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# ALLERGY IN A CHALLENGING WORLD - INTERCONNECTION AND INNOVATION

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Various allergic pathologies have become of real interest due to their increased prevalence during the last decades. Research takes into account their impact on the quality of life and health of patients; while focusing on social, professional and economic consequences. Studies have assigned significant importance to biomarkers guiding diagnosis and personalized selection of targeted therapies to establish a better control of the disease progression.

Common diseases such as atopic dermatitis, urticaria and angioedema emphasize the importance of immune system imbalances, whether associated with allergy, hypersensitivity or autoimmunity. Various epidemiological studies present changes in the physiological response leading to allergic diseases, with lifestyle and climate change playing a key role. The exposome approach is particularly useful in allergies and asthma for understanding the mechanistic links between exposure and health and for developing a risk profile instead of single predictors. To improve diagnostic methods and treatment measures, a thorough understanding of the pathogenesis of allergic and immunological diseases is important.

The objectives of this review are to illustrate the connection between the environment and allergic diseases, to understand the impact of westernization and to identify epigenomic and metabolomic assessment methods, supporting the idea that, in a world of change, all these are interconnected.

*Keywords:* allergic diseases, environment, epigenomics, metabolomics, exposome.

## INTRODUCTION

Throughout the ages, medicine has waged a battle against communicable diseases, but noncommunicable pathologies such as cancer, allergies, metabolic diseases, neurodegenerative diseases, psychological disorders and autoimmune diseases have also gained momentum. Industrialization has made allergic diseases endemic, with a marked increase in incidences in developing countries. Western lifestyles have led to an increase in the prevalence of allergic diseases, represented by allergic rhinitis, asthma, food allergies, urticaria, atopic dermatitis, and anaphylaxis. This has spawned the original hygiene hypothesis and the concept of allergies as genetic as well as environmental diseases. There has been a significant difference in the prevalence of allergic diseases, determined by the impact of the environment and lifestyle, which has become progressively more uniform over the last 30 years.[4] The rapid evolution of allergic diseases seems to be driven by environmental changes rather than genetic drift.[3]

The "hygiene hypothesis" states that infections play a protective role for allergic diseases, while environmental pollution favors their development. There has been an increasing diffusion of pollutants into the environment, leading to an upsurge in allergies, as a result of the increased usage of xenobiotics like pesticides and herbicides.[5] In developing countries, the harmful consequences of pollution outweigh the protective effects of infections at a rate similar to that in developed countries.

There is now a major interest in analysing environment-gene and/or environment-human interactions at all levels – organs, cells, biomarkers, microstructures and DNA. The ultimate goal of allergology research is to prevent allergic diseases

by understanding the triggers and the effectors pathways and linking all the gained knowledge.[6]

Exposome research is valuable tool for reducing adverse health outcomes by understanding the mechanistic links between exposure and health. The exposomic approach is particularly useful in allergies and asthma by providing a risk profile instead of single predictors. Exposure to the environment causes biological changes that modulate the vulnerability of subsequent exposures, which explains the interaction between exposome and biology. The biological impact of exposure is represented by the balance between the biological effects of exposure (structural changes, disruption of enzyme functions, binding to macromolecules and damage through reactive oxygen or nitrogen species) and specific biological responses (ubiquitination, proteolysis, autophagy, DNA repair, antioxidation).[7]

## INTERACTIONS BETWEEN GENES AND ENVIRONMENTAL FACTORS

Studies on gene-environment interactions have led to a better understanding of the importance of environmental factors in the onset of allergic diseases. Considerable progress has been made in unravelling the contribution of these factors to a subject's individual predisposition, subsequent development and severity of allergic disease. Initially, it is necessary to consider the host on which these factors act. The individual genetic background predisposes the human host to be more or less susceptible to developing allergic diseases. The genetic predisposition to develop an allergic disease is hereditary and contributes to its occurrence, but does not actually cause it. The genetic background consists of several dozen to several hundred more or less relevant genes and is subject to modification by environmental and lifestyle factors. Epigenetic changes in various allergy susceptibility genes may occur through chronic exposure to inhalant pollutants, psychosocial stress, unhealthy diet or lack of exercise. These changes will then be passed on to the next generation.

Genes involved in innate immune signalling, such as CD14 and TLR, are among the earliest allergy susceptibility genes. Furthermore, the quest of defining a "typical allergen" has led to the key finding that activation of innate immune signalling, for example via TLRs or the inflammasome, is a prerequisite to allergic sensitization. This explains how the "Westernised lifestyle" could have an impact on the predisposition to develop allergic diseases. Some damaging or protective environmental factors act as early as childhood and adolescence, sometimes even in the womb. Beneficial factors favour the formation of extremely diverse microbiota on the body's barrier organs (skin, mucous membranes of the respiratory, gastrointestinal and urogenital tracts). These factors include a high-fibre diet, high dietary diversity, early contact with siblings/colleagues and growing up in a rural environment in contact with farm animals ('farm effect'). The early interaction of the microbiota with the host's developing immune system is essential for the adjustment of the innate immune system. Harmful factors are associated with a more or less severe dysbiosis in the body's barrier organs that alters the innate immune response from infancy, with loss of peripheral tolerance and the development of hypersensitivity later in life. These factors include a diet high in industrially processed foods, obesity, lack of exercise, growing up in an urban environment with reduced microbial diversity, single parenting and exposure to antibiotics.[3]

## ANTHROPOGENIC MODIFIERS

Urbanisation, deforestation, agriculture, industrialisation pollute air, soil and water and contribute to climate change. Deforestation reduces the Earth's capacity to remove $CO_2$. Since 1850–1900, greenhouse gas emissions have been responsible for a rise in temperatures of about 1.1°C on land and in the oceans. The absorption of excess $CO_2$ by the oceans has also altered their pH, increasing by 25% more than in pre-industrial times. Global warming is leading to melting glaciers and thermal expansion of the seas with rising global sea levels. Environmental change is having a meteorological impact, increasing the intensity and frequency of weather phenomena such as heat waves, hurricanes, heavy rainfall and floods, droughts and wildfires.[8]

Environmental antigens and allergens are constantly subject to changes caused by environmental factors. Biotic and abiotic stressors act on pollen-producing plants, causing the production of secondary metabolites such as lipid mediators and host defence proteins, which can be allergenic.

Mullein is found in areas with high levels of ambient ozone and has increased allergenicity due to the major allergen Bet v 1 and chemotactic lipid mediators in pollen. In addition, pollen particles can be non-sterile and thus carry pathogens, which trigger T-cell responses through dendritic cell activation

*in vitro*.[9] Specific microbial communities, *i.e.* a pollen-specific "microbiome", are found in birch and grass pollen. In particular, in environments with high $NO_2$ levels, a reduced diversity of birch pollen-associated microbiota was found.

Air pollutants, which are anthropogenic environmental stressors, have a negative impact on the quality of life: either directly by initiating airway inflammation, or indirectly by increasing the immunostimulatory or allergenic potential of plant pollen.

Climate change plays an important role because it can influence the allergenicity of plant pollen and fungal allergens. In some parts of the world, heavy rainfall, episodes of high humidity and storms may occur more frequently due to local climate changes. Storms can be considered a cause of asthma, as they cause atmospheric spikes of sub-pollen particles that can be easily inhaled, and fungal spores.[10]

In some areas of Europe, both an early onset of flowering of plants with larger pollen peaks, and the increased spreading of ragweed (*Ambrosia artemisiifolia*) due to climatic changes have been observed (Kuan Chen KW, 2018). Ragweed pollen is small in size and once inhaled it settles in the lower airways. Ambrosia and the native weed mugwort (*Artemisia vulgaris*) show increased cross-reactivity, thus explaining the occurrence of symptoms by conjunctival challenge with ragweed extract in patients primarily sensitized to Artemisia pollen.[12] Therefore, even without genuine ragweed sensitization, new, potentially severe allergies to ragweed pollen may occur.

In many parts of Europe, due to climate change, stable populations of ragweed plants are expected to gradually spread and pollen loads to increase.[2]

A study conducted in a Bavarian Alpine region in patients with chronic lung disease and in a cohort of tourists showed a general tendency to perceive the health consequences of climate change to be positively correlated with symptom severity in both groups of patients.[14]

## EPIGENOMICS

If genes are silent and do not synthesize proteins until stimulated by environmental factors via epigenetic factors, it means that not only genes but also epigenetic factors play a major role in the development and variability of organisms' phenotypes. Epigenetics can better explain how stem cells develop into differentiated cells, so even without DNA modification cells will be able to differentiate from each other by updating different parts of their genetic dowry. On the other hand, if genetic predispositions to a particular disease will only act when stimulated by environmental factors via epigenetic factors, it means that not only genes but also the epigenome play a special role in human pathology.

The environment has no influence on our DNA gene sequence, only the expression of genes. The expression of genes refers to how genes function, not how genes are. Several environmental factors such as food and drugs, and exposure to toxins or pollutants are capable of altering gene expression. These changes might be subtle, and may not have any visible effects, yet they can make a dramatic difference. Certain important genes in our DNA might be switched on and off at times, if their expression changes so dramatically that it's the opposite.[15]

A crucial role in the pathogenesis of asthma, allergic rhinitis, atopic dermatitis, food allergy, and other allergic disorders is played by epigenetic mechanisms. These environmental factors in the long term modulate the effects of the immune system, thus making them well-recognized immune modifiers leading to allergy.

Globally, asthma remains an important public health problem, with a reported increase in asthma prevalence in recent decades. Existing evidence suggests that accelerated industrialization/ urbanization is associated with the increasing incidence of asthma. This increase in asthma prevalence seems to be related to increased exposure to pollution as well as a decreased exposure to natural environmental factors such as agriculture and related micro-organisms or traditional diets. Most studies investigating the role of epigenetic changes in asthma have focused on DNA methylation. Changes in DNA methylation status in genes specific to different subsets of T helper cells (CD4þ) are a very good example of how epigenetic modulation can influence the development of allergic diseases and asthma. In the case of CD4þ T cells, allergic sensitization induces demethylation of the gene encoding interleukin 4 (IL-4) in its promoter region, thereby generating allergic airway inflammation. Differential DNA methylation in the promoter regions of IL4 or the Interferon-gamma locus has been observed between asthmatic and non-asthmatic patients. In children with allergic asthma treated with house dust mite allergen (HDM)-specific immunotherapy, sensitivity to HDM and production of IL-4, IL-5, and IL-2 by peripheral blood mononuclear cells (PBMCs) were lower, while DNA methylation in the IL-4 promoter

region was higher after allergen challenge compared with the untreated group. In patients with severe asthma, distinct patterns of DNA methylation have been reported to be associated with abnormalities in airway smooth muscle cell (ASMC) phenotype.

Similar to DNA methylation, histone modifications also contribute to the development and pathophysiology of asthma by altering the accessibility of genomic DNA to the transcription machinery. Comparative analysis of ASMC from asthmatic patients and non-asthmatic individuals demonstrated that asthmatic patients had higher H3K18 acetylation and higher levels of histone acetyltransferase p300 binding to the IL-8 promoter

Atopic dermatitis has a strong genetic component and can be associated with other allergic disorders, including allergic rhinitis or asthma. The natural history of atopic dermatitis involves loss of integrity and structural function of the skin's epidermal barrier due to a genetically mediated deficiency in structural proteins such as filaggrin (FLG), followed by type 2 immune responses. To this complex interplay between genetic, immune and environmental mechanisms, other factors such as the skin microbiota are added that lead to the development of atopic dermatitis in its various clinical forms. There is increasing evidence that epigenetic mechanisms, including DNA methylation and histone modifications, contribute to the physiology of atopic dermatitis through gene-environment interactions.

Lesional epidermis obtained from patients with atopic dermatitis shows substantial differences in DNA methylation compared to healthy control epidermis. It is partly correlated with the altered expression levels of genes primarily relevant to innate immune responses and epidermal differentiation.

On the other hand, significantly higher levels of DNA methylation in the promoter region of the human b-defensin-1 (HBD-1) gene were detected in skin samples with atopic dermatitis lesions compared to skin samples with non-lesional atopic dermatitis or normal skin.[16]

Studies on immune cells isolated from patients with allergic rhinitis (AR) have shown that histone deacetylase (HDAC) is increased and that inhibition of HDAC may help improve AR. HDAC1 is increased in nasal epithelial cells compared to healthy controls, and interleukin-4 (IL-4) can increase HDAC1 expression, producing nasal epithelial barrier dysfunction. Many studies have reported that expression of TWIK-related potassium channel-1 (TREK-1) is significantly down-regulated in patients with AR. These findings indicate that an increase in HDAC activity may contribute to the pathogenesis of AR by increasing proinflammatory cytokines and decreasing anti-inflammatory cytokines. Changes in DNA methylation differentiate allergic patients from healthy individuals and correlate with CD4+ T-cell patterns and numbers in AR. DNA methylation changes at CpG sites in blood mononuclear cells and airway epithelial cells are common in allergic children. In addition, DNA hypermethylation can lead to decreased IFN-γ expression in AR patients. DNA hypomethylation has been shown to increase mRNA expression of IL-33 and IgE.[17]

## METABOLOMICS

The metabolome of a living organism is composed of its own metabolites and metabolites from the microbiome (especially the gut), metabolites from xenobiotics (drugs) and metabolites from food.[17,19] Their levels in the body are influenced by various factors such as environment, stress, age, gender and physical activity.

In metabolomics, two main complementary approaches are used: untargeted and targeted analyses. Untargeted analysis measures as many metabolites as possible in a single run, which are considered the patient's metabolic fingerprint. So, in a given disease state, depending on its course there will be a set of metabolites that will change and characterise the disease. By this strategy, new potential biomarkers of a disease or phenotype are obtained. Targeted analysis precisely quantifies a limited set of metabolites, an approach that resembles classical biochemistry. The measurement and quantification of metabolites is based on prior knowledge that they could be mislocalised.[20]

Metabolomic strategies used to discover new disease biomarkers homogeneously include patients with different stages of disease progression. This is difficult to achieve because patients are treated with different drugs aimed at disease control, thus altering the systemic signature associated with disease progression and will obscure the underlying endophenotype.

Severe patients uncontrolled with any combination of pharmaceuticals represent a unique group, essential for understanding disease progression and identifying systemic molecular signatures associated with disease progression. Potential factors influencing disease progression include genetic factors and exposure that determine the likelihood of developing a severe allergic phenotype. With regard to exposome, it has

been observed that patients exposed to high levels of allergens are more likely to develop severe allergic disease.[7]

An epidemiological study based on molecular allergy showed that patients overexposed to grass pollen were frequently sensitised to profilin and patients overexposed to olive pollen had an increased prevalence of sensitisation to the minor allergen Ole 7.[20,22] A significant proportion of patients living in areas overexposed to pollen and who showed these sensitization profiles were observed to develop a more severe disease phenotype. At the same time, in areas with high exposure to house dust mites, patients develop anaphylactic reactions to the consumption of mite-coated foods in the absence of food allergy. The three groups of patients show more severity-related clinical features (asthma, severe anaphylactic reactions) and do not respond to allergen-specific immunotherapy (AIT).[20]

Metabolomic analysis revealed significant differences in several metabolic pathways. Energy metabolism was altered, with severe patients showing high levels of lactic acid and low levels of pyruvic acid, corresponding to a metabolic phenomenon called the Warburg effect, common in cancer progression. This metabolic change may be associated with increased T-cell activity during a systemic inflammatory response.[23] On the other hand, increased serum lysophospholipids, a detail previously observed in asthmatic patients, have been observed in this severe allergic phenotype.[24,25] Patients overexposed to grass pollen showed an increased proliferative T-cell response to profilin compared to less exposed patients. This supports the role of T cell proliferation in the development of severe respiratory phenotypes.[26] Stress of sphingolipid metabolism was detected in the same patients. The continuous increase in sphingosine 1-phosphate (S1P) was accompanied by signals of metabolic precursor depletion. S1P is involved in mast cell activation and degranulation and in the induction of angiogenesis and fibrosis triggered by endothelial and epithelial cells. It also plays an important role in increasing T-cell lifespan and recruiting T-cells to the lesion site. The data suggest that a global inflammation-related system is pushed to the limits in patients with severe disease.[22]

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