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HIGHLIGHTS

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REVIEW

Asthma and allergic diseases: Cross talk of immune system and environmental factors

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Air pollution and immune-related diseases including allergy and asthma are constantly on the rise worldwide. Thus, a comprehensive investigation of environmentally induced immune regulation is required for a deeper understanding of disease pathogenesis, progression as well as prevention. Here, we summarize the current knowledge on environmental factors such as microbiome or geographical locations with harmful or protective effects for human health and their different routes of exposure. This review comprises a brief outline regarding the latest findings on the interaction of environmental factors with innate and adaptive regulation of the immune system, exemplarily for one protective and one harmful environmental factor, respectively.

Keywords: Air pollution · Allergy · Asthma · Environment · Immune regulation

Introduction

Over the last decades, the prevalence of immune-related diseases including allergy and asthma has increased progressively within the last decades [1–3]. There is growing evidence suggesting a decisive role of environmental influences in shaping early immune maturation including the host's responses to allergens [4–6]. Thus, an increase in immune-related diseases is suggested to be influenced by (disadvantageous) environmental changes including the increment of harmful and the loss of protective exposures associated with progressive western/industrialized/urban-associated lifestyle. The rapidly advancing change in lifestyle as well as environments have in a way challenged the regulatory capacity of the healthy human immune system prompting an increasing interest to identify and evaluate harmful and protective factors.

This review summarizes the current knowledge on environmental factors with harmful or protective effects and their different routes of exposure. In addition, a brief outline about the latest findings on the interaction of environmental factors with innate and adaptive components of the immune system from *in vivo* studies is given exemplary for one protective and one harmful environmental factor, respectively.

Routes of exposure

The human organism is constantly exposed to diverse biological, chemical, and physical influences from the external environment. Conceptually, cumulative lifetime environmental exposure and related physiological responses are termed *human exposome* [7] that affects health, behavior, and physiology. In humans, several efficient barrier organs regulate the responses to environmental exposures that enter primarily via the skin, mucosal tissue, and inhalation. Importantly, the microbiota is involved

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in early-life imprinting of local immune compartments, thereby promoting immune tolerance to antigens and wound healing [8, 9].

Skin exposure

The multiple layers and mechanical barriers of the skin control penetration of environmental substances, thereby protecting the organism from exposure-related effects. Physical defense mechanisms including functional integrity of barriers formed by hair follicles, skin glands, and blood vessels prevent systemic entry and effects of external factors. The outermost barrier bordering the external environment, the stratum corneum, consists of tightly connected differentiated keratinocytes that perform first defense innate immune functions [10]. Additionally, innate and adaptive immune cells including dermal and epidermal dendritic cells, macrophages, lymphocytes, mast cells, as well as complement factors are involved in immune responses in the skin. However, absorption of skin-penetrating substances through an intact and functional dermal epithelial barrier is possible [10].

Mucosal tissue exposure

Mucosal surface integrity and mucus secretion in the eye and nose, the upper respiratory tract, the gastrointestinal tract (GIT), and the urogenital tract are critical to impede diffusion and mediate elimination of invaded pollutants. Dysfunctional mucosal epithelial barriers have been associated with antigen invasion, inflammatory activation of epithelial cells, and allergic reactions leading to the development of allergic diseases [11, 12]. The GIT that is exposed to the external environment through ingested particles taken up by diet, inhalation, or other interventions exhibits a barrier formed by tightly connected epithelial cells lined with mucus and microbiota. However, exposure to noxious factors can mediate intestinal barrier defects resulting in epithelial translocation of microbes and initiate inflammatory immune reactions [13]. Mucosal tissue is further exposed by inhaled particles and substances circulating in the air are trapped by nasal hairs and cilia in the nasal cavity, avoiding deeper penetration into the trachea. Mucus secreted by goblet cells and hair-like cilia lining the trachea and bronchi trap foreign particles and push them back outwards through constant cilial movement. Despite these highly efficient mechanisms, particulate matter (PM) with a diameter of $\leq$10 μm (PM_{10}) reach the upper respiratory tract and ultrafine particles ($PM_{0.1}$) can even get deep inside the lung affecting lung alveoli and local microbiota, penetrating the lung epithelial barrier and entering the systemic blood circulation [14]. The extent of inhalation exposure depends on the size and penetration capacity of inhaled matter, on indoor and outdoor air quality, and preliminary organ damage.

Environmental factors with immunoreactive potential

Environmental exposures influencing the human organism comprise small particles and chemical residuals, physical influences, microbes, geographical location, as well as lifestyle choices. Depending on the exposure time, extent, and dosage, environmental factors can either elicit immune-potentiating or immunosuppressive responses. Importantly, environmental exposures add up during an individual's lifespan and can mediate delayed reactions. Importantly, evidence suggests that combinations of environmental influences such as combined wood smoke and diesel particles will act in an additive or synergistic manner [15]. For the sake of brevity, we here review the immunoreactive effect of individual environmental factors and will not discuss the impact of the combination of environmental influences.

Some environmental factors have beneficial effects on immune priming and function as well as disease prevention such as plant-derived bioaerosols and dust. Specifically, farm-related exposures induce anti-inflammatory immune reactions, alleviate allergic and autoimmune responses, and if occurring in the prenatal or early-life period, reduce the risk for autoimmune diseases [16–21]. Other naturally occurring bioactive compounds with beneficial immunomodulating properties comprise polyphenols that are subclassified into flavonoids and non-flavonoids and display an anti-neuroinflammatory potential and alleviate inflammation-associated depressive symptoms [22].

In contrast, air pollutants such as PM, a complex air suspension of solid and liquid, organic and inorganic particles, as well as nanoparticles, environmental contaminants of small dimensions (1–100 nm), can negatively alter immune activity and function [23, 18]. In mice, chronic ultrafine PM ($PM_{2.5}$), diesel exhaust particles, and engineered nanoparticles induced systemic and neuroinflammatory immune responses [4, 23]. In humans, maternal exposure to traffic-related air pollutants, such as nitrogen oxide, PM, and ozone (O_3), has been associated with increased inflammatory cytokine levels in newborns, impairing immune system development and postnatal immune functions [24, 23]. Further airborne factors with immunoreactive and inflammatory potential comprise cigarette smoke [25], organic agricultural dust [26], and microplastics [27, 28]. Chemicals, that is, poly- and perfluorinated alkyl substances (PFAS), were detected in human blood sera and have been associated with impaired vaccine-induced antibody responses [29–31]. However, the authors from a recent review article on the immunomodulation and exposure of PFAS conclude that more evidence is needed due to inconsistent results on the immunomodulatory effect of PFAS exposure [29]. In addition, prenatal exposure to phthalates that act as endocrine disruptors has been associated with male reproductive disorders in mice. Few clinical studies were performed which revealed that phthalate metabolites can cross the placental barrier subsequently impairing genital development in human male fetuses [32, 33]. Moreover, environmental phthalate exposure in children was associated with allergic symptoms such as atopic dermatitis, asthma, and allergic rhinitis [34]. Chemical

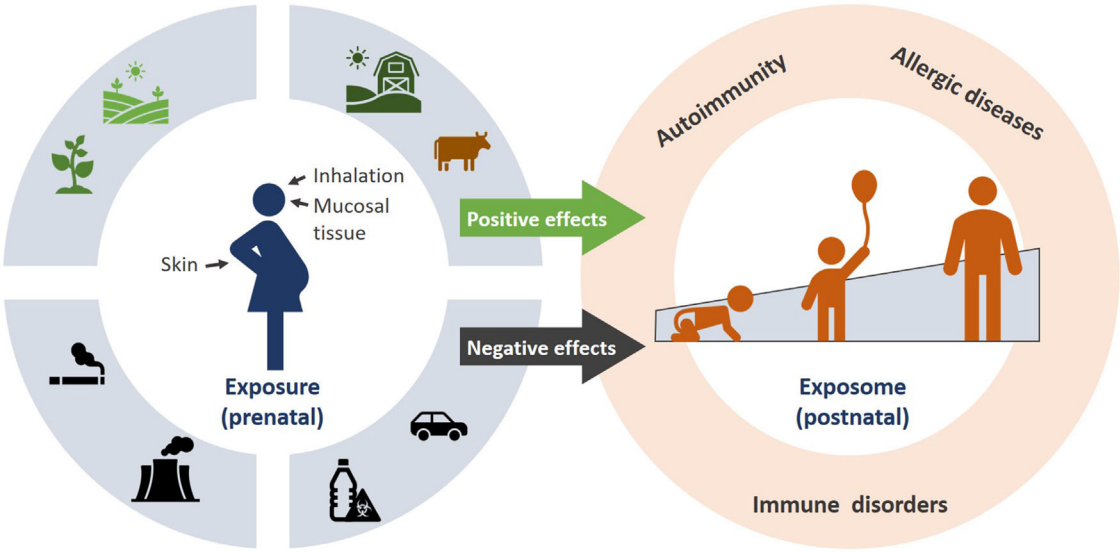

Figure 1. Prenatal and postnatal exposures: routes, effects, and outcomes. Starting in the prenatal period through maternal exposure, individuals are exposed to a variety of environmental influences by different routes (left circle). These can either elicit positive and beneficial effects on immune priming or predispose for the development of immune-related diseases later in life. Accumulation of environmental influences over the lifetime (exposome) results in the development of immune disorders at different ages.

exposure also affects the microbiota that is essential for intact host immune functioning. In children, the chemical exposome was related to altered early-life microbiota development, potentially favoring altered immune functions and associated diseases later in life such as asthma [35, 13].

Overall, environmental exposure is especially critical during vulnerable developmental periods and *in utero* or neonatal exposure alter immune maturation, function, and development (Fig. 1).

Influence of environmental factors on innate and adaptive immune responses

As a result of the variability of environmental factors, the following paragraph aims to set the spotlight exemplarily on one of each protective and harmful factor for asthma and allergic diseases (Fig. 2). Concerning protective properties, several epidemiological studies worldwide have shown significantly lower prevalence in asthma and allergic diseases for children growing up on farms, a phenomenon known as "protective farm effect". Herein, contact to livestock and fodder, consumption of raw milk and microbial diversity are crucial [20, 36–40, 21, 41]. Environmentally mediated allergy and asthma-protective effects were replicated robustly in Amish children compared to children from Hutterite people (5.2% vs. 21.3% asthma prevalence). Despite their similar geographic and genetic background, both groups differ in their farming lifestyle with more traditional farming in the Amish and highly industrialized practices in the Hutterites [42]. The protective capacity of these rural agricultural environments has already been linked to a variety of immunological components. Regarding the innate part of the immune system, farm exposure was associated with altered functional properties of dendritic cells (DC), cells that are in first contact with environmental factors and thus influence T-cell responses. Immunomodulatory effects by decreasing myeloid dendritic cell (mDC) proportions related to farming lifestyle were shown [43, 44] coinciding with significantly elevated expression of the pathogen sensing innate immune receptors, such as Toll-like receptor (TLR)2, TLR7, TLR8, and cluster of differentiation (CD) 14 [6, 45]. In addition, gene-by-environment interaction for the single nucleotide polymorphism rs2230626 in the tumor necrosis factor, alpha-induced protein 3 (*TNFAIP3*) gene could have been connected with asthma and allergy protective effects in children growing up in farm-related environments [46]. Regarding the adaptive branch of the immune system, reduced lymphocyte proliferation in farm children and a positive association between early (*in utero*) exposure to farming lifestyle and regulatory T lymphocyte (T_{reg}) numbers as well as T_{reg} function was shown. However, an immunological switch results in lower T_{reg} levels in farm children at school age suggesting *inter alia* the existence of a critical window during early healthy immune maturation both in terms of flexibility and variability but also in timing of immunity [5, 47–49]. Moreover, farm exposure was connected to a T helper lymphocyte (T_H)1 dominating cytokine profile with elevated interleukin (IL)-12, tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) levels [50, 51] accompanied by reduced levels of the T_H2 cytokine IL-5 [5].

The rapid increase in asthma prevalence in recent decades may therefore be partly mediated by the absence of a protective farm-related environment due to progressively dominating urbanized lifestyles accompanied by a growing trend for exposure to harmful environmental factors potentially playing a causal role in disease development. Epidemiological data, published by the

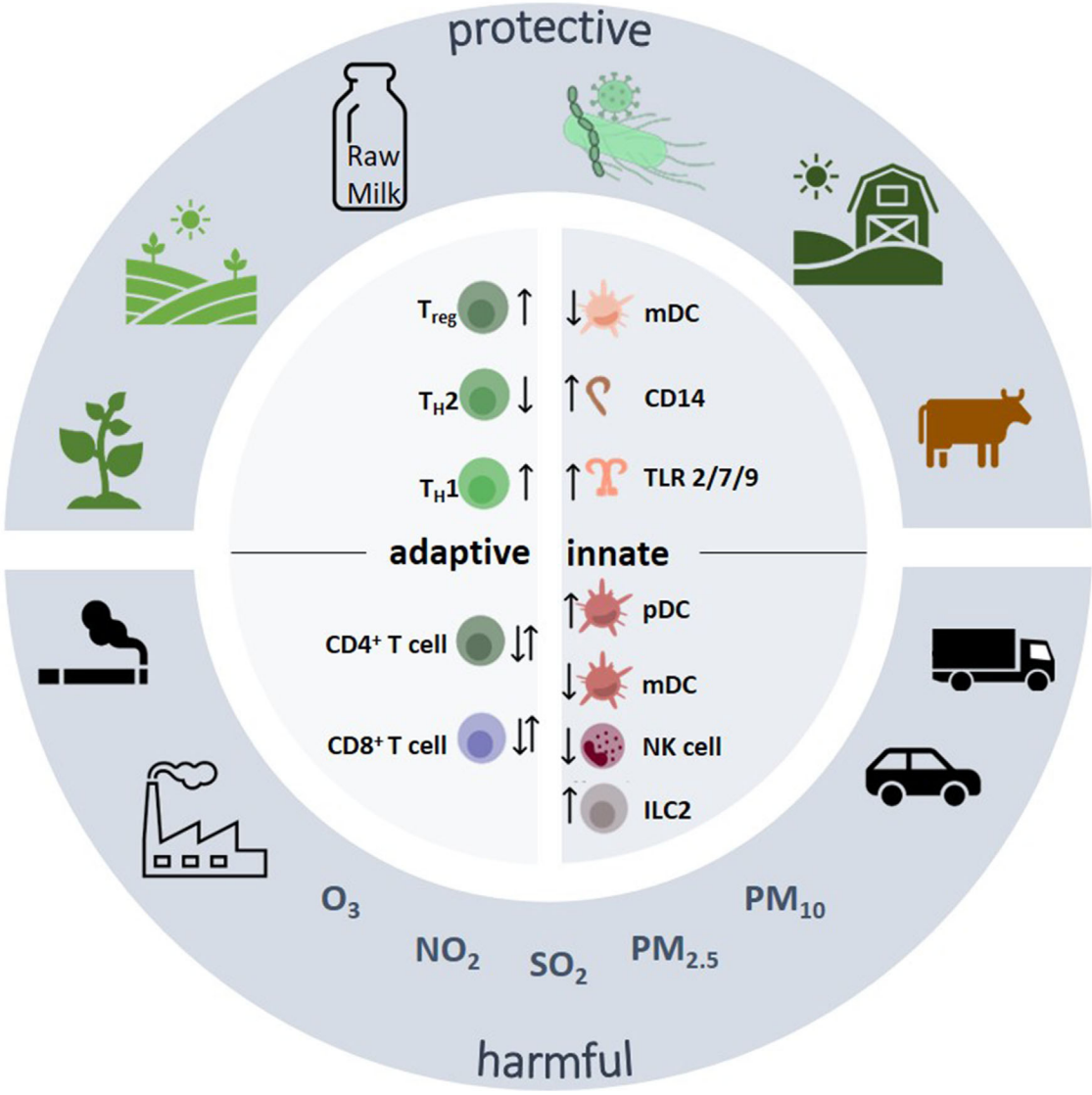

Figure 2. Influence of asthma and allergy protective as well as harmful environmental factors on innate and adaptive immune cells as described in *in vivo* studies. Arrows indicate changes in cellular composition (↑: upregulation, ↓: downregulation, ↑↓: different findings in different studies, T_{reg}: regulatory T Lymphocyte, T_H1: T helper lymphocyte 1, T_H2: T helper lymphocyte 2, CD: cluster of differentiation, mDC: myeloid dendritic cell, pDC: plasmacytoid dendritic cell, TLR: Toll-like receptor, NK: natural killer, ILC2: innate lymphoid cell 2, NO_2: nitrogen dioxide, O_3: ozone, PM_{10}: particulate matter with a diameter of ≤10 μm, $PM_{2.5}$: particulate matter with a diameter of ≤2.5 μm, SO_2: sulfur dioxide).

World Health Organization (WHO) as part of the 2018 update, indicate that 90% of people are exposed to air containing high levels of indoor and outdoor pollutants. Moreover, more than 80% of urban living people breathe air containing pollutant levels that exceed the WHO guidelines [52]. Thus, elevated asthma risk in children could have already been linked to prenatal harmful environmental exposure, namely cigarette smoke, accompanied by impaired T_H1 responses shifted toward a T_H2 dominating phenotype and increased pro-inflammatory conditions (secretion of IL-17A, IL-8, IL-6, and TNF-α) [53]. However, a causal link between asthma and air pollution in general, not only cigarette smoke, has been suggested. Regarding the innate branch of the immune system, higher numbers in plasmacytoid dendritic cells (pDCs) as well as reduced numbers ofmDCs and natural killer (NK) cells were described after *in utero* exposure to air pollution [54]. Moreover, in a human study including 118 healthy and asthmatic patients, exposure to PM_{10} and $PM_{2.5}$ was shown to positively correlate with innate lymphoid cell type 2 (ILC2) frequencies, innate cells functioning in a similar way to asthma and allergy-mediating T_H2 lymphoid cells [55, 56]. Furthermore, PM_{10} exposure was related with increasing ILC2 frequencies in severe asthmatics compared to mild asthmatics with PM_{10} exposure shown to act in a rather chronic way since ILC2 levels were shown to correlate with the altitude of exposure level. No such correlation for $PM_{2.5}$ in severe asthmatics could be described. ILC1 cells were shown to correlate with O_3, NO_2, and carbon monoxide (CO) exposure, but not with PM [56]. Concerning the adaptive branch of the immune system, latest publications described, although contradictory,

disturbed lymphocyte distributions after *in utero* exposure to air-polluting substances including $PM_{2.5}$, PM_{10}, NO_2, or SO_2. While Martins Costa Gomes and co-workers described reduced numbers of $CD4^+$ and elevated numbers of $CD8^+$ cells after SO_2 exposure, Garcia-Serna and colleagues reported reduced numbers of $CD8^+$ T cells, decreased numbers of T_{reg} cells, and elevated numbers of T_H1 cells connected with PM exposure during pregnancy [57, 54]. Moreover, gestational exposure to traffic-related air pollution (TRAP; mix of NO_2, $PM_{2.5}$, PM_{10}, O_3) was also shown to increase pro-inflammatory (IL-1β and IL-6), T_H2 related (IL-13), and immunomodulatory (IL-10) cytokines in newborn offspring [24]. Contrarily, Hahn and colleagues showed a reduced production of IL-6, TNF-α, and IL-10 in cord blood mononuclear cells (CBMCs) of children from mothers exposed to higher levels of $PM_{2.5}$ during pregnancy [58]. Beyond the *in vivo* data, the focus of this review, Deckers et al. as well as Krusche et al. described recent findings regarding the mechanisms that confer protection against asthma and allergies including mouse and *in vitro* studies [59, 60].

Conclusion

Multiple environmental factors, classified either as protective or harmful, interact with and thus modulate the innate as well as the adaptive part of the human immune system and its functionality via different routes of exposure. Here, early life represents a critical window of opportunity but also vulnerability influencing the subsequent development of a child's immune system. Pre- as well as postnatal environmental exposures shape the still developing immune system by regulation of innate and adaptive cellular differentiation, (un)balancing T cell responses, as well as modulation of cytokine secretion. However, the exact cellular mechanisms underlying these harmful or protective environmental factors on disease prevention and/or disease progression including asthma and allergic diseases still require further research. This is key for future prevention strategies as well as for efficient counselling of government and authorities.

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Abbreviations: **CD**: cluster of differentiation · **ILC**: innate lymphoid cell · **PM**: particulate matter · **PM10**: particulate matter with a diameter of $\leq 10\ \mu m$

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