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Critical Review

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Air Pollution and Climate Change Effects on Allergies in the Anthropocene: Abundance, Interaction, and Modification of Allergens and Adjuvants

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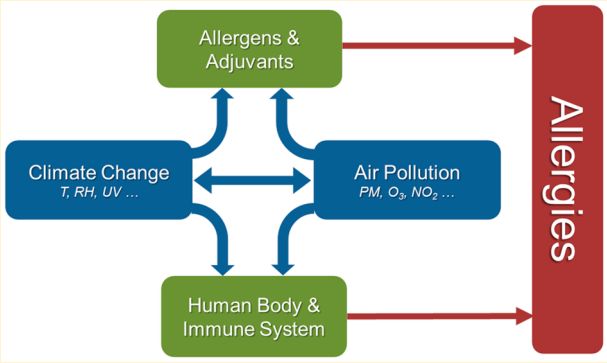
Supporting Information

ABSTRACT: Air pollution and climate change are potential drivers for the increasing burden of allergic diseases. The molecular mechanisms by which air pollutants and climate parameters may influence allergic diseases, however, are complex and elusive. This article provides an overview of physical, chemical and biological interactions between air pollution, climate change, allergens, adjuvants and the immune system, addressing how these interactions may promote the development of allergies. We reviewed and synthesized key findings from atmospheric, climate, and biomedical research. The current state of knowledge, open questions, and future research perspectives are outlined and discussed. The Anthropocene, as the present era of globally pervasive anthropogenic influence on planet Earth and, thus, on the human environment, is characterized by a strong increase of carbon dioxide, ozone, nitrogen oxides, and combustion- or traffic-related particulate matter in the atmosphere. These environmental factors can enhance the abundance and induce chemical modifications of allergens, increase oxidative stress in the human body, and skew the immune system toward allergic reactions. In particular, air pollutants can act as adjuvants and alter the immunogenicity of allergenic proteins, while climate change affects the atmospheric abundance and human exposure to bioaerosols and aeroallergens. To fully understand and effectively mitigate the adverse effects of air pollution and climate change on allergic diseases, several challenges remain to be resolved. Among these are the identification and quantification of immunochemical reaction pathways involving allergens and adjuvants under relevant environmental and physiological conditions.



1. INTRODUCTION AND MOTIVATION

Allergies are hypersensitivities initiated by specific immunologic mechanisms (abnormal adaptive immune responses).[1−3] They constitute a major health issue in most modern societies, and related diseases, such as allergic rhinitis, atopic asthma, eczema (atopic dermatitis), and food allergies, have strongly increased during the past decades.[4−12] While some of the perceived rise in allergies may be due to improved diagnosis, the prevalence of allergic diseases has genuinely increased with industrialization

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and with the adoption of a "Western" lifestyle.[13] The development of allergies is a complex multifactorial process that involves various factors influencing the body's predisposition and immune response, and the manifestation of allergic diseases depends on exposure to allergens, adjuvants and other environmental and lifestyle factors (Figure S1 and section S1).[3,4,14−16] Among the risk factors for allergic diseases are the genetic predisposition of the individual (referred to as atopy), reduced childhood exposure to pathogens and parasites ("hygiene hypothesis"), diet/nutrition, psychological/social stress, and environmental pollution, including outdoor and indoor air pollutants (ozone, nitrogen oxides, diesel exhaust particles, tobacco smoke, etc.).[4,12,17−35] As outlined in Figure 1,

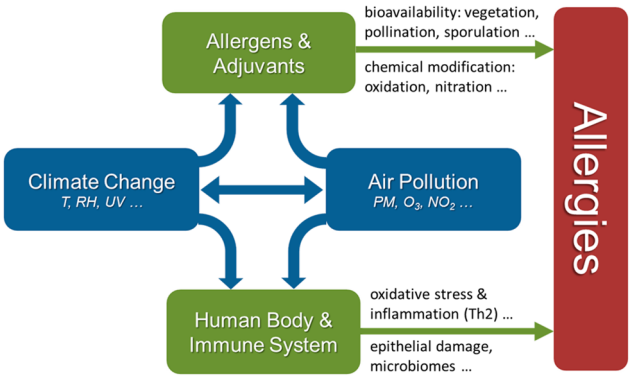

Figure 1. Interplay of air pollution and climate change can promote allergies by influencing the human body and immune system, as well as the abundance and potency of environmental allergens and adjuvants.

climate change and air pollution can influence the bioavailability and potency of allergens and adjuvants in multiple ways, including changes in vegetation cover, pollination and sporulation periods, and chemical modifications. Moreover, climatic conditions and air pollutants may skew physiological processes and the immune system toward the development of allergies, for example, by oxidative stress and inflammation, disruption of protective epithelial barriers, and disturbance of related microbial communities (microbiomes).[4,8,35−38]

The term Anthropocene describes the present era of globally pervasive and steeply increasing anthropogenic/human influence on planet Earth, including the land surface, biosphere and atmosphere.[38−44] Human activities have become a driving force that changes many characteristics of our environment such as biodiversity and air quality on local, regional, and global scales, for example, through land use change, agriculture, fossil fuel burning, traffic emissions, and the release of industrial products.[38,39,41,43,45−49] While the basic concept of the Anthropocene, as introduced by Nobel laureate Paul J. Crutzen and colleagues,[39,44,50] is widely accepted and increasingly used across the sciences and humanities, the actual beginning of the Anthropocene as a new geological epoch is still under investigation and discussion.[38,45−47,51−64] The proposed dates range from early human history via the 19th century (industrialization) to the 1960s (nuclear weapon testing and "Great Acceleration").[45−47,58−64] Since the industrialization of the 19th century and especially during the "Great Acceleration" of the 20th century, the primary emission, secondary formation, and concentration of air pollutants like ozone, nitrogen, and sulfur oxides, soot, and a wide range of other reactive trace gases and aerosols have greatly increased relative to preindustrial times, especially in densely populated and industrialized areas but also in agricultural environments and around the globe.[38,47,65−69] For example, the average mixing ratios of ozone in continental background air have increased by factors of 2−4 from around 10−20 ppb from the beginning of the 19th century to 30−40 ppb in the 21st century, and the number and mass concentrations of aerosol particles in polluted urban air are typically by 1−2 orders of magnitude higher than in pristine air of remote continental regions ($\sim 10^2-10^3$ cm^{-3} and $\sim 1-10$ μg m^{-3} vs $\sim 10^3-10^5$ cm^{-3} and $\sim 10-100$ μg m^{-3}).[38,70]

Numerous studies indicate that ozone and air particulate matter have strong effects on human health and mortality as well as on agricultural crop yields.[71−80] In view of these findings, it appears unlikely that the strong environmental changes of the Anthropocene would have no effect on the interaction of the human immune system with environmental stimuli, including allergens and adjuvants. Indeed, it seems necessary to address the question whether human activities are creating a hazardous atmosphere that may severely affect public health.[35,37,38,81,82] Figure 2 illustrates how climate parameters and air pollutants can exert proinflammatory and immunomodulatory effects.[8] As detailed in the following sections, both air pollutants and climate parameters can influence the environmental abundance of allergenic bioparticles and the release of allergenic proteins and biogenic adjuvants. Moreover, air pollutants can chemically modify and agglomerate allergenic proteins, and they can act as adjuvants inducing epithelial damage and inflammation.

Several reviews have addressed the general determinants of allergenicity[3−8,83−85] and various environmental risk factors for allergic diseases.[4,9,12,34,36,86−101] In this Critical Review, we attempt to summarize, update, and synthesize the different perspectives and most relevant findings reported in earlier reviews and recent research articles addressing the effects of air pollutants and climate parameters on allergies. A central aim of this article is to review and outline both proven and potential effects of the globally pervasive environmental changes that are characteristic for the Anthropocene; a holistic view of environmentally caused changes in the abundance, interaction, and modification of allergens and related substances is provided. Our target audience comprises physical, chemical, and biomedical scientists interested in environmental effects on public health. Sections 2−4 deal with specific environmental processes and air pollutants that are likely to affect the development of allergies in the Anthropocene, that is, in an environment strongly influenced by human activity. Section 5 provides an outlook identifying key questions and promising directions of future research. For orientation of readers not familiar with the basics of allergic sensitization and response, section S1 outlines key features of the immunochemical interactions involved in IgE-mediated allergies (type I hypersensitivities)[3−5,14−16,84,102−136] on which this article is mainly focused and which usually involve Th2 cell-mediated inflammation[137,138] (Figure S2).

2. ABUNDANCE AND RELEASE OF ALLERGENS AND ADJUVANTS

Environmental allergens are mostly proteins derived from plants, animals, and fungi that can trigger chemical and biological reaction cascades in the immune system leading to allergic sensitization and formation of IgE antibodies (section S1).[8,84,103,105−109] Prominent examples are major allergens of

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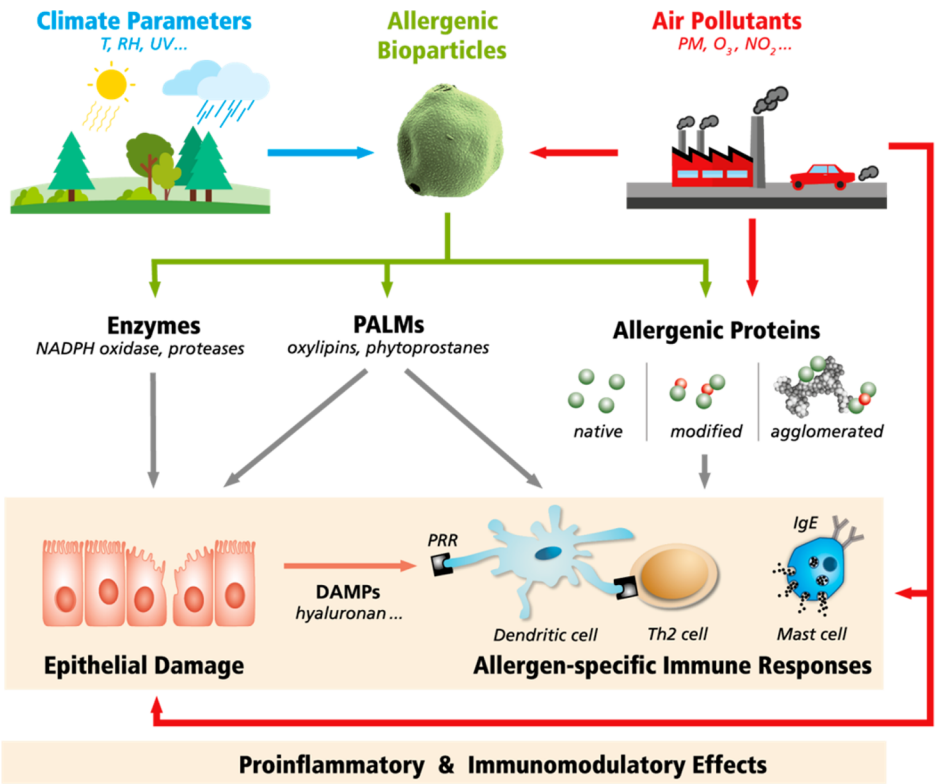

Figure 2. Pathways through which climate parameters and air pollutants can influence the release, potency, and effects of allergens and adjuvants: temperature (T), relative humidity (RH), ultraviolet (UV) radiation, particulate matter (PM), ozone and nitrogen oxides (O_3, NO_x), reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, pollen-associated lipid mediators (PALMs), damage-associated molecular patterns (DAMPs), pattern recognition receptors (PRR), type 2 T helper (Th2) cells, immunoglobulin E (IgE), allergenic proteins (green dots), and chemical modifications (red dots).

birch pollen (Bet v 1), timothy grass pollen (Phl p 1), ragweed (*Ambrosia*, Amb a 1), molds (*Alternaria alternata*, Alt a 1, *Cladosporium herbarum*, Cla h 1, *Aspergillus fumigatus*, Asp f 1), and dust mites (Der p 1).[4,139,140] Besides allergens, also adjuvants and their interaction with the immune system play a critical role in the development of allergies. Here, we use the term adjuvant generically for substances that are promoting pro-allergic immune responses. Adjuvants can trigger the immune system by inducing tissue damage and subsequent enhanced uptake of allergens, by inducing oxidative stress and activation of immune cells, by coexposure with the allergen favoring Th2 responses, or by modification of allergens enhancing their allergic potential. An overview of biogenic and anthropogenic adjuvants, including particulate matter as well as trace gases, and their effects on the immune system is given in Table 1.

Climate change is influencing vegetation patterns and plant physiology through spatial and temporal changes in temperature and humidity (Figure 1),[141−143] and increasing atmospheric carbon dioxide (CO_2) affects plant biology by supplying more carbon for photosynthesis, biomass production, and growth (CO_2 fertilization).[144,145] These factors can influence the spread of invasive plants, the beginning, duration, and intensity of pollination, the fruiting patterns and sporulation of fungi, as well as the allergen content and allergenicity of pollen grains, fungal spores, and other biological aerosol particles (Figure 2).[12,90,93,96−98,145−162] Specific examples of climate change effects on allergenic plants and fungi are outlined in Table 2. Climate and land use change are also expected to influence the composition and spread of microbial surface communities (cryptogamic covers), from which allergenic cyanobacteria and other microbial allergens or adjuvants can be emitted to the atmosphere.[163−174] Moreover, the frequency and intensity of dust storms are expected to increase,[141,175−179] and dust particles are known to carry biological and organic components with pathogenic, allergenic, and adjuvant activity.[152,154,180−187] Dust storms have been shown to cause and aggravate respiratory disorders including atopic asthma and allergic rhinitis.[181,188−191] So-called "thunderstorm asthma" is characterized by acute asthma exacerbations possibly caused by the dispersion of inhalable allergenic particles derived from plant pollen and fungal spores by osmotic rupture.[145,192] On the other hand, climate change-related regional enhancements of outdoor humidity and indoor home dampness may also lead to an increase of respiratory symptoms and atopic asthma induced by allergenic and adjuvant substances from fungi, other microbes, and mite.[12,193−196]

Pollen grains generally belong to the coarse fraction of air particulate matter (particle diameters >10 μm), but fungal spores and pollen fragments are also found in fine particulate matter (<2.5 μm; PM2.5), which can penetrate deep into the human respiratory tract and alveolar regions of the lung.[152,153,197−203] Allergenic proteins can be released from pollen and spores after cell damage or under humid conditions.[204] In particular, pollen rupture due to an osmotic shock during rain can lead to outbreaks of thunderstorm asthma.[145,192,205,206] Furthermore, peaks of high concentrations of pollen, fungal spores, and other primary biological aerosol (PBA) particles have been observed at the onset of heavy rain

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Table 1. Biogenic and Anthropogenic Adjuvants with Reported Pro-allergic Effects: (I) Pollen-Associated and Microbial Compounds, Such as Pollen-Associated Lipid Mediators (PALMs), Bacterial Lipopolysaccharides (LPS), and Fungal β-Glucans and (II) Anthropogenic Pollutants and Chemicals Including Air Particulate Matter, Gaseous Oxidants, and Organic Compounds

substances	effects
(I) Pollen-Associated and Microbial Compounds	
proteases	disrupt intracellular adhesion; stimulate protease activated receptors (PAR) inducing inflammation and enhanced IgE production[204,447,448]
	fungal proteases activate TLR4[449]
leukotrien-like PALMs	attract and activate innate cells like neutrophils and eosinophils[450]
phytoprostane PALMs	inhibit IL12 production and enhance IgE production[107]
NADPH oxidase	ROS production and inflammation[451]
adenosine	Th2 cytokine profile and inflammation[452]
flavonoids	modulate immune responses as ligands of allergenic proteins, e.g., a natural ligand of Bet v 1 is a quercetin and binds to the C-terminal helix[372,453]
	the pollen-derived flavonoid isorhamnetin modulates the immunological barrier function of the epithelium[454]
bacterial LPS	trigger TLR4 in dose dependent manner, induce a Th2 bias and allergic inflammation[455]
gram-positive bacteria	induce DC maturation by upregulation of CD80, CD83, and CD86[445]
fungal β-glucans	activate C-type lectin receptor[105]
fungal VOC	stimulate inflammatory response[456]
(II) Anthropogenic Pollutants and Chemicals	
air particulate matter (PM)	diesel exhaust particles (DEP) increase Th2 sensitization to coinhaled allergens (IgE isotype switching and production, mast cell and basophil degranulation, cytokine production (e.g., IL-4); exaberates allergic airway responses[86,457−462]
	PM and DEP induce ROS production and inflammation[86,463−465]
	DEP suppress alveolar macrophage function[466,467]
	DEP and cigartette smoke can increase thymic stromal lymphopoietin (TSLP) expression in epithelial cells[468,469]
	DEP induce permeability of epithelial cells; disrupt tight junctions by a ROS-mediated pathway[470,471]
	PM increase the expression of costimulatory molecules on DCs (MHC class II, CD40, CD80, CD86)[86,469]
	ultrafine particles (UF*P* < 100 nm) and DEP alter soluble protein levels (e.g., surfactant protein D, complement protein C3), increase levels of e.g., glycerin-aldehyde-3-phosphate-dehydrogenase (GADPH), manganese superoxide dismutase (MnSOD), or mitochondrial heat shock protein (Hsp 90)[472,473]
	PM2.5 and DEP activate complement proteins (C3)[474,475]
	black carbon (BC) and DEP induce epigenetic effects: DNA methylation in genes associated with Th2 polarization[476−478]
	DEP and cigarette smoke induce epithelial damage, oxidatitive stress, and inflammation[460]
	prenatal and postnatal exposure to environmental tobacco smoke (EST) is associated with asthma and wheezing[34,479,480]
	transition metals and other redox-active compounds (organic peroxides, quinones) induce ROS production and inflammation via Fenton-like reactions[38,129,309,311,481−483]
	colocalization of allergens on gold nanoparticles can facilitate IgE-receptor cross-linking[244]
ozone (O_3)	cause oxidative stress, airway inflammation, increased airway permeability[329,362,368,484]
	formation of protein ROI (reactive oxygen intermediates) and protein dimers[329,362] elevated levels of complement protein C3a[485]
	degradation of high molecular weight to low molecular weight hyaluronan, which is a DAMP that activates the TLR4 pathway[407,486]
nitrogen oxides (NO_x = NO + NO_2)	nitration of allergens[328,329]
	skew towards Th2 response,[487] increase eosinophilic inflammation,[488] and enhance airway permeability[484]
volatile, semivolatile and low-volatile organic compounds (VOC, SVOC, LVOC)	significant positive association between formaldehyde exposure and childhood asthma[272]
	antimicrobial endocrine disrupting compounds such as parabens and triclosan are associated with allergic sensitization[489,490] Bisphenol A can increase Il-4 and IgE levels[491]
	dermal and pulmonary exposure to indoor VOC elicit irritant and allergic responses[270,271]

and moist weather conditions;[200,207,208] and increased concentrations of free allergen molecules in fine air particulate matter have been observed after rainfall.[209] Prominent airborne fungi, such as *Cladosporium herbarum*, *Alternaria alternata*, and *Aspergillus fumigatus*, have been found to release higher amounts of allergens after germination under humid conditions,[210] and certain allergens are expressed only following germination.[210,211] Air pollutants, such as ozone, nitrogen oxides, and acids, can also interact with PBA particles, damage their envelope, and facilitate the release of allergenic substances, such as cytoplasmic granules from pollen (Figure S3).[205,212,213]

Besides allergenic proteins, pollen and fungal spores also release other compounds that can act as adjuvants (Table 1). In particular, the release of nonallergenic, bioactive, pollen-associated lipid mediators (PALMs) with pro-inflammatory and immunomodulatory effects can trigger and enhance allergies (Figure 2).[8,109,214−217] For example, skin prick tests of pollen allergens elicited larger wheals when tested together with low molecular weight compounds extracted from pollen.[218] The release of these substances can be influenced by climatic conditions and air pollution, and significantly higher levels were found for pollen collected near roads with heavy traffic.[205] Leukotriene-like PALMs (oxylipins) have the potential to attract and activate innate immune cells like neutrophils and eosinophils.[214,217] Other PALMs such as phytoprostanes (lipophilic counterparts of prostaglandins) are water-soluble and can inhibit the production of interleukin 12 (IL-12) by dendritic cells in the lower respiratory tract, thus favoring an allergenic Th2 T cell response.[8,215] A recent study showed that the low-molecular-weight fraction of phytopros-

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Table 2. Climate Change Effects on the Abundance and Properties as Reported for Selected Plants and Fungi Emitting Aeroallergens

allergenic species	effect of increasing temperature and CO_2 concentration
Ambrosia artemisiifolia (ragweed)	increased pollen and allergen production, plant migration and spreading[157,492−495]
	changes in pollen transcriptome, changes in allergenic potential, increase in flavonoid metabolites[158]
Betula spp. (birch)	earlier pollination start, increased pollen production[161,267,496]
Phleum pratense L. (timothy grass)	increased pollen production[159]
Alternaria spp. (mold)	increased spore numbers, decreased allergen per spore[146,156,160]
Aspergillus fumigatus (mold)	modified allergenicity and Asp f 1 content, increased spore numbers[146,155,497]
Cladosporium spp. (mold)	increased spore numbers[146]
Penicillium spp. (mold)	increased spore numbers[146]

tane E1 (PPE1) in ragweed pollen extract specifically enhanced IgE production in Th2 primed B cells. It was suggested that pollen-derived nonallergenic substances might be responsible for aggravation of IgE-mediated allergies.[219]

Fine aerosol particles and a wide range of inorganic, organic and biological substances from both natural and anthropogenic sources (e.g., secondary organic material, sulfuric and nitric acid, microbial compounds) can agglomerate and accumulate on the surface of pollen, fungal spores, and other PBA particles as illustrated in Figure S3.[152,205,220−223] An overview of reported air pollutant effects on the allergenic potential of plant pollen and fungal spores is given in Table S1.[38,205,221,224−240] Moreover, free allergens and adjuvants can bind to particulate pollutants, such as dust, soot, black/elemental carbon (BC/EC), and diesel exhaust particles (DEP) carrying the allergens and adjuvants into peripheral and deep airways.[241−243] The colocalization of allergens and adjuvants on particle surfaces (sorption layers, protein coronas) might also promote allergic sensitization and response by providing multiple/multivalent epitopes that facilitate receptor cross-linking (similar to parasitic organisms, against which IgE is naturally deployed).[244,245]

During recent years, great progress has been made in the development and application of efficient sampling and measurement methods for bioaerosol particles and components, including microscopic, spectroscopic, mass spectrometric, genomic, and proteomic analyses.[152,246−253] These and related advances in measurement and modeling techniques for health and climate relevant air contaminants (aerosols and trace gases) are expected to enable comprehensive characterization and forecasting of allergenic and adjuvant substances, as well as their mixing state in outdoor and indoor air.[38,70,254−268] Note that indoor air quality is usually influenced by both outdoor air pollutants (O_3, NO_x, PM2.5, etc.) and additional pollutants from indoor sources (e.g., formaldehyde and other organic compounds).[35,37,265,269−274] The data from ambient and individual monitoring and modeling of aeroallergen and adjuvant exposure can then be applied in epidemiological studies to better understand the risk factors of allergic sensitization and disease.[74−76,275−280]

Several epidemiological studies and meta-analyses reported that respiratory allergies and atopic dermatitis are associated with exposure to traffic-related air pollution (TRAP), but different results were obtained for different diseases and locations/studies.[281−293] TRAP is a complex mixture comprising variable proportions of particulate matter and gaseous pollutants from traffic-related primary emissions, as well as secondary pollutants formed by chemical reactions in the atmosphere.[283] Among the pollutants from primary emissions (combustion and noncombustion sources) are road dust, tire and break wear, soot/DEP, BC/EC, metals, polycyclic aromatic

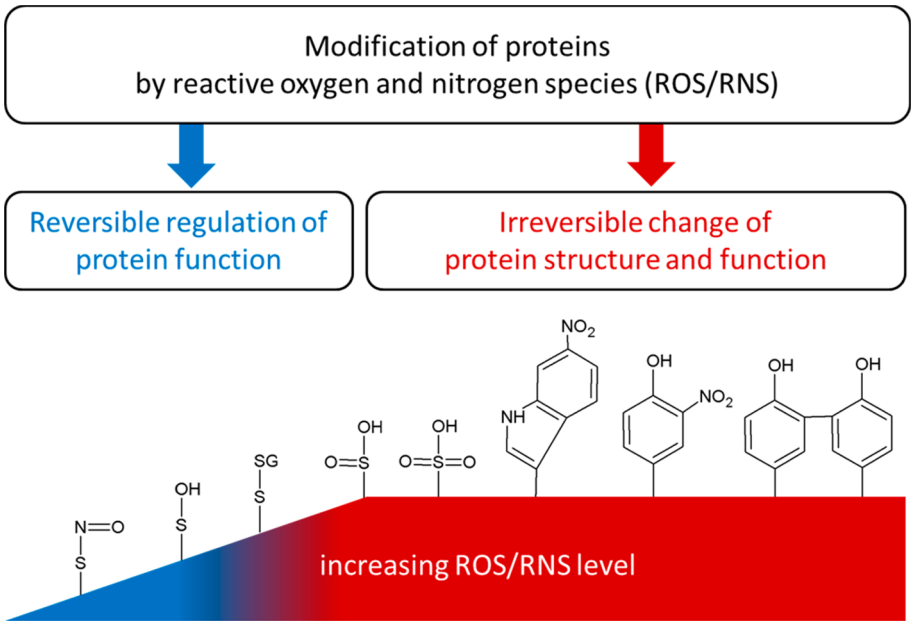

Figure 3. Upon interaction with reactive oxygen and nitrogen species (ROS/RNS), proteins can undergo a wide range of reversible and irreversible chemical modifications. Among the most commonly formed functional groups and products are *S*-nitrosothiol (SNO), sulfenic acid (SOH), disulfides with protein thiols or low molecular mass thiols (e.g., with glutathione, SSG), sulfinic acid (SO_2H), sulfonic acid (SO_3H), nitrotryptophan, nitrotyrosine, and dityrosine. Adapted from ref 317. Copyright 2013 American Chemical Society.

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hydrocarbons (PAH), and nitrogen oxides (NO_x); among the secondary pollutants are ozone, nitrates, and secondary organic aerosols (SOA).[38,70,273,283] A recent review concluded that epidemiological studies were restricted by imprecise methods of assessing both TRAP exposure and related health effects.[283] Accordingly, several studies called for more comprehensive investigations of TRAP markers, personal exposure, and lifetime outcomes.[281,294,295] The application of improved measurement and modeling techniques as outlined above should enable refined epidemiological studies and more targeted testing of hypotheses by resolving different types of TRAP (e.g., freshly emitted DEP vs resuspended road dust; soot and polycyclic hydrocarbons vs trace metals; ozone vs nitrogen oxides; etc.).

3. CHEMICAL MODIFICATION OF PROTEINS AND AMINO ACIDS

Chemical modification by air pollutants can lead to changes in the structure of protein macromolecules (amino acid oxidation, peptide backbone cleavage, conformational changes, cross-linking, and oligomerization), and affect protein stability and other properties, such as hydrophobicity and acidity of binding sites.[296−303] These and other posttranslational protein modifications may induce multiple effects in the molecular interaction of allergens with the immune system: (1) stability effects influencing the accumulation and degradation of allergenic proteins, the duration of exposure times to cellular receptors, and the process of antigen presentation via major histocompatibility complex (MHC) class II;[304,305] (2) epitope effects, that is, generation of new epitopes or modification of existing epitopes, changing the binding properties of antibodies and receptors, by direct chemical modification or as a result of conformational changes; (3) adjuvant effects, that is, generation of new adjuvant functions or modification of existing adjuvant functions such as lipid-binding capacities due to modified ligand binding sites; and (4) agglomeration effects, that is, multiplication or shielding of epitopes or adjuvant functions by cross-linking (oligomerization) of allergenic proteins, which may enhance the cross-linking of effector cell receptors (FcεRI) or sterically hinder molecular and cellular interactions.[307,308306229]

In the atmosphere, reactive oxygen and nitrogen species (ROS/RNS) are generated via photochemistry and gas-phase, heterogeneous, and multiphase reactions involving atmospheric oxidants and aerosol particles. In the human body, ROS/RNS can be formed upon exposure to air pollutants[38,309−312] or radiation (UV, X-rays, γ-rays),[313] and by regular physiological reactions.[314] For example, ROS/RNS are generated during oxidative metabolism as well as in cellular responses to foreign or danger signals (cytokines, xenobiotics, bacterial invasion).[315] Low amounts of ROS/RNS are involved in intra- and intercellular redox signaling processes, for example, oxidizing low molecular mass thiols and protein thiols (Figure 3).[316,317] An imbalance between oxidants and antioxidants in favor of oxidants (e.g., induced by air pollutants) can lead to irreversible damage of cellular lipids, proteins, nucleic acids, and carbohydrates, eventually resulting in cell death.[38,317,318] Rising levels of atmospheric oxidants and air particulate matter may lead to protein modifications in the atmosphere, as well as in the human body because of elevated oxidative stress levels, especially in the epithelial lining fluid (section 4).[38] Moreover, air pollutants and climatic stress factors, such as UV radiation, drought, salinity, and temperature extremes, can also induce higher ROS/RNS levels inside plants, which may lead to chemical modification of plant proteins, including allergens.[38,142,143] In the course of the Anthropocene, the ambient concentrations of many ROS/RNS have strongly increased because of emissions from traffic and combustion sources, as well as other industrial and agricultural activities like nitrogen fertilization of soils.[37,38,82,319,320]

In the following, we focus on irreversible modifications of allergenic proteins, such as oxidation, nitration, and cross-linking (Figure 3) by endogenous and exogenous ROS and RNS, like ozone (O_3), hydroxyl radicals (OH), hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), nitric oxide (NO), nitrogen dioxide (NO_2), nitrous acid (HONO), nitric acid (HNO_3), peroxyacetylnitrate (PAN), peroxynitrite ($ONOO^-$), and nitrate radicals (NO_3). ROS and RNS can react with oxidation-sensitive amino acids, such as cysteine (Cys), methionine (Met), tryptophan (Trp), tyrosine (Tyr), phenylalanine (Phe), and histidine (His), as well as with aliphatic side chains and the peptide backbone.[317,321−324] For example, OH radicals can cause backbone cleavage by abstracting hydrogen atoms from the α-carbon of any amino acid in the polypeptide backbone. Subsequent reactions lead to oxidative degradation of the protein and the formation of amide and carbonyl groups.[321,325,326] Oxidation reactions can result in aggregation, fragmentation, and denaturation of proteins.[327−329] While oxidative degradation appears likely to reduce the recognition of allergenic proteins, other chemical modifications, such as nitration or cross-linking may enhance the potency of allergens.[8,229,306−308,328,330−332]

The reaction of proteins with nitrating agents leads mainly to the nitration of the aromatic amino acid tyrosine forming 3-nitrotyrosine (NTyr).[333] The addition of the rather bulky NO_2 group at the ortho position of the aromatic ring induces a significant shift in the pK_a value of the tyrosine residue (Tyr) from ∼10 to ∼7, thus increasing the acidity of the hydroxyl group. These structural and chemical changes of the amino acid can affect the conformation and function of proteins.[334,335] For example, the modification of tyrosine residues can influence cell signaling through the important role of receptor tyrosine kinases, which are key regulators of cellular processes.[336] Moreover, nitrotyrosine has been reported as a biomarker for oxidative stress, inflammation, and a wide range of diseases.[296,301,337,338]

Early immunological studies already suggested that dinitrophenyl derivatives of proteins and peptides evade immune tolerance and boost immune responses.[339,340] As early as 1934, the allergic reaction to dinitrophenol was described,[341] and dinitrophenyl haptens became very popular reagents for the experimental induction of allergies.[342−344] Thus, nitrated aromatics and especially nitrophenols can be considered corner stones in the field of allergy research, suggesting that protein nitration by air pollutants might play a role in the development of allergies.[330]

Indeed, several studies showed enhanced allergenic potentials for nitrated pollen allergens,[229,305,306] nitrated fungal allergens,[237] and nitrated food allergens.[304,345] For example, the most efficiently nitrated tyrosine residue in the food allergen ovalbumin (OVA) is part of human and murine IgE epitopes and also belongs to a human T cell epitope.[304] Recent studies suggest that nitration may also affect the allergenic potential and adjuvant activity of α-amylase/trypsin inhibitors (ATIs) from wheat and other gluten-containing grains, which act as aeroallergens in baker's asthma and are involved in hyper-

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sensitivities and chronic inflammation of the gastrointestinal tract.[346−351] Nitrated variants of the major birch pollen allergen Bet v 1 induced enhanced levels of specific IgE in murine models, possibly because of the formation of neo-epitopes.[229] Nitration of Bet v 1 also increased the presentation of allergen-derived peptides by antigen presenting cells (APC).[305] Moreover, increased proteolytic stability, up-regulation of CCL17 (Th2-associated chemokine secreted by dendritic cells, DC), and alterations of T cell proliferation and stimulatory capacities have been observed for nitrated Bet v 1.[306] Nitrated proteins also have been observed to modulate the antioxidant levels in murine pneumocytes.[352] In a recent study, in vivo fumigation of ragweed pollen with NO_2 resulted in an altered proteomic pattern including nitrosylation products and the treated pollen showed higher IgE recognition in immunoblots.[239] Enhanced allergenic potential was also observed for *Betula pendula*, *Ostrya carpinifolia*, and *Carpinus betulus* pollen after NO_2 exposure (Table S1).[236]

Reaction product studies and kinetic experiments have shown that environmentally relevant O_3 and NO_2 concentrations can induce protein nitration on tyrosine residues.[237,328−330,333,353−355] This is in line with earlier observations that atmospheric oxidation and nitration processes leads to the formation of nitrophenols and dinitrophenols,[356] and that nitration is an important reaction pathway particularly in the atmospheric aqueous phase.[357,358] Especially, aromatic amino acids like tyrosine and tryptophan can react with atmospheric nitrating agents, such as ozone/NO_2 mixtures or peroxyacetylnitrate (PAN).[330,359] Under photochemical smog conditions in polluted urban environments (high O_3 and NO_2 concentrations), proteins on the surface of aerosol particles can be efficiently nitrated within minutes to hours.[328,330] The reaction kinetics also depends strongly on ambient relative humidity: At high relative humidity and especially during aqueous phase processing (when aerosol particles are activated as cloud or fog droplets), nitration may proceed efficiently also within the particle bulk.[328,360,361]

Mechanistically, the reaction between O_3/NO_2 and tyrosine involves the formation of long-lived reactive oxygen intermediates (ROI), likely via hydrogen abstraction from the phenolic OH group, yielding tyrosyl radicals (phenoxy radical derivatives of tyrosine) that can further react with NO_2 to form nitrotyrosine residues as shown in Figure 4.[329,362,363] The two-step protein nitration by air pollutants is similar to the endogenous nitration of proteins by peroxynitrite ($ONOO^-$)[298,328,364] formed from nitrous oxide (NO) and superoxide anions (O_2^-).[301,365,366] For endogeneous protein nitration by $ONOO^-$, both radical and electron transfer reaction pathways have been proposed.[367] Besides nitration, tyrosyl radicals can also undergo hydroxylation or self-reaction (cross-linking) to form dityrosine derivatives (Figure 4).[368]

The site selectivity of protein nitration is influenced by the molecular structure of the protein, the nitrating agent, and the reaction conditions. For example, different preferred reaction sites were observed for the birch pollen allergen Bet v 1, the egg allergen ovalbumin, and bovine serum albumin.[304,328,333,354] Upon exposure of Bet v 1 to atmospherically relevant concentrations of O_3/NO_2 and physiologically relevant concentrations of $ONOO^-$, the preferred sites of nitration were tyrosine residues with high solvent accessibility and within a hydrophobic environment. Accordingly, nitrated tyrosine residues occurred mainly in the C-terminal helix and in the hydrophobic cavity (Figure S4).[328] Both are key positions for

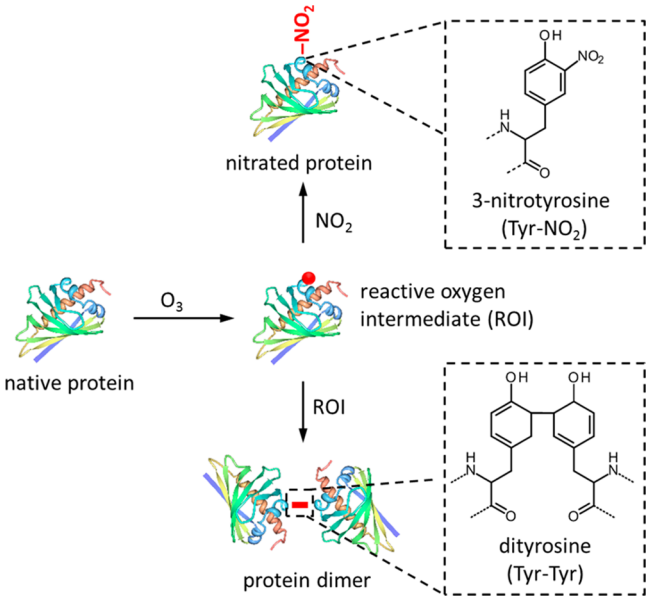

Figure 4. Posttranslational modification of proteins exposed to ozone (O_3) and nitrogen dioxide (NO_2). The initial reaction with O_3 leads to the formation of reactive oxygen intermediates (ROI, tyrosyl radicals), which can further react with each other to form cross-linked proteins (dityrosine) or with NO_2 to form nitrated proteins (nitrotyrosine). The shown protein is Bet v 1.0101 (PDB accession code 4A88,[370] created with the PDB protein workshop 3.9[498]), for which nitration and cross-linking were found to influence the immunogenicity and allergenic potential.[229,305,306,328] Red dot indicates a tyrosyl radical; red bar indicates dityrosine cross-link.

the binding of specific IgE,[369] as well as ligands like fatty acids, cytokines, and flavonoids.[370−372] The binding of such ligands may be involved in allergic and inflammatory immune responses by stabilizing Bet v 1 against endo/lysosomal degradation.[373] Moreover, nitration-related changes in ligand-binding capacity might influence the interaction of allergenic proteins like Bet v 1 with adjuvant substances like lipopolysaccharide (LPS) and induce a shift from Th1 to Th2 responses, thus resulting in increased allergenicity.[306]

Dimerization and oligomerization are supposed to have a strong influence on the immunogenicity of allergenic proteins and are common features of major allergens like Bet v 1.[307,308] The cross-linking of IgE receptors (FcεRI) on effector cells is a key element of allergic reactions and requires IgE antibody clustering on the cell surface,[374,375] which may be facilitated by multivalent allergens, such as oligomers of allergenic proteins providing multiple epitopes of the same kind.[122,376] Moreover, cross-linking can make proteins less susceptible to enzymatic proteolysis and influence immune responses.[313,373,377] Indeed, immune responses to oligomers and aggregates of certain allergenic proteins were found to be enhanced compared to the monomeric form of the allergenic protein.[307,308,378−380] The clustering of allergenic proteins on nanoparticle surfaces (protein coronas) can also modulate allergic respones depending on protein and particle properties.[244] Accordingly, the investigation and effects of allergen colocalization on the surface of inhalable ambient particles, such as pollen fragments or soot (DEP), are potentially important research perspectives.

Oxidative protein cross-linking can occur upon (a) tyrosyl radical coupling through dityrosine cross-links, (b) Schiff-base coupling of oxidation-derived protein carbonyl groups with the ε-amino groups of lysine residues, and (c) intermolecular

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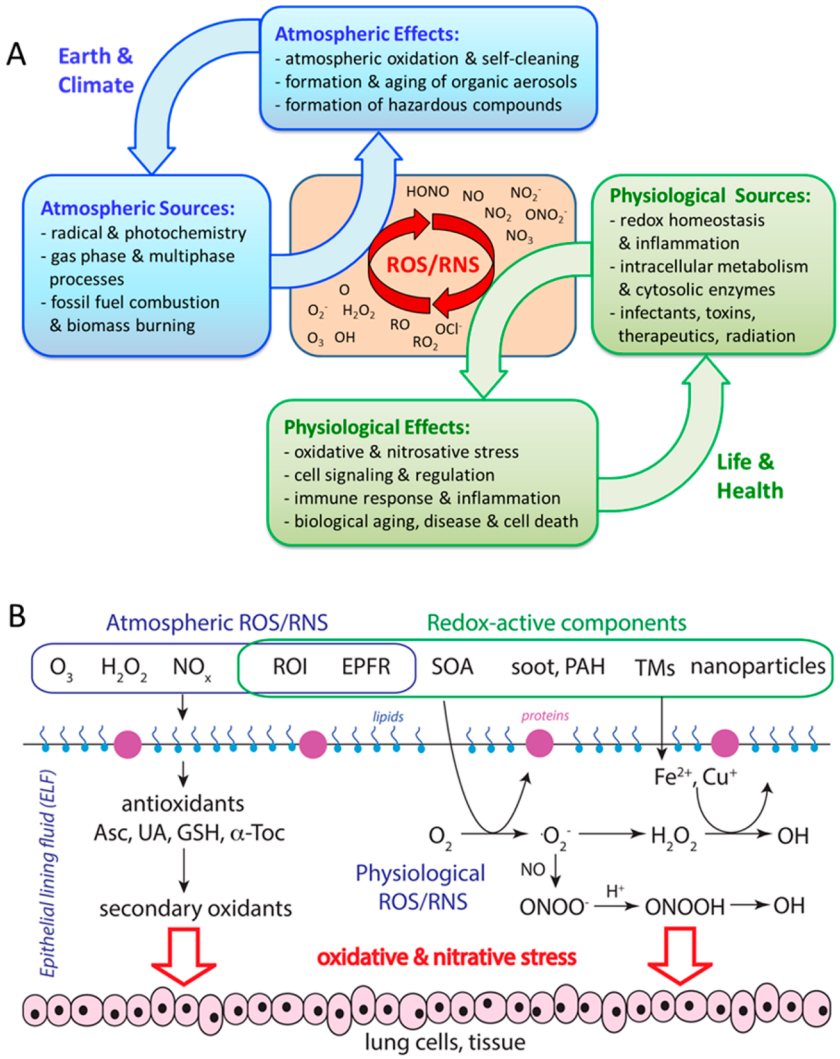

Figure 5. (A) Sources, effects, and interactions at the interface of atmospheric and physiological chemistry with feedback loops involving Earth System, climate, life, and health. (B) Interactions of atmospheric and physiological ROS/RNS with antioxidants (ascorbate, uric acid, reduced glutathione, α-tocopherol) in the epithelial lining fluid (ELF) of the human respiratory tract. Redox-active components, including reactive oxygen intermediates (ROI), soot, quinones and transition metals can induce ROS formation in vivo, leading to oxidative stress and biological aging. Adapted from ref 38. Copyright 2015 American Chemical Society.

disulfide coupling.[381] Recently, protein cross-linking and oligomerization upon exposure to atmospherically relevant concentrations of O_3 have been shown to proceed via the formation dityrosine cross-links as outlined in Figure 4, yielding up to ~10% of dimers, trimers, and higher oligomers of a model protein within minutes to hours of exposure under summer smog conditions.[368] Similar reaction mechanisms involving reactive oxygen intermediates may also be responsible for the protein cross-linking observed upon reaction with physiological and synthetic nitrating agents like $ONOO^-$ and tetranitromethane, respectively.[306,313,382,383] Cross-linking upon reaction with tetranitromethane was suggested to alter the immunogenicity and enhance the allergenicity of Bet v 1 through decreased endolysosomal degradation leading to extended MHC class II antigen presentation.[306] On the other hand, oligomerization of allergens induced by modification with glutaraldehyde, that is, formation of glutaraldehyde bridges between nucleophilic amino acid residues (in particular lysine), was suggested to reduce immunogenicity and allergenicity due to delayed allergen uptake and presentation by dendritic cells.[384,385]

As illustrated in Figure S2, the processes of allergic sensitization and response involve a wide range of interactions between protein molecules dissolved in liquids (blood, lymph, etc.) and embedded in semisolid structures (membranes, cells, tissues), which can be regarded as protein multiphase chemistry.[38] Protein reactions with ROS/RNS are generally pH-dependent and yield a mixture of hydroxylated, nitrated, cross-linked, aggregated or degraded products.[386−391] To assess immune responses to specific posttranslational modifications of proteins, it is necessary to carefully characterize the investigated samples and avoid artifacts or misinterpretations that might arise from interferences between different reaction products and pathways, for example, nitration vs dimerization or oligomerization of proteins exposed to oxidizing and nitrating agents (Figure 4).

4. EPITHELIAL SURFACE INTERACTIONS

The deposition of particles in the respiratory tract is size-dependent and deposited particles are removed by a number of physical, chemical, and biological clearance processes, including

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mucociliary movement, endo- and phagocytosis, dissolution, leaching, and protein binding.[201] Thus, the first step of an inhaled allergen-carrying particle is evading the mechanical defenses of the respiratory tract and passing, for example, alveolar macrophages, which prevent inappropriate immune activation by removing inhaled allergens via phagocytosis.[392−394] The epithelial surface is a protective barrier, which protects the underlying tissue from many inhaled substances. The epithelial cells are covered by a viscous mucosal lining rich in immune cells and soluble components, such as antioxidants, complement proteins, and surfactant proteins.[201,395,396] As the epithelium is more than a passive protective barrier, it recruits and activates more specialized immune cells and promotes inflammatory responses,[397] allergy is also discussed to be an epithelial barrier disease.[15,131,398−400] For example, nasal epithelium is clearly different between healthy and allergic subjects and only in allergic subjects the transport of Bet v 1 is caveolar-mediated.[401]

Air pollutants interacting with epithelial surfaces can act as adjuvants promoting pro-allergic innate and adaptive immune reactions as outlined in Table 2 and section S1. For example, they can induce inflammation and disrupt epithelial barriers, facilitating the access of allergens to immunogenic effector cells.[8,86] In particular, air particulate matter can trigger ROS production through Fenton-like reactions and the activation of macrophages, mitochondria and enzymes related to the oxidant/antioxidant balance (e.g., NADPH oxidase, glutathione peroxidase).[309,310,402−405] Additionally, pollution-derived ROS can induce proinflammatory responses by the production of damage associated molecular patterns (DAMPs oxidized phospholipids, hyaluronic acid, etc.) and trigger immune reactions leading to acute or chronic inflammation,[29,406] for example, through feedback cycles involving Toll-like receptors (TLR) and other pattern recognition receptors (PRR) (Figure S5).[407] Ozone and particulate matter can prime the airways for pro-allergic responses, and TLR signaling plays an important role in pollutant-induced inflammation.[408,409] During inflammation, inducible nitric oxide synthase (iNOS) that is mainly expressed in innate immune cells (monocytes, macrophages, dendritic cells) provides high amounts of nitrogen oxide (NO), which can react with superoxide radicals to form peroxynitrite ($ONOO^-$), a central endogenous nitrating agent for proteins.[301] In addition, particulate and gaseous pollutants may also drive pro-allergic inflammation through the generation of oxidative stress involving elevated levels of $ONOO^-$.[410]

As illustrated in Figure 5A, epithelial surfaces are interfaces coupling the atmospheric and the physiological production, cycling, and effects of ROS/RNS.[38] Specific interactions of atmospheric ROS/RNS with antioxidants in the epithelial lining fluid are shown in Figure 5B. An increase of ozone from typical background concentration levels (∼30 ppb) to summer smog conditions (>100 ppb) reduces the chemical half-life of antioxidants from days to hours,[309] which may be comparable or shorter than the physiological replenishment rates.[411] Furthermore, the adjuvant effect of ambient ultrafine particles was correlated with their oxidant potential.[412] Major contributors to the redox properties of ambient particles are transition metals, polycyclic aromatic hydrocarbons, and derivatives (PAH, nitro/oxy-PAH), and semiquinones.[38,312,412−415] In addition, the deposition of acidic particles may reduce the pH of the epithelial lining fluid (ELF). For healthy people the mean pH is ∼7.4, while in people with diseases (e.g., asthma, acid reflux) it can be as low as ∼4.[416,417] Oxidant exposure and changes of pH can alter reaction pathways of antioxidants[418] and also decrease the activities of antioxidant-related enzymes in the ELF, which are also reduced in smokers and people suffering from lung diseases.[419−421]

Recent studies yielded chemical exposure-response relations between ambient concentrations of air pollutants and the production rates and concentrations of ROS in the ELF of the human respiratory tract.[309] As illustrated in Figure 6, the total

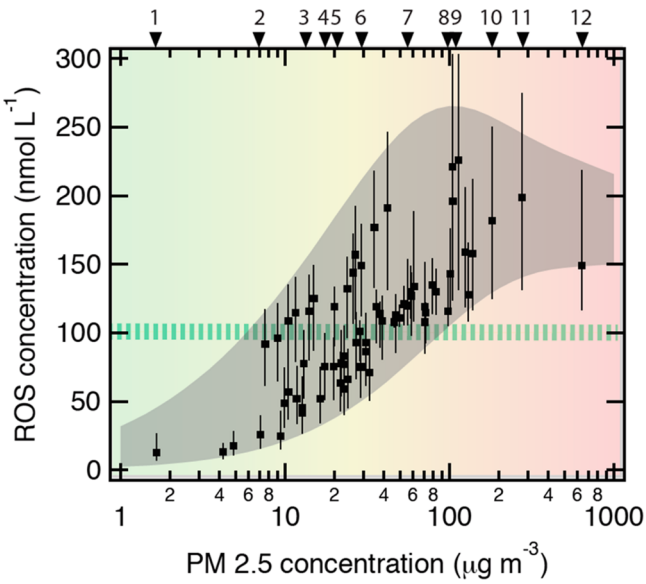

Figure 6. Chemical exposure-response relations between ambient concentrations of fine particulate matter (PM2.5) and the concentration of reactive oxygen species (ROS) in the epithelial lining fluid (ELF) of the human respiratory tract. The green-striped horizontal bar indicates the ROS level characteristic for healthy humans (∼100 nmol L^{-1}). The gray envelope represents the range of aerosol-induced ROS concentrations obtained with approximate upper and lower limit mass fractions of redox-active components observed in ambient PM2.5. The data points represent various geographic locations for which measured or estimated mass fractions are available, including (1) Amazon, Brazil (pristine rainforest air); (2) Edinburgh, UK; (3) Toronto, Canada; (4) Tokyo, Japan; (5) Budapest, Hungary; (6) Hong Kong, China; (7) Milan, Italy; (8) Guangzhou, China; (9) Pune, India; (10) Beijing, China; (11) New Delhi, India; (12) Sumatra, Indonesia (biomass burning/peat fire smoke). Adapted from Lakey, S. J. P.; Berkemeier, T.; Tong, H.; Arangio, A. M.; Lucas, K.; Pöschl, U.; Shiraiwa, M. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. *Sci. Rep.* **2016**, *6*, 32916. DOI: 10.1038/srep32916.[309] Copyright 2016 Lakey et al.

concentration of ROS generated by redox-active substances contained in fine particulate matter (PM2.5) deposited in the ELF ranges from ∼10 nmol L^{-1} under clean conditions up to almost ∼250 nmol L^{-1} under highly polluted conditions. Thus, the inhalation of PM2.5 can increase ROS concentrations in the ELF to levels that exceed physiological background levels (50−200 nmol L^{-1}) and are characteristic for respiratory diseases.[309,422] In addition to the effects of PM2.5, ambient ozone readily saturates the ELF and can enhance oxidative stress by depleting antioxidants and surfactants.[309] Ozone also reacts with skin lipids (e.g., squalene) and generates organic compounds (e.g., mono- and dicarbonyls) that can act as irritants.[269] These and related organic compounds were found to act as adjuvants in the development of respiratory allergies as well as atopic dermatitis.[270,271,423,424] Some air pollutants and

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chemical reaction products formed at epithelial interfaces are sufficiently long-lived and mobile to diffuse through membranes and interact with the neural, cardiovascular, and immune system networks of the human body.[314,425−429] Through these and related physiological interactions involving DAMPs, inflammatory mediators, cytokines, leukocytes etc., oxidative stress and inflammation caused by air pollutants may propagate from the respiratory tract and skin to other parts of the human organism and exert systemic influence on the development of allergies, reaching also the gastrointestinal tract.[38,429]

A wide variety of commensal, symbiotic, and pathogenic microorganisms are found on the epithelial surfaces of the human body, such as the skin, lungs, and the gastrointestinal tract. Recent research suggests that the human microbiome is important to maintain physiological functions and to induce immune regulation by balancing the activities of Th1 and Th2 cells.[430−433] Normal microbial colonization in early life can promote tolerance to aeroallergens via induced regulatory T cells.[434] The development and composition of the human microbiome are influenced by many factors such as diet, infections, medical treatment, and also environmental factors.[435] For example, air pollutants and climatic stress factors may disturb microbial communities through oxidative stress, inflammation, and changes in environmental biodiversity.[4,36] Modifications in the composition of the gastrointestinal and lung microbiome can in turn affect the development of allergies in accordance with the "hygiene hypothesis"[36,436−440] and may also promote pathogenic species that can contribute to these diseases.[4,441−443] Recent studies revealed differences in the structure and composition of microbiota in the lower airways of healthy and asthmatic people: *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* are the most common phyla found in airways of healthy subjects, whereas increased concentrations of pathogenic Proteobacteria, such as *Haemophilus*, *Moraxella*, and *Neisseria* spp., were found in asthma patients.[442,443] Moreover, viral infections can exacerbate allergies.[31] It is still unclear, however, if these changes are a cause or a consequence of the disease. Moreover, it has been suggested that air pollutants, especially air particulate matter, ingested together with food can trigger and accelerate the development of gastrointestinal inflammatory diseases by altering the gastrointestinal microbiome and immune functions.[444] Besides the human microbiome, also microbes associated with allergenic pollen (pollen microbiome) and other aeroallergens may act as adjuvants when deposited on epithelial surfaces.[235,445]

5. CONCLUSIONS AND OUTLOOK

As the globally pervasive anthropogenic influence continues to shape planet Earth and the human environment in the Anthropocene, it becomes increasingly important to understand and assess the potential effects of environmental change on human health. The widespread increase of allergies and their complex dependence on multiple influencing factors, including environmental pollution, indicate that allergic diseases are a major challenge with regard to maintaining and improving public health.

Anthropogenic emissions of atmospheric trace substances are affecting air quality and climate on local, regional, and global scales. Changes in atmospheric aerosol composition, oxidant concentrations, and climate parameters can induce chemical modifications of allergens, increase oxidative stress in the human body, and skew the immune system toward allergic reactions. In particular, air pollutants can act as adjuvants and alter the immunogenicity of allergenic proteins, while climate change affects the abundance and properties of bioaerosols as carriers of aeroallergens. The production, release and properties of allergens and adjuvants are subject to various human interferences with the biosphere and climate system, including air pollutant interactions with natural and agricultural vegetation, fertilization and land-use change, as well as plant breeding and genetic engineering.

The following key questions remain to be resolved to understand and mitigate potential effects of air pollution and climate change on the observed increase and future development of allergies:

(Q1) Which air pollutant and climate change effects have the largest potential to influence on the abundance and potency of allergens and adjuvants in the human environment (indoor and outdoor)?

(Q2) Which elements and reaction pathways of the immune system are particularly susceptible to disturbance by air pollutants, and what are the most relevant chemical and physiological mechanisms (adjuvant activity vs allergen modification)?

(Q3) Which environmental and physiological parameters are needed and best suited to account for and assess air pollutant and climate change effects in epidemiological studies of allergic diseases (attribution and prediction of environmental risk factors)?

(Q4) How important are air pollutant and climate change effects relative to other environmental, lifestyle, genetic and epigenetic risk factors for allergic diseases?

Recommendations on how to address these key questions in future research are listed in Table S2, building on and extending suggestions given in related review and perspective articles (e.g., refs 8, 12, 93, and 280). Beyond addressing the above questions, it appears worthwhile to explore which components of the immune system could be modulated to prevent adverse effects of air pollution, for example, whether therapeutic monoclonal antibodies against relevant cytokines (e.g., IL-4, IL-5, IL-13) or IgE antibodies could make a difference. Further information about ongoing efforts and future perspectives of mitigating the health effects of climate change and air pollution is available from various national and international government agencies, medical institutions and related organizations (e.g., refs 4, 37, and 446). For efficient scientific progress, it will be important to combine and optimize state-of-the-art methods and results of environmental, immunological and epidemiological studies, tightly coupling physical, chemical, biological, and medical techniques and knowledge. One of the challenges consists in identifying and quantifying the mechanisms and feedback loops of immunochemical reactions in response to environmental influencing factors, including chemical modifications and interactions of allergens and adjuvants under realistic environmental and physiological conditions. For this purpose, the results of laboratory experiments and monitoring networks with improved detection methods for allergens, adjuvants and reactive intermediates should be used to design and inform epidemiological studies targeting the effects of different types and combinations of air pollutants and climate parameters.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b04908.

Allergic sensitization and response, air pollution effects on the allergenic potential of plant pollen and fungal spores, research activities proposed to address the key questions, essential steps and influencing factors in the development of IgE-mediated allergies, simplified scheme of major processes involved in allergic sensitization and response, scanning electron micrographs of oak and birch pollen, 3D-structure of the major birch pollen allergen Bet v 1.0101, and TLR4-radical cycle of inflammation (PDF)

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Notes

The authors declare no competing financial interest.

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Supporting Information:

Air Pollution and Climate Change Effects on Allergies in the Anthropocene: Abundance, Interaction and Modification of Allergens and Adjuvants

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The supplementary material includes: Supplementary Section S1, Supplementary Tables S1-S2, Supplementary Figures S1-S5

Section S1. Allergic Sensitization and Response

Essential steps and influencing factors in the development of IgE-mediated allergies (type I hypersensitivities) are outlined in Figure S1. Here, the term atopy refers to the genetic predisposition to mount IgE-responses to common allergens.[1] Genetic and epigenetic effects can also influence the further development of allergies that can be triggered by lifestyle and environmental factors. Among the lifestyle and environmental risks are allergen exposure, reduced childhood exposure to pathogens and parasites (hygiene hypothesis), diet/nutrition, psychological/social stress, and environmental pollution, including outdoor and indoor air pollutants (ozone, nitrogen oxides, diesel exhaust particles, tobacco smoke, etc.), which may effectively lead to an over- or under-stimulation of the immune system.[2-22] Figure S2 shows a simplified overview of cellular and molecular interactions that are central to the processes of allergic sensitization and response, involving elements of both adaptive and innate immunity.[2]

Allergic sensitization and Th2 cells

The term allergic sensitization describes the first induction of an allergic immune response upon exposure to an allergen, which is a multifactorial process that depends on the status of the immune system, the epithelium, the type and concentration of allergens and adjuvants, as well as the timing of exposure.[2, 23-28] During the sensitization process, the allergens cross epithelial barriers and are internalized by antigen presenting cells (APC), primarily dendritic cells (DC) as sentinels of the immune system. In the endolysosomal compartments of the DC, allergenic proteins are enzymatically cleaved, the allergen-derived immunodominant peptides are bound by the major histocompatibility complex (MHC) class II, and the MHC class II-peptide complex is presented on the surface of the DC. Depending on cytokines and other factors derived from epithelial cells and the surrounding micromilieu (e.g., IL-25, IL-33, TSLP), the DC are activated and migrate to secondary lymphoid organs such as the local draining lymph nodes or mucosal-associated lymphoid tissues.[29-32] There the DC interact with naïve T helper cells, and at least one of the allergen-derived immunodominant peptides presented by the DC is recognized as a T cell epitope binding to a T cell receptor (TCR). Recognition by the TCR induces T helper cell activation and differentiation into Th cells with a Th2 cytokine profile (mainly IL-4 and IL-13) depending on additional costimulatory signals from the DC and the

surrounding micromilieu, which are influenced by adjuvants as detailed below. These secondary signals involve various types of molecules (e.g., CD80, CD86, PD-1, ICOS, CLTA-4, CD40, OX-40) that can promote the development of an inflammatory allergic reaction or favor immune regulation leading to tolerance of the allergen.[33]

Through interaction with complement molecules of the innate immune system (opsonization) and with follicular dendritic cells, allergens are also collected in the follicles/germinal centers of secondary lymphoid organs.[34-44] There, the allergenic proteins interact with B cells via the B cell receptors (BCR), which recognize epitopes on the protein surface (B cell epitopes). The BCR contains the same antigen-binding fragment (Fab) as the antibodies produced by the B cell. Th2 cytokines and ligation of CD40 on the B cell surface with CD40 ligand on the Th2 cell surface induce an immunoglobulin class switch to the production of allergen-specific IgE antibodies. The binding between the allergen and the Fab region is optimized in the course of affinity maturation by somatic hypermutation of the Fab region and clonal selection of B cells, leading to a differentiation of B cells into antibody secreting plasma cells and memory cells.[25] The IgE production by B cells is controlled by T helper cells and regulatory T cells (Treg), whereby Th1 and Treg cells secreting IFN-gamma, IL-10 and TGF-beta dominate the regulation in healthy individuals and during successful allergen-specific immunotherapy.[45-46] Allergic diseases are mainly characterized by Th2 cell-mediated inflammation, whereas bacterial or viral infections normally lead to Th1 cell-mediated inflammation.[47]

Allergic response and IgE antibodies

Upon re-exposure of sensitized individuals to the allergen, the allergenic proteins (B cell epitopes) are recognized by specific IgE antibodies bound to the high affinity IgE-receptors (FcεRI) on effector cells like mast cells and basophils. The recognition and binding of allergens induces IgE cross-linking and activation of the FcεRI receptors, which leads to effector cell degranulation with release of highly vasoactive mediators like histamine that are responsible for the allergic symptoms, such as vascular leakage, edema, and inflammatory cell attraction and activation. Multivalent allergens like protein oligomers exhibiting multiple IgE binding sites (epitopes) on the protein surface are particularly effective in IgE cross-linking and FcεRI

activation, thus initiating especially strong cellular responses over a wide concentration range.[48-50]

Once the allergy is established, enhanced mucosal and tissue levels of IgE favor an immediate or early-phase reaction to the allergen (within minutes), explaining the immediate onset of symptoms upon allergen exposure. The rapid release of mast-cell derived mediators (histamine, leukotrienes, prostaglandins, tumor necrosis factor α) in the early-phase contributes to the rapid influx of other cells characteristic of promoting allergy (e.g. eosinophils, basophils, monocytes). The influx of these cells characterizes the late-phase allergic reaction (which can start 4-12 hours after allergen exposure and persist up 48 hours) with the release of other pro-inflammatory mediators such as lipid mediators and reactive oxygen and nitrogen species (ROS/RNS). The term chronic phase is used to describe persistent inflammation induced by prolonged or repetitive allergen exposure and the presence of large numbers of innate and adaptive immune cells leading to damage of the affected tissues and epithelia (e.g., the pulmonary mucosa in allergic asthma).[51-52] As IgE antibodies and related immune reactions are normally involved in the defense against parasitic infections, allergic reactions can be regarded as "false alarms" of the immune system.[53-56]

Adjuvants and pattern recognition receptors

Adjuvants and their interaction with the immune system play a critical role in the development of allergies. Here we use the term adjuvant generically for substances that are promoting pro-allergic innate and adaptive immune responses. Adjuvants can trigger the immune system by inducing tissue damage and subsequent enhanced uptake of allergens, by inducing oxidative stress and activation of immune cells, by co-exposure with the allergen favoring Th2 responses, or by modification of allergens enhancing their allergic potential. An overview of biogenic and anthropogenic adjuvants and their effects on the immune system is given in Table 2.[26, 57-107] Major substance groups are pollen-associated and microbial compounds (pollen associated lipid mediators (PALMs), lipopolysaccharides (LPS), β-glucans, etc.) and anthropogenic air pollutants (particulate matter, ozone and nitrogen oxides).

Many allergenic proteins have intrinsic adjuvant functions which are mediated, e.g., by protease activity, lipid-binding functions, and carbohydrate residues interacting with the innate

immune sytem.[26, 62, 108-111] More than half of the known major allergens are lipid-binding proteins, and many allergens can bind ligands exhibiting pathogen-associated molecular patterns (PAMPs).[109] PAMPs are structural characteristics of microbial substances like lipopolysaccharides (LPS), flagellin, glucanes, and other biomolecules that are recognized by pattern recognition receptors (PRR) such as transmembrane Toll like receptors (TLR) and C-type lectin receptors.[109, 112-113] For example, the major house dust mite allergen Der p 2 can mimic the function of MD-2, which is a key protein involved in TLR4 activation by LPS.[114]

Besides pathogen-associated molecular patterns, also damage-associated molecular patterns (DAMPs) formed upon oxidative, radiative or heat-induced stress can be recognized by PRR and activate the innate immune system.[93, 112-113, 115] PRR play a critical role in regulating the function of APC and the type of adaptive immune response[110, 116], and the involvement of TLR and other PRR may enhance endocytosis, drive adaptive immune responses, and determine a cytokine bias, linking adaptive and innate immunity.[112, 117] Moreover, TLR and other PRR can mediate self-sustaining cycles of inflammation and may be involved in the development of allergies and related diseases.[93, 115] These cyclic processes comprise the release and formation of cytokines, ROS/RNS, and DAMPs, which in turn can reactivate PRR (see Figure S5, supporting information). They can be triggered by external influencing factors including air pollutants and related oxidative stress.[93, 115]

By recognizing characteristic structures of allergens through PRR, epithelial cells can influence the activation of DC as outlined above as well as the activation of other innate immune cells such as eosinophils, basophils and innate lymphoid cells (ILC), also called non-T, non-B effector cells or natural helper cells. Depending on their capacity to produce Th1, Th2, and other cytokine patterns, ILC are grouped into different subsets. The subset ILC2 can generate high amounts of IL-13, IL-5 and IL-9 in response to IL-25, IL-33 and TSLP leading to eosinophilia and mucus production. They are increased in lung parenchyma, nasal polyps and peripheral blood from asthmatic patients as well as in the skin from patients with atopic dermatitis.[118-123]

Because of the wide variety and complex nature of the cellular and molecular interactions involved in the development of allergies, air pollutants and climate parameters may influence the underlying physiological mechanisms and chemical reactions in many ways.

Table S1. Air pollution effects on the allergenic potential of plant pollen and fungal spores.

Allergenic Species	Exposure	Effects
Ambrosia artemisiifolia (ragweed)	high-traffic roads vs. vegetated areas (Lombardy region, Italy)	increased IgE-binding capacity of pollen protein extracts from polluted environments[124]
	NO_2 exposure	increased IgE reactivity, modified cell wall morphology, increased allergen content, and changed proteomic pattern including S-nitrosylation products and upregulation of other proteins (e.g., 14-3-3 protein)[125]
	O_3 exposure	stimulates NADPH oxidase activity (ROS production) leading to pollen damaging and decreased viability[126]
	O_3 exposure	enhances stress-induced RNA transcripts, cell wall components and wax of the pollen, Amb a 1 content not affected[127]
Canna indica (indian shot)	city vs. rural (Tehran, Iran)	increased number of eosinophils and IgE levels induced by pollen extracts from polluted environments[128]
Cupressus arizonica (arizona cypress)	high-traffic roads vs. vegetated areas (Spain)	increased Cup a 3 content of pollen collected in polluted environments[129-130]
Phleum pratense L. (timothy grass)	high-traffic roads vs. rural site (Bavaria, Germany)	decreased Phl p 5 content of pollen collected in polluted environments[131]
		Increased release of eicasanoid-like pro-inflammatory substances in pollen collected near roads with high traffic[132]
Zinnia elegans (common zinnia)	city vs. rural (Tehran, Iran)	increased skin prick test response observed in guinea pigs, decreased protein content of pollen collected in polluted environments[133]
Betula pendula (birch)	city vs. rural (Munich, Germany)	increased ozone levels increase allergenicity (skin prick test) and Bet v 1 content of pollen[134]
		changes in pollen proteome (e.g., upregulation of 14-3-3 protein), no difference in Bet v 1 content, and enhanced chemotactic activity of pollen extracts from polluted environments[135]
		differences in pollen microbiome, higher bacterial diversity was correlated with the allergen and PALMs content[136]
	NO_2 exposure	decrease in pollen viability, decrease in soluble protein content, increased IgE reactivity[137]
Acer negundo (maple), *Platanus x acerifolia* (London plane)	O_3 exposure	increased IgE reactivity[138]

Aspergillus fumigatus (mold)	exposure to outdoor air (urban area, Israel), and $O_3/NO_2/O_3+NO_2$	exposure time dependent changes of IgE binding capacity, suggested links to chemical modifications of Asp f 1 (e.g., nitration and deamidation) [139]
	combined exposure of mice to DEP and allergen	changes in methylation of genes favoring Th2 polarization and increased IgE production *in vivo* (epigenetics)[92]

Table S2 Research activities proposed to address the key questions raised in the outlook section (Sect. 5, Q1-Q4).

ENVIRONMENTAL STUDIES (Q1)

- Quantify the atmospheric abundance and mixing state of allergenic bioparticles, major allergenic proteins and adjuvant substances (DEP, LPS, PALMs, flavonoids, glucans …) in relation to air quality, meteorological, climate and ecosystem parameters (T, RH, PM, O_3, NO_x, CO_2, vegetation cover, nutrient status ...) using advanced physical, chemical and biological measurement techniques (mass spectrometry, fluorescence spectroscopy and microscopy; genomic and proteomic analyses; immunological assays, etc.)

- Identify and quantify the products, kinetics and molecular mechanisms of air pollutant interactions with natural allergens and adjuvants (nitrated, oxidized, and oligomerized proteins, lipids, flavonoids, etc.) in field studies and laboratory experiments under conditions relevant for outdoor and indoor environments

- Establish and maintain long-term observations to document ongoing and future changes in the release, distribution, and allergenic potential of aeroallergens and adjuvants

IMMUNOLOGICAL STUDIES (Q2)

- Characterize and quantify air pollutant effects on epithelial transport and signaling (permeability, cytokine and mediator release)

- Determine air pollutant effects on the uptake, processing, and presentation of allergens by APCs, changes in allergen epitopes and adjuvant functions, and generation of multivalent allergens

- Investigate the role of air pollutant interactions with airway mast cells and basophils as a potential cause of initial IL-4 release polarizing immunity to Th2 responses

- Explore which components of the immune system could be modulated to prevent adverse effects of air pollution, e.g. whether therapeutic monoclonal antibodies against relevant cytokines (e.g., IL-4, IL-5, IL-13) or IgE antibodies could make a difference.

- Investigate immunological effects of co-exposure to realistic mixtures of allergens and adjuvants (e.g., O_3/NO_x; SOA, DEP, PALMs, LPS, microbes, … etc.) and identify mixtures/synergies leading to particularly strong effects/(immune) responses, including complement interactions and epigenetic effects (e.g., activation of C3 proteins; regulation of genes associated with Th2-polarization and epithelial barrier functions)

- Quantify the effects of chemical modification on the potency of allergens using atmospherically and physiologically relevant rather than artificial reactants and conditions (e.g., allergenic protein and bioparticle exposure to O_3/NO_x and $ONOO^-$ rather than TNM) and resolve potential interferences between different reaction products and pathways, (e.g., nitration vs. dimerization or oligomerization or degradation of protein macromolecules exposed to oxidizing and nitrating agents)

- Explore how chemical modifications of food components due to environmental pollution and related physiological processes may influence the development of chronic inflammation and hypersensitivities in the gastrointestinal tract (e.g., through nitration of amylase/trypsin inhibitors, ATIs)

EPIDEMIOLOGICAL STUDIES (Q3 & Q4)

- Establish and optimize (micro)monitoring networks and air quality models for the assessment and prediction of regional and local sources, concentration levels, and effective allergenic potential of allergens and adjuvants as well as the resulting personal exposure as input for refined epidemiological studies

- Assess the relative importance and potential interrelations of air pollution, other forms of environmental pollution and other influencing factors/risk factors for allergies (e.g., potential effects of air pollution and fertilization and pesticides on the allergenic potential of foods)

- Establish characteristic levels of allergen and air pollutant co-exposure (exposure-response relations) that constitute a substantial risk for the development of allergic diseases

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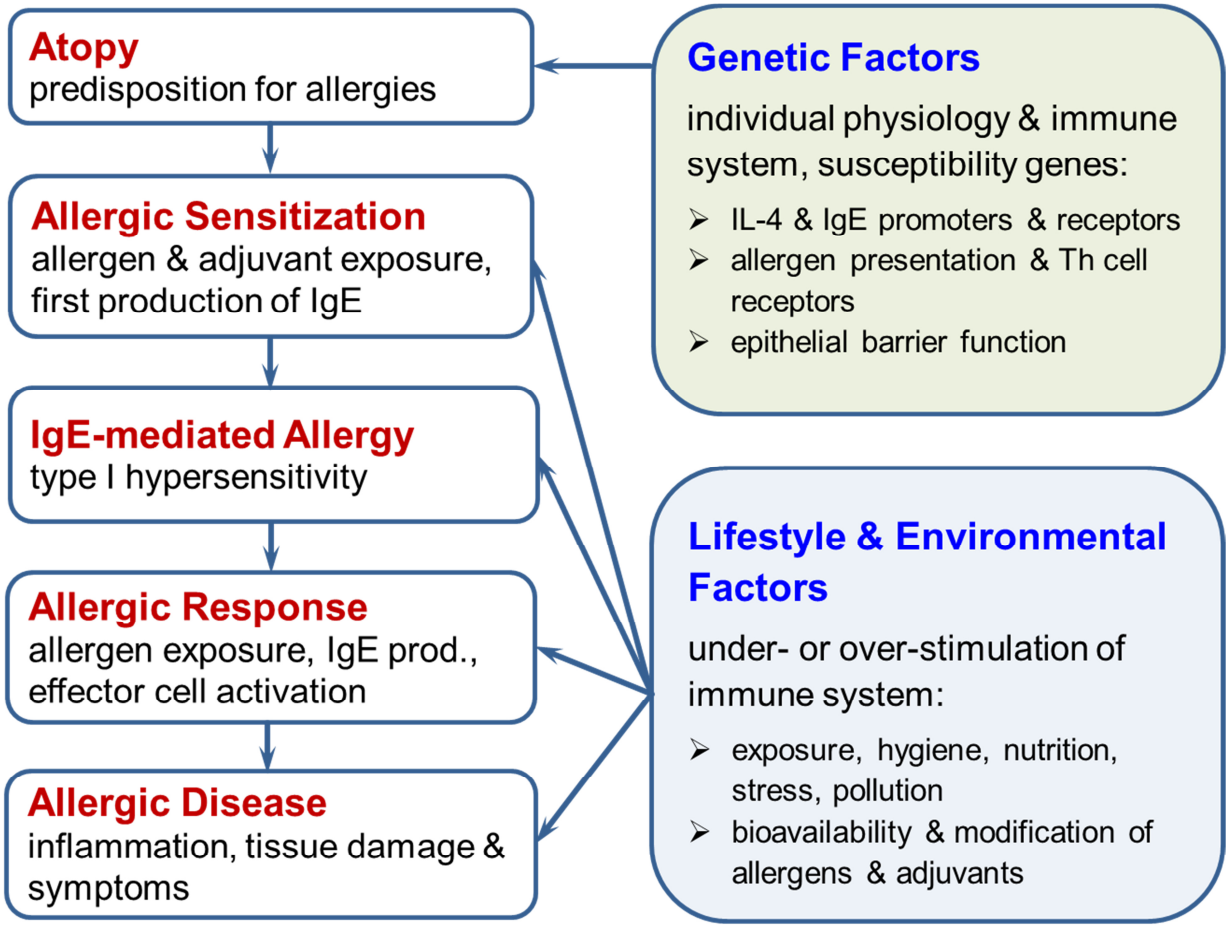

Figure S1.

Essential steps and influencing factors in the development of IgE-mediated allergies (type I hypersensitivities) and related diseases.

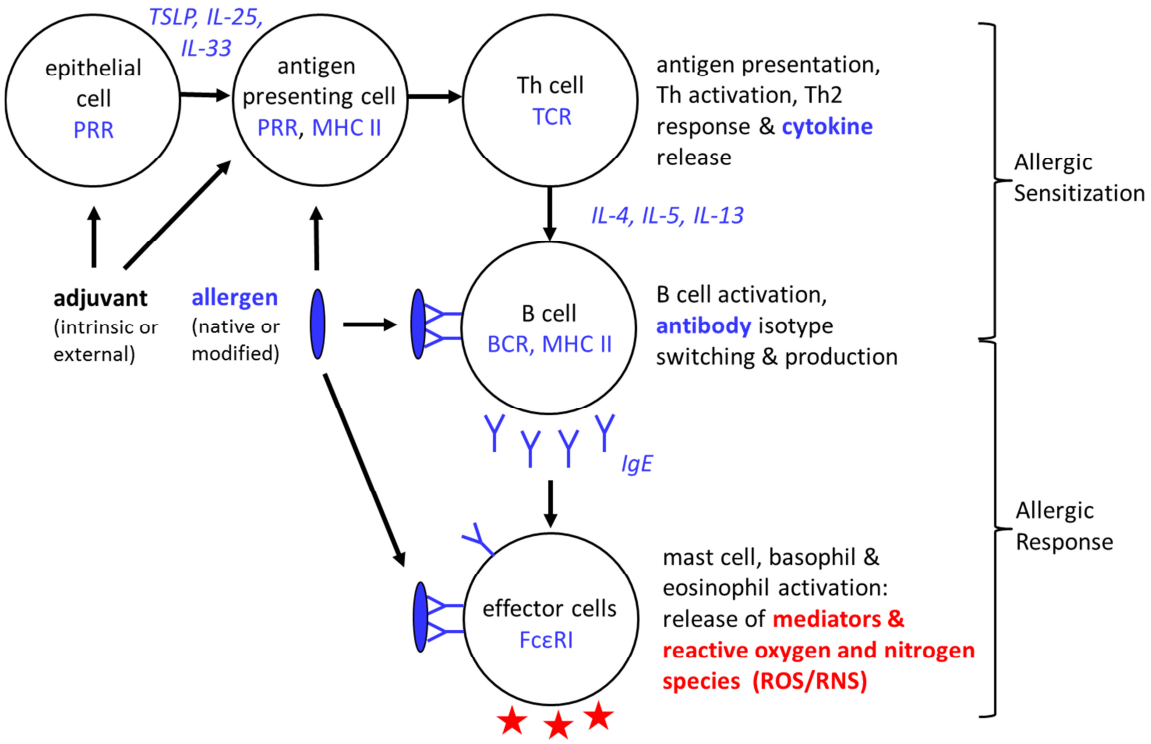

Figure S2.

Simplified scheme of major processes involved in allergic sensitization and response: molecular and cellular interactions of the innate and adaptive immune system with allergens and adjuvants (blue: proteins; red: pro-inflammatory mediators & ROS/RNS).

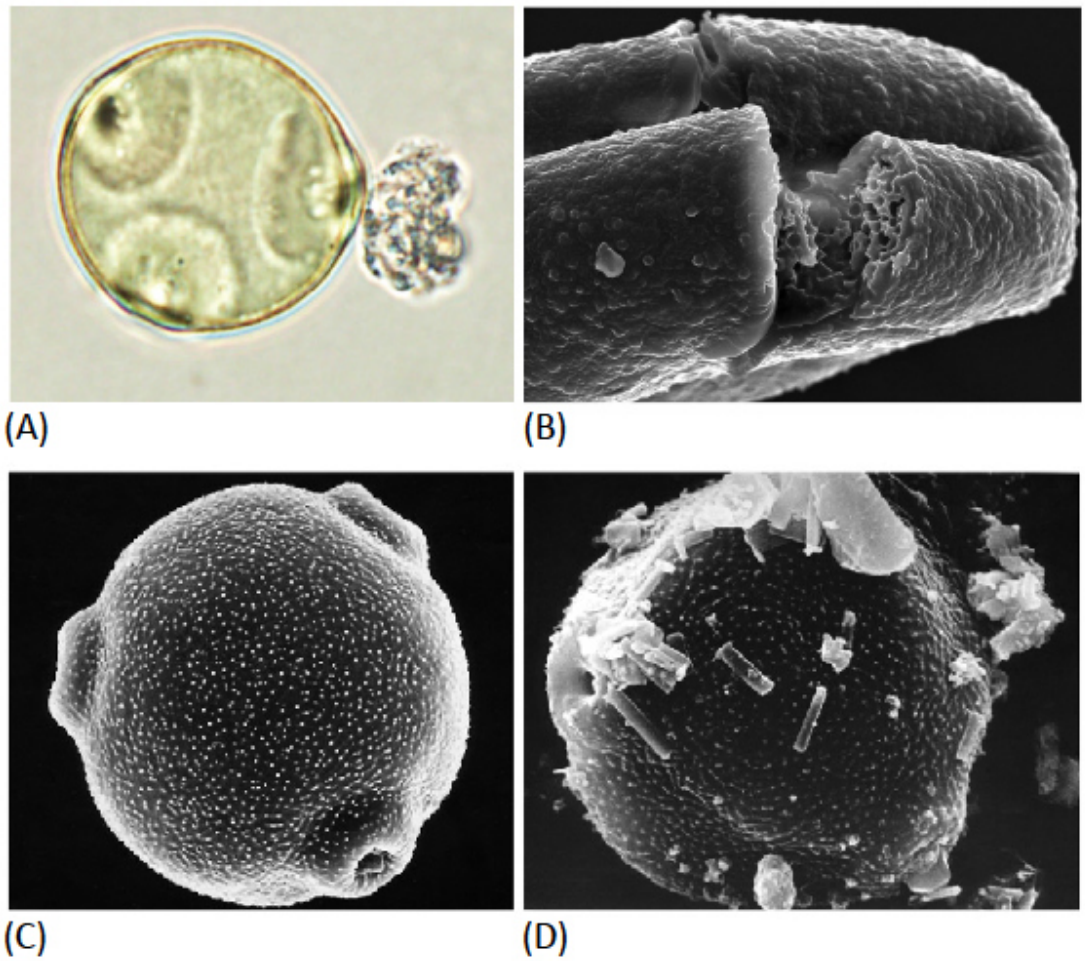

Figure S3.

Scanning electron micrographs of oak and birch pollen. (A) Release of pollen cytoplasmic granules (PCG) from oak pollen grain from pores after the contact with acid solution[140]; (B) oak pollen grains after exposure to 1ppm NO_2 (×4500 magnification)[140]; (C) birch pollen from a rural (C)[141] and (D) an urban collection site[142] . (A) and (B) are reproduced with permission from John Wiley and Sons[140], (C) is reproduced with permission from Elsevier[141], and (D) is reproduced with the permission from Hogrefe and Huber Publishers (now Hogrefe Publishing).[142]

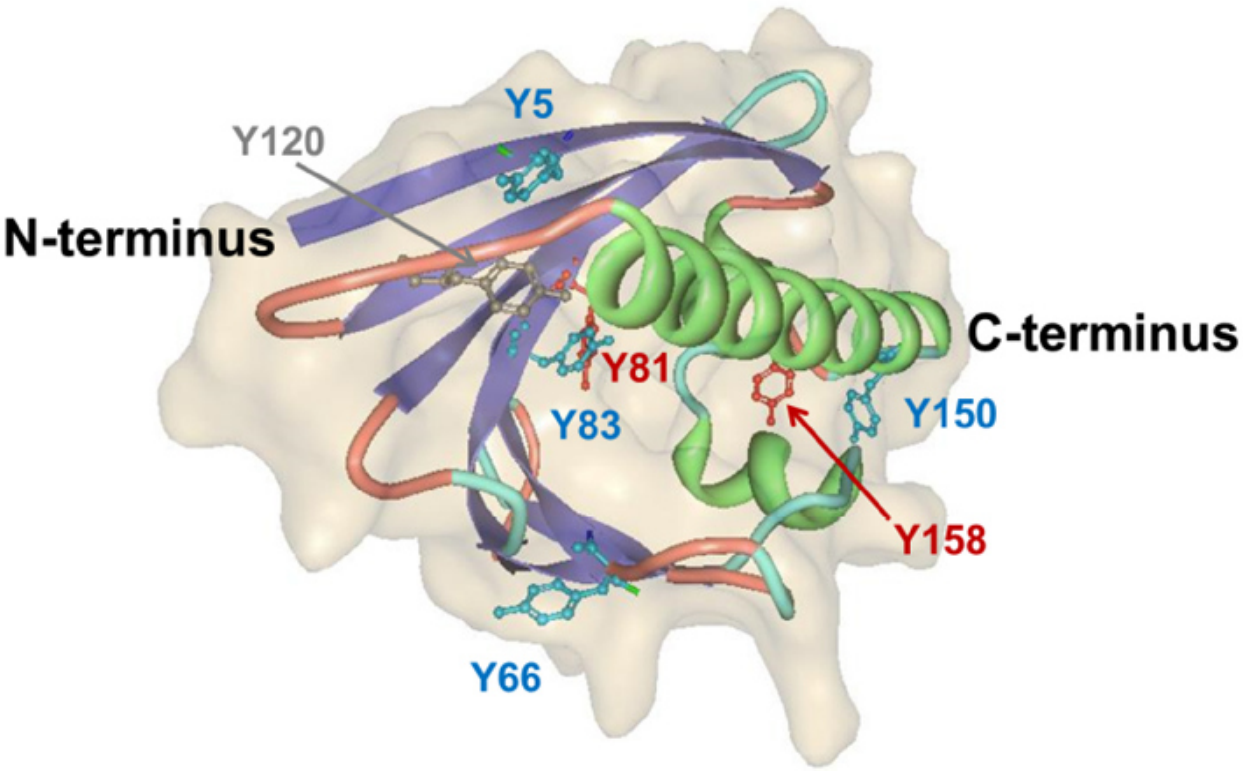

Figure S4.

3D-structure of the major birch pollen allergen Bet v 1.0101 highlighting the position of tyrosine residues in the amino acid sequence of the protein. Tyrosine residues mainly nitrated during exposure to environmentally relevant concentrations of O_3/NO_2 are given in red. Reprinted from [104]. Copyright 2014 (American Chemical Society).

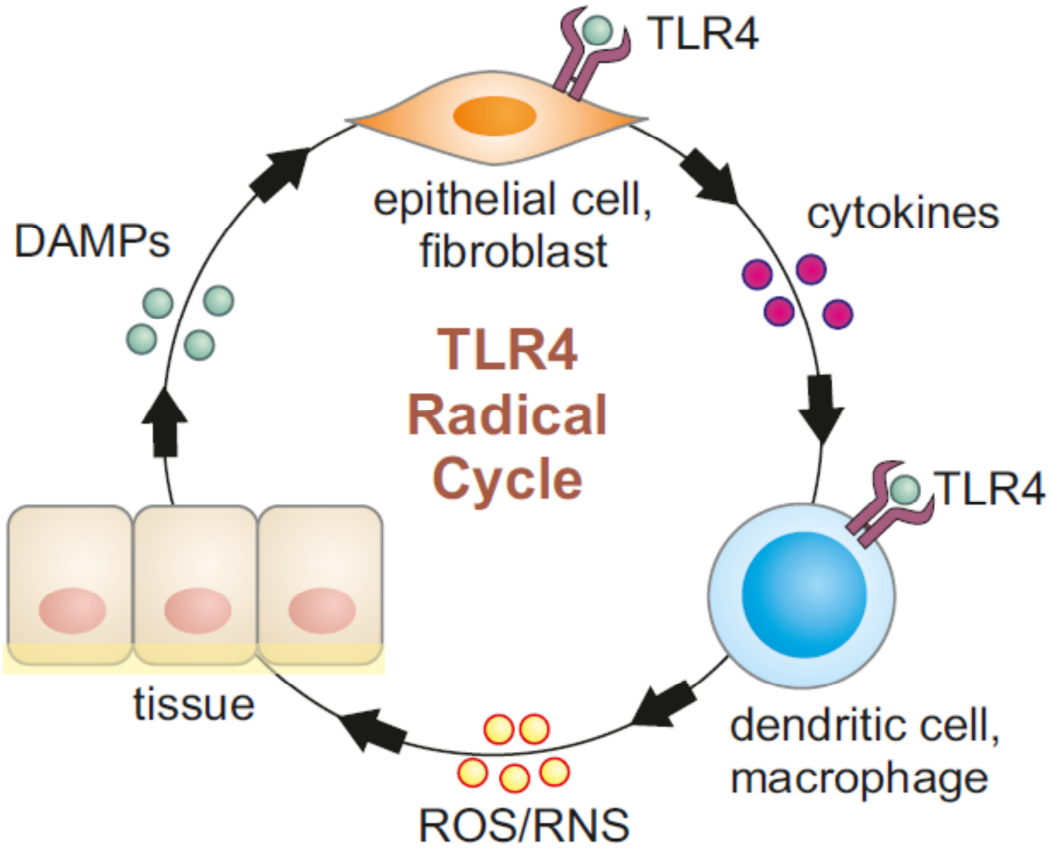

Figure S5.

TLR4-radical cycle of inflammation as an example of cyclic immunochemical processes that may be involved in the development of allergies and triggered by external influencing factors including air pollutants and related oxidative stress. Atmospheric and physiological reactive oxygen and nitrogen species (ROS/RNS) can cause the formation of damage-associated molecular patterns (DAMPs) that can activate the Toll-like receptor 4 (TLR4) and other pattern recognition receptors, leading to the release of more ROS/RNS and formation of more DAMPs.

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