The environment-pathogen-host axis in communicable and non-communicable diseases: Recent advances in experimental and clinical research

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Summary

Allergies and autoimmune diseases are spreading worldwide. Control of infections, on the other hand, remains an issue, even in the post-antibiotic era. Chronic or poorly controlled infections occur in immune compromised individuals such as HIV patients, hospitalized patients exposed to multi-resistant bacteria, or patients on immunosuppressive treatment. They may become an even more emerging issue in an ageing population. At the same time, profound environmental changes such as global warming, urbanization, increasing environmental pollution and novel food engineering technologies may alter the abundance or aggressiveness of allergens/allergen carriers in our environment. Likewise, changes in dietary habits – and possibly also use of antibiotics – have an impact on the composition of our natural microbial flora in the gut, airways and skin, which may alter susceptibility for common diseases, among them allergies, asthma and atopic eczema. At the recently founded Institute of Environmental Medicine of the Technische Universität Munich, located in Augsburg at the UNIKA-T, experimental, clinical and translational research is focused on the complex interactions of environment, pathogen and host in expression or control of communicable and non-communicable diseases. We present our research concept and recent findings in environment – host interactions.

Introduction

Both allergens and pathogens are encountered at the same sites of the body: the epithelia of the respiratory tract, gastrointestinal tract and skin. In a healthy organism, epithelia form a physical and immunological barrier against microorganisms, irritants and allergens. The physical barrier of epithelia, which limits access of pathogens to sub-epithelial tissues, consists of tight junctions and mucosal or cornified outer layers. The immunological barrier consists of antimicrobial peptides, antigen-presenting cells and pattern-recognition receptors, triggering the rapid recruitment of innate immune cells, which then in turn instruct the adaptive immune system. Indeed, the epithelial arsenal against invading pathogens is so large that it might appear astonishing that, under conditions of constant, diverse environmental exposure, it is kept in check for most of the time. Hence, maintenance of peripheral tolerance to harmless agents or commensals is of critical importance in providing epithelial barrier integrity. When a pathogen is recognized via its signature of danger

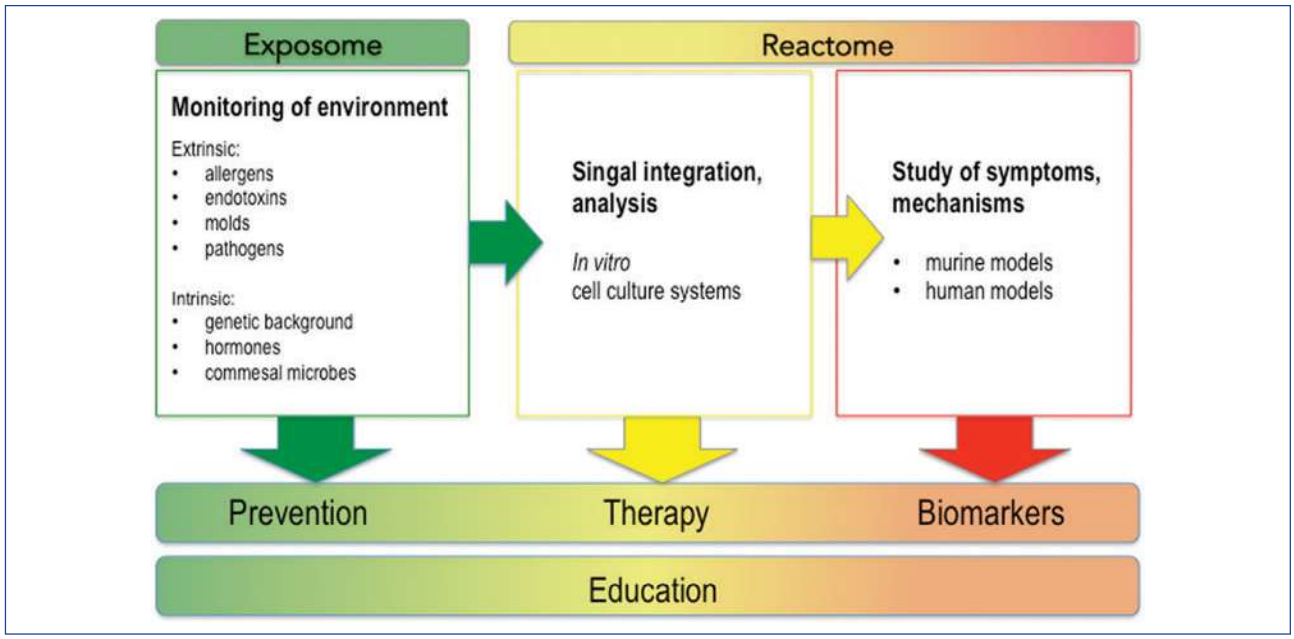

Figure 1 Research concept: From exposome to reactome. An individual's "exposome" consists of extrinsic and intrinsic environmental factors. Extrinsic factors are pollutants, allergens, molds, bacterial products and pathogens. Intrinsic factors comprise the genetic background, hormones and commensal microbes. We will monitor both extrinsic and intrinsic environmental factors, followed by separate and integrated in vitro analysis using cell culture systems. For the assessment of clinical relevance, we will go back to murine and human in vivo models. The aim is to elucidate how complex environmental signals are integrated by the tissue and immune system to maintain homeostasis or lead to disease. This approach will lead to the development of prevention or education strategies, the identification of biomarkers and will point out targets for therapy.

signals integrated at the site of exposure, this results in a concerted effort of cells of the innate and adaptive immune system, the aim of which is to eliminate the pathogen. If this effort remains ineffective, the result is chronic inflammation and uncontrolled spreading of pathogen. On the other hand, if the effort is inappropriate because a self-antigen or "harmless" allergen is erroneously sensed as pathogen, this results in autoimmunity or allergy. Thus, the feature both uncontrolled infection and allergy have in common is a "misunderstanding" of the signals that pathogens or allergens deliver to the tissue. A focus of our work is therefore to identify mechanisms by which the danger-sensing machinery of epithelia and associated immune cells is changed in environmentally triggered diseases. These mechanisms may be mediated by host-intrinsic factors, such as mutations in immune related and epithelial barrier genes, by chronic inflammation or epithelial remodeling resulting from a disease or by factors associated with life-style, diet or gender. Moreover, there are also extrinsic – environmental – factors that disturb the intricate balance between tolerance and immunity. Therefore, our general research concept is to comprehensively analyze the axis between environment, pathogen or allergen and the human host.

Research concept of environment host interaction analysis

The first step of research in this field is to "measure" environment. Here environment has to be defined in a holistic approach whereby environment is defined as the sum of exposure to physical, biological and psychosocial factors [1]. Recent advances in environmental research enables us to decipher the biological exposome, e. g. pinpointing allergen concentrations in different fractions in the air and measuring microbial products [2]. In order to understand in depth environment host interaction we have to correlate exposome to reactome (Figure 1). Thus, we will try to link environmental factors with immunological reactions in exposed people combined with clinical symptoms. This kind of research will enable us to decipher environmental factors responsible for the increment of diseases or "good" environmental factors responsible for tolerance induction or maintenance. A good example for this kind of research was the finding of protective farm environment for allergy development [3].

In the next paragraphs we will provide examples for successful translational and environmental research projects.

Chronic mucocutaneous candidiasis – pathomechanisms underlying a rare, uncontrolled infectious disease

Chronic mucocutaneous candidiasis (CMC) is a rare congenital disease characterized by recurrent infections of oral mucosa, skin and nails with the fungal pathogen *Candida albicans*, ultimately leading to the development of squamous cell carcinomas [4]. Treatment options are limited to antifungal therapy, the efficacy of which often decreases over time due to the development of resistance.

We previously described altered T-cell responses to Candida antigen in PBMCs of CMC patients [5]. Notably, PBMCs of CMC patients stimulated with fungal and mitotic stimuli contained decreased numbers of skin homing, $CCR6^+$ $IL\text{-}17^+$ $IL22^+$ T cells [6]. In healthy individuals, Candida infection is constantly controlled by the host immune system. Recognition of fungal cell-wall components, specifically β-glucans, by the pattern-recognition receptors Dectin-1 and TLR2 on dendritic cells leads to the secretion of pro-inflammatory cytokines, among them IL-1β and IL-6. These cytokines, together with TGF-β, are driving STAT-3 dependent differentiation of Th17 cells known to be key players in the defense against bacteria and fungi. Recently, whole exome sequencing of CMC patients identified an autosomal-dominant, gain-of-function mutation of the STAT-1 gene [7]. This mutation was shown to inhibit nuclear dephosphorylation and inactivation of the transcription factor. Over-activity of STAT-1 in T cells prevents the production of the cytokines IL-17A, IL-17F and IL-22, thus impairing the differentiation of functional Th17 cells. The example of CMC shows how a host intrinsic defect – a single mutation in a transcription factor gene critical for T-cell differentiation – causes impaired sensing of pathogen-derived signals, which results in the inability to clear infection and consequently the development of chronic inflammation and neoplastic transformation. It also illustrates our clinical research approach, starting from defined patients´ material, dissecting the immunological and molecular pathways underlying the disease phenotype and ultimately pointing to novel treatment options.

Modulation of pollen allergenicity by intrinsic, non-allergenic compounds and by anthropogenic environmental factors

Pollen from anemophilous plants are the most important source of allergens in out-door air, causing allergic rhinitis, asthma, pollen-associated food allergies and, in some atopic eczema patients, acute eczema flares. Why pollen proteins elicit a Th2-dominated, IgE-driven immune response in susceptible individuals is incompletely understood. The fact that pollen are respirable particles and their proteins are released in conjunction with numerous other plant products such as proteases and oxidases might account for some of their allergenic potential. Our own work highlighted the role of pollen-associated lipid mediators (PALMs) [8]. Some PALMs are chemoattractants for neutrophils and eosinophils [9, 10]. This example illustrates how pollen grains erroneously transduce a danger signal to the innate immune system. Other PALMs, which are structurally related to mammalian prostaglandins, prime dendritic cells in such a way that they tend to induce Th2 but fail to induce Th1 differentiation of naive T cells [11–13]. Furthermore, dendritic cells primed with PALMs produce chemoattractants for Th2 cells [14]. Finally, the Th1 inhibiting effect of PALMs and mast cell activation by non-allergenic compounds from pollen was demonstrated in murine models [15, 16]. By screening of the birch pollen metabolome, adenosine was identified as another active immune modulator [17]. Whereas the function of adenosine in the plant is unknown to date, we could show that pollen-derived adenosine licenses human dendritic cells to the differentiation of Tregs. However, dendritic cells derived from pollen-allergic donors had a defect in transmitting this tolerogenic signal and failed to induce functional Tregs in response to pollen-derived adenosine, illustrating how host-intrinsic features change the sensing of signals supplied by the allergen.

In the past, extensive research was dedicated to the question how anthropogenic environmental factors impact on the prevalence and expression of atopic diseases. We have previously shown that ultra-fine particles such as Diesel exhaust particles exacerbate allergic lung inflammation in a murine model [18, 19]. Overall, there is solid evidence for industrial and traffic related air pollutants increasing the incidence and exacerbating atopic diseases (reviewed in [20]). However, many of these factors also act on the allergen carrier, i. e. the pollen-producing plant. We could recently demonstrate that pollen collected from birch trees grown in their natural environment are subject to urbanization related changes in their allergenic potential [21]. Briefly, pollen from birch trees exposed to elevated ambient ozone levels have a lower content of immunomodulatory PALMs, are more potent chemoattractants for neutrophils, contain higher levels of major allergen Bet v 1 and elicit stronger cutaneous immune responses (wheal-and-flare reaction) in skin prick tests. This is an example for anthropogenic environmental factors impacting on the allergen carrier, thus indirectly altering the manifestation of an allergic reaction in humans.

Environment-pathogen-host interactions in complex diseases – outlook and perspectives

The default response to commensal microbes and allergens is tolerance, whereas the default response to fungal, bacterial

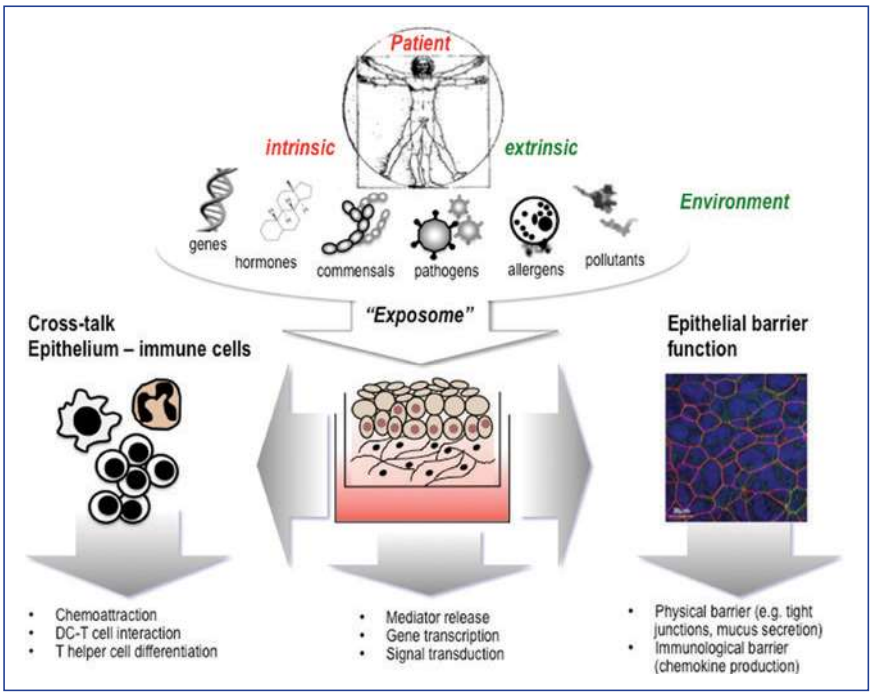

Figure 2 Workflow for the analysis of environment-host interactions. Starting from well-characterized patient material, we will define intrinsic (and extrinsic) environmental factors associated with disease. The so-defined "exposome" will be simulated in vitro for stimulation of cultured cells (e. g. 3D skin or airway epithelial models). These models are suitable for the detailed study of disease mechanisms, e. g. by assessing epithelial barrier function and crosstalk with classical immune cells such as granulocytes, dendritic cells and T cells.

and viral pathogens is an intricately orchestrated immune response, resulting in pathogen clearance. As demonstrated by the examples from our clinical and experimental research, intrinsic and extrinsic environmental factors can lead to disease by triggering inappropriate or erroneous immune responses.

Commensal microbes are an important regulator in the maintenance of peripheral tolerance and epithelial integrity. A future strategy to study communicable and non-communicable diseases is to start with healthy patient skin (or mucosa), to define its specific microbial composition and to isolate and culture relevant microbes. In the next step, impact of the microbial composition on skin homeostasis will be analyzed in vitro using cell culture, organ culture (3D skin and airway model) and cell-cell interaction (epithelial cell-DC-T cell) models (Figure 2).

Allergies are complex diseases mediated by genetic, life-style associated and environmental factors. Some genes, e. g. FceRI alpha and filaggrin, have been linked to complex atopic traits like asthma or atopic eczema. However, most associations are comparatively weak and cannot explain the fast rise in incidences within populations. Furthermore, it is poorly understood how sensitization occurs in humans. A future challenge will be to define an individual´s "exposome", i. e. the overall exposure to allergens, allergen-associated and environmental co-factors, and to find out how this "exposome" is translated into tolerance or sensitization. In the future, we plan to address allergy related questions in the population-based cohort and correlate these data to on-site allergen measurements. Finally, we will expand our research on the axis environment-allergen-host by analyzing how factors associated to global change are influencing the allergenic potential of pollen producing plants.

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