Advances and novel developments in environmental influences on allergic diseases

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Abstract

Atopic diseases have increased in prevalence over the last few decades and the rapid increases suggest that the predominant driving forces behind these increases are environmental factors rather than genetic alterations. A number of environmental factors have been implicated in the increased prevalence of allergic diseases. Predominant among them are increased exposure to pollutants and decreased exposure to microbes and parasitic infections. The hygiene hypothesis suggests that increased hygiene and lack of exposure to microbes and parasitic infections at an early age prevents the necessary stimulus to train the developing immune system to develop tolerogenic responses. Lifestyle factors, such as increased time spent indoors, use of antibiotics, and consumption of processed foods and decreased exposure to farm animals and pets, limit exposure to environmental allergens, infectious parasitic worms, and microbes. The lack of exposure to these factors is thought to prevent proper education and training of the immune system. Other factors that are also associated with increased risk of allergic diseases are Caesarian birth, birth order, tobacco smoke exposure and psychosomatic factors. Here, we review current knowledge on the environmental factors that have been shown to affect the development of allergic diseases and the recent developments in the field.

Introduction

Both genes and the environment shape human health and disease. Although IgE-mediated allergic diseases (atopic diseases) have a genetic component and are more prevalent in individuals with a family history of allergic disease, the observed rapid increases in allergic diseases suggest that environmental factors are the predominant driving forces behind these increases rather than genetic alterations.[1, 2] Common atopic diseases include atopic dermatitis, food allergy, allergic rhinitis, and allergic asthma. Human diets and lifestyle have undergone major alterations. The exposome, which is the sum total of all the exposures of an individual in a lifetime, has undergone major shifts in the last few decades, affecting human health and disease.

A number of factors have been implicated in the increased prevalence of allergic diseases. Predominant among them are increased exposure to pollutants and decreased exposure to microbes and parasitic infections. Air pollution has increased significantly in the last few decades. The hygiene hypothesis suggests that increased hygiene and lack of exposure to microbes and parasitic infections at an early age prevents the necessary stimulus to train the developing immune system to develop tolerogenic responses. Lifestyle factors, such as increased time spent indoors, use of antibiotics, and consumption of processed foods and decreased exposure to farm animals and pets, limit exposure to environmental allergens, infectious parasitic worms, and microbes.

The lack of exposure to these factors is thought to prevent proper education and training of the immune system. Other factors that are also associated with increased risk of allergic diseases are Caesarian birth, birth order, tobacco smoke exposure and psychosomatic factors.

Increased human population, pollution, and rapid industrialization have affected our environment bringing about climate change. Climate change has led to greater variability in temperature, and increases in air pollution, forest fires, heat waves, droughts, and floods.[3] Thunderstorms during the pollen season have been linked with increased asthma exacerbations and emergency room visits.[4, 5] During thunderstorms, whole pollen grains are swept into the clouds where they are broken up into smaller allergenic pollen fragments and eventually carried back to ground level.[6] Similarly, dust storms and wildfires have been shown to increase inflammatory responses and asthma exacerbations.[7-9]

A number of recent high-throughput "omic" technologies are accelerating our understanding of allergic diseases and have revolutionized research. The use of the term "omics" suggests a comprehensive high-throughput and systematic investigation of biological parameters. Examples of omic technologies include genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and exposomics.[10] These technologies generate exponentially growing data sets requiring sophisticated bioinformatics and computational techniques that can integrate, analyze and interpret the data to generate hypothesis, which can then be further tested. Of these, epigenomics has been key in giving us insight to gene-environment interactions. It has provided us a greater understanding of the mechanisms by which the environmental factors modulate epigenetic modifications and expression of genes involved in inflammatory responses and allergy. Technologies such as bisulfite sequencing, ATAC seq and cytometry by Time-Of-Flight (EpiTOF) have made it possible to study DNA methylation and histone modifications, and chromatin accessibility across the whole genome and at a single cell level.[11-14] Here, we review current knowledge on the environmental factors that have been shown to affect the development of allergic diseases and the recent developments in the field.

Factors modulating allergic disease

Air pollution

Direct effects

Air pollutants considered major risk factors for the development of allergic diseases are ground-level ozone, particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2).[15, 16] CO, SO_2, and NO_2 are released from combustion of fossil fuels. Ground-level ozone is a secondary pollutant that is produced when nitrogen oxides and volatile organic compounds released from industrial sources react in the presence of sunlight.

PM with diameters [?]10μm or smaller (e.g. PM_{10} and $PM_{2.5}$) can carry organic and inorganic components such as heavy metals and penetrate deeply into the respiratory tract and skin barrier. In a prospective birth cohort study of over 5,000 children during the first 6 years of life, strong positive associations were found between the distance to the nearest main road and asthmatic bronchitis, hay fever, eczema, and sensitization.[17] An association between eczema and traffic-related pollutants was also found in children from small towns, where exposure to was much lower than in urban areas.[18] Some studies speculate that ultrafine particles (UFPs) with diameter [?] 100nm may have greater effects due to their increased capacity to penetrate the lung alveoli and cardiovascular system.[19] A recent meta-analysis estimated that increases in UPFs per 10000 particles/cm^3 were associated with 7%, 11%, and 5% increase in exacerbations, emergency department visits, and hospital admissions for asthma, respectively.[20]

A recent study estimated that exposure to ambient NO_2 may cause 4 million new cases of pediatric asthma per year, with over 60% occurring in urban areas.[21] Norbäck et al. observed robust relationships between lifetime exposure to NO_2 and allergic diseases including asthma, eczema, wheeze and rhinitis for children ages 3–6 years in China.[22] Similar associations have been observed with SO_2 and CO. A study by Penard–Morand et al. found that SO_2 exposure significantly increases the prevalence of asthma in children.[23] Similarly, Samoli et al. found an association between SO_2 and PM_{10} exposure and the number of pediatric asthma

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hospital admissions among children aged 0 to 14 years in Athens, Greece.[24] Several time-series studies in China reported positive associations between exposure to CO within a few days and the risk of hospital admission/mortality from asthma.[25] Another Korean study found that for children aged 6–7 years, the odds ratio (OR) for life-time allergic rhinitis was 1.10 per 100 ppb increase in CO concentration during the first year of life. In addition, the OR for current atopic dermatitis was 8.11 for every 1 ppb increase in the average CO concentration during the preceding 12 months.[26] In the US, the risk for emergency department visits was estimated to increase by 0.8% for asthma or wheeze and 3.7% for bronchitis per IQR increase in the preceding 3-day average concentration of CO.[27]

Ozone in the stratosphere is protective as it shields living things from ultraviolet radiation from the sun. However, ground-level ozone, which forms just above the earth's surface has been associated with adverse health effects. A birth cohort study in Canada reported that ozone exposure at birth was associated with the onset of asthma and allergic rhinitis during a follow-up at age 17.[28] In France, a higher annual outdoor concentration of ozone was associated with increased total IgE levels.[29] A study estimated that 7-day exposure to ozone was associated with significant increase in physician visits for atopic dermatitis, contact dermatitis and urticaria.[30]

The pathophysiological mechanisms by which air pollution mediates allergic disease are poorly understood; however, oxidative stress, enhanced sensitization to allergens, inflammatory and immunological responses, and epigenetic modifications have been suggested as possible mechanisms. [31-33] Exposure of human nasal epithelium cells to $PM_{2.5}$ was found to decrease loss of barrier function, as determined by measures of transepithelial resistance, permeability, decreased expression of tight junction proteins, and production of proinflammatory cytokines, such as thymic stromal lymphopoietin (TSLP).[34] A genome-wide DNA methylation study found that long-term ambient air pollution exposure impacts DNA methylation of a number of genes, some of which play a role in inflammatory responses.[35] Short-term and long-term exposures to high levels of CO, NO_2, and $PM_{2.5}$ were associated with alterations in differentially methylated regions of Foxp3.[36]

Indirect effect on plants and ecosystems The effects of air pollution reported above on the increase in allergies are direct the immune system or barrier function in humans. However, there is also an indirect effect: air pollution as well as other effects of climate change affect pollen, plants and biodiversity per se. Air pollution (and climate change) affect not only plant growth, pollen and flower production, and duration of the whole pollen season but can also display more indirect health effects by increasing the amount of allergenic encoding transcripts and proteins of the pollen.[37, 38] When ragweed plants were grown in climate chambers under controlled conditions and fumigated with enhanced levels of NO_2, transcript levels of amb were upregulated, indicating potentially higher allergenicity due to NO_2.[37] On exposure of ragweed to varying NO_2 levels during the growing season, a significantly higher allergenicity for Amb a 1 was observed.[38] Elevated CO_2 levels and drought stress was also found to increase allergenic ragweed proteins (Amb a).[39] Therefore, under global change scenarios the allergenic potential of pollen is also expected to change. Epidemiologic studies have demonstrated that urbanization, high levels of vehicle emissions, and westernized lifestyle are correlated to an increase in the frequency of pollen-induced respiratory allergy prevalent in people who live in urban areas compared to those who live in rural areas – this can in part be due to the effects of pollution on the pollen and plants themselves and therefore indirectly impacting human health.

Tobacco smoke and e-cigarettes

Epidemiological studies and meta-analyses indicate that pre- or post-natal maternal smoking increases the risk of wheezing and asthma in children [?]2 years[40] and that secondhand smoke during infancy without prior exposure in utero leads to an enhanced risk of food sensitization and eczema.[41] Tobacco smoke and e-cigarettes may mediate their effects via a number of inflammatory mechanisms. For instance, tobacco smoke provokes oxidative stress[42] which leads to upregulation of TSLP[43] and IL-33[44] suggestive of a pro type-2 inflammation in the lungs. In addition, phagocytic activity of alveolar macrophages from smokers is reduced compared to non-smokers.[45] Repetitive exposure to cigarette smoke in normal human airway epithelial cells was found to impact the adhesive intercellular junctions and disrupt monolayer integrity. Cortical tension of epithelial cells was observed due to increased actin polymer levels, which further destabilized

cell adhesion.[46]Tobacco smoke may also mediate its effect through microbiome dysbiosis. A study found that sensitization to *Staphylococcus aureus*enterotoxins is increased in smokers with asthma, and it may be a marker of eosinophilic inflammation and severe asthma.[45]E-cigarettes were also found to be associated with inflammation. A study found that e-cigarette vapors and cigarette smoke altered virulence of key lung pathogens (*Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus and Pseudomonas aeruginosa*), which may increase bacterial persistence and inflammatory potential.[47]

Microbiome

The microbiome has been shown to play a key role in the development of the immune system with microbiome dysbiosis mediating immune deviation.[48] Characterizing the constituents of the human gastrointestinal, skin, and airway microbiota as well as microbial peptides and metabolites that influence host immunity and immune response to allergens in food allergy, atopic dermatitis, and asthma is the focus of ongoing research.[48, 49] Advances in our understanding of host-microbe interactions have been made possible by 16S rRNA sequencing, which permits precise identification and quantification of bacteria. 16S ribosomal RNA gene is a highly conserved locus in the bacteria genome, yet different in sequences among different bacterial species. Another approach is to sequence the total DNA present in one ecosystem using whole genome shotgun techniques, and subsequently map the genes related to microbes, including viruses and fungi.[50] These techniques have enabled us to make inroads in identifying the species found in a healthy microbiota and those that cause dysbiosis. In atopic dermatitis, *S aureus* has been shown to be clearly correlated with severity and to decrease during treatment and to rebound after the end of treatment indicating its use as a potential diagnostic and prognostic biomarker.[51]

Studies in mice and humans have shown associations between intestinal bacteria and allergic response to food. In a murine model, germ-free mice were colonized with feces from healthy or cow's milk allergic (CMA) infants. The healthy and CMA mice showed different transcriptome signatures in ileal epithelium, and the healthy mice were protected against anaphylactic responses to cow's milk allergen. The study identified a clostridial species that protected against the allergic response.[52] *Bifidobacterium breve* is a species commonly isolated from the intestines of healthy breastfed infants and from human milk and is thought to have a significant impact on the development of immune tolerance.[53] In a longitudinal study of a Canadian child cohort, it was found that infants at risk of asthma showed gut microbial changes during the first 100 days of life. Four bacteria taxa were reduced in high-risk children and this was accompanied by reduced deregulation of enterohepatic metabolites. To understand causality, the same study also found that inoculating the four taxa of bacteria (Lachnospira, Veillonella, Faecalibacterium, and Rothia) in germ-free mice decreased airway inflammation.[54] Individuals with atopic dermatitis have reduced skin lipids and increases in *Staphylococcus aureus* .[55] A study found a correlation between Staphylococc*us* species–dominated dysbiosis in the skin microbiome and dysregulation of the skin barrier transcriptome in patients with AD, but whether the microbiome dysbiosis is the cause for or result of the skin barrier defect is unclear.[56]*S. aureus* has also been directly correlated with increased expression of inflammatory cytokines, IL-4, IL-13, IL-22, and TSLP and with decreased expression of cathelicidin.[57] *C. difficile* colonization during infancy was associated with a higher risk of developing allergic diseases during early childhood.[58]

A number of factors affect the composition of either the skin or gut microbiome. Vaginal delivery, breast feeding, presence of older siblings and exposure to a variety of microorganisms promote healthy microbiota in infants. In contrast, Caesarean section, formula milk, and exposure to antibiotics have a negative impact.[59] Dietary factors also play a role in microbiome health. Some of these factors are discussed below.

*Diet*In addition to prebiotics and probiotics, other dietary factors that have been shown to play a role are vitamin D and omega-3 and omega-6 polyunsaturated fatty acids (PUFAs). A study found that higher second trimester n-6 PUFAs were associated with atopic dermatitis in children of women with atopy.[60] A meta-analysis found that intake of ω-3 PUFA started during pregnancy may reduce the risk of sensitization to egg and peanut.[61] Levels of ω-3 and ω-6 were measured in the second trimester and found that higher ω-6 PUFAs were associated with a higher risk of all respiratory outcomes among children if the mother has asthma, but that male children born to women with asthma and a higher PUFA ratio had the highest risk for

asthma.[62] A meta-analysis of ω-3 consumption suggests that introduction of fish at 6-9 months and routine consumption once a week reduces asthma and wheeze in children up to 4.5 years old.[63] The association between vitamin D insufficiency and increased risk of food allergies have been shown by multiple studies. While controlling for regional and population characteristics, places in northern latitudes were found to have more epinephrine autoinjector prescriptions than those in southern latitudes in both USA and Australia.[64, 65] In another study, food allergies were found to be more likely in infants with low vitamin D.[66] In children with asthma, vitamin D deficiency was associated with asthma severity and increased serum IgE levels.[67] *Farming Environment and Pet Ownership* Childhood environments have been shown to play an important role in the protection against allergies. Individuals living at short distances from farms had a lower risk of atopy, as measured by IgE, compared with those living further away. This decrease in atopy risk was even greater for those who grew up on a farm.[68] Children in rural South African communities with higher exposure to pets and farm animals than children from urban communities were found to be at lower risk of allergic disease.[69] Marrs et al. reported there was an association between dog ownership at three months of age and protection against food allergies.[70] However, urban children with pet exposure in the South African cohort had an increased rate of any allergy compared to urban children without pets so conflicting data exists regarding pet ownership in relation to allergies.[69] *Antibiotics* Antibiotic usage has been documented to perturb the gut flora of individuals, which places them at an increased risk for the development of allergies and asthma. In mice models of atopic dermatitis, antibiotic use was associated with significantly aggravated phenotypes, including clinical score, transepidermal water loss, and histopathology, compared to those treated with healthy feces or probiotics.[71] Timing, dose, and frequency of antibiotics in prenatal and infant populations have also been associated with the development of childhood allergies and asthma.[72, 73] Short chain fatty acids (SCFAs) which are fermentation end products of insoluble fibers by intestinal microorganisms have been implicated in the maintenance of epithelial integrity and IgA production.[74] Antibiotics-induced dysbiosis of intestinal microbiota has been shown to increase severity of atopic dermatitis in mice through alterations in SCFA's and decreases in the number of Foxp3+ T regulatory cells.[71] *Vaginal versus caesarean section births* The composition of gut flora in children born by caesarean section (C-section) versus vaginal delivery is different and this difference in gut microbiota colonization may impact the development of the immune system.[75] A vaginal mode of birth exposes the baby to maternal vaginal and fecal flora.[76] Studies indicate that babies born via C-section have a higher incidence of allergy, atopy, and asthma, increased susceptibility to infectious wheezing[77] and decreased gut microbiome diversity.[78] In addition, long-term studies show greater incidence of childhood asthma up to the age of 12 years.[79] **Other factors** In addition to environmental and lifestyle factors, household composition has also been shown to affect the risk of allergic diseases. A study that followed 17,414 British children for 23 years found a strong association between the birth order of a child and the risk of hay fever.[80] Specifically, contact with older siblings was hypothesized to increase immunological protection due to an increase in infections in early childhood through unhygienic contacts with siblings. A study on 10,834 children enrolled in the Chicago Family Cohort Food Allergy study found that younger siblings of kids with food allergies had significantly less prevalence of food sensitization and clinical food allergy.[81] Current research shows that psychosocial stress and poor mental health in mothers increase the risk of allergic diseases in their children.[82-88] Stressful life events in childhood, for example parental divorce, have also been shown to increase the risk for development of atopic eczema later in life.[89] Psychosocial stress might trigger or worsen allergic symptoms[90] Also, in adults with allergies, psychoneuroimmunologic mechanisms might play an important role.[91] An association of anxiety and depression with allergies was reported in many studies.[92, 93]

Summary and Future Directions

There have been exciting new developments in understanding the role of the environment in mediating allergic diseases. Epigenetics has provided us better insight into how pollution and other environmental factors alter gene expression. Novel high throughput technologies are enabling characterization of a healthy microbiota and the imbalance that is created with microbial dysbiosis. This knowledge can assist with preventative strategies that can restore a healthy microbiota. It is now recognized that early infancy offers a "critical window" of colonization during which microbial communities shape immune maturation and this

window may enable opportunities for preventative treatments with pre- and probiotics.[94] In humans, this critical period appears to be within the first 100 days of life.[95] A study found that supplementing infants with a probiotic mixture together with at least partial breastfeeding corrected undesired changes in microbiota composition and function caused by antibiotic treatments or caesarean birth.[96] Host microbe interactions are highly complex and their role in medicating allergy and asthma continues to be an area of intense research.[97] Development of tolerance towards food allergens also appears to occur at an early age. A large study, the Learning Early About Peanuts (LEAP) study, found that the early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy.[98] Current guidelines for allergy prevention now encourage active introduction of allergenic foods to all infants from 4-6 months of age.[99]

Atopic diseases have common underlying mechanisms. Epidemiological studies show a natural history for the progression of these diseases, starting with atopic dermatitis in early infancy and progressing to food allergy, allergic rhinitis, and allergic asthma. This natural progression of atopic diseases is termed the Atopic March. Studies are now evaluating if by prevention of atopic dermatitis, we can prevent the subsequent manifestation of other atopic diseases. In addition to the development of targeted therapeutics, studies are determining if the use of emollients to treat skin barrier disruption can prevent atopic dermatitis and other atopic diseases.[100]

Ultimately understanding the role that genes, epigenetics, and the environment play in shaping our immune health at the DNA, RNA, and protein level is key to developing targeted therapies for preventing and treating allergic diseases.

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Box 1:

- Characterization of microbes in healthy and allergic individuals
- Identifying type and optimal timing of introduction of probiotics and prebiotics for tolerance induction
- Identifying epigenetic alterations and changes in gene expression on exposure to pollutants
- Evaluating emollients as treatment for prevention of atopic dermatitis and other atopic disorders.
- Targeted therapy for precision medicine
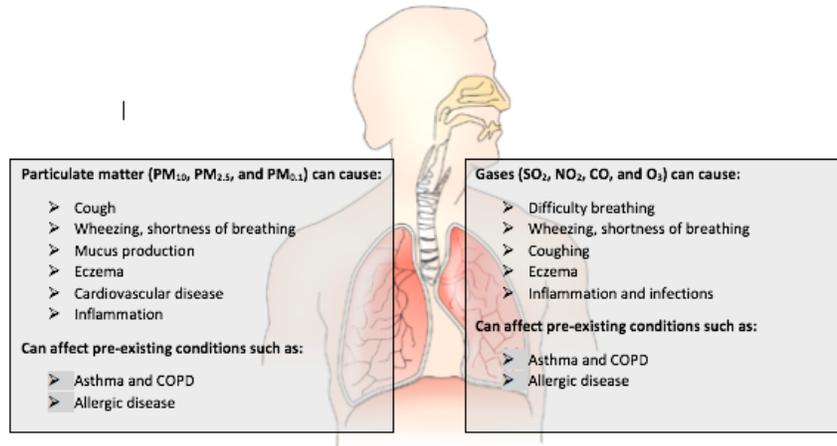
Figure 1

Figure 1: Air pollution affects risk of allergic disease. Air pollutants include particulate matter (PM) and gases. Particulate matter that cause allergic disease include PM with diameters [?]10μm or smaller (e.g. PM_{10} and $PM_{2.5}$). Major gaseous pollutants that affect include SO_2, NO_2, CO, O_3.
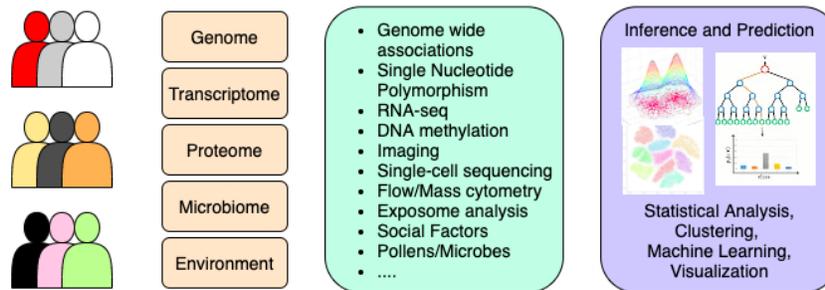
Figure 2

Figure 2: High throughput omics technologies enable generation of large amounts of data that are analyzed and interpreted by sophisticated bioinformatics and computational tools to give us mechanistic information on immune pathways at the DNA, RNA, and protein level.