes: (1) clinical relevance (i.e. related to the disease or pathophysiological process of interest), (2) strong, mechanistic molecular or biochemical basis in the pathophysiology of a disease, (3) sensitivity and

Fig. 1. Role of biomarkers in children's environmental studies.