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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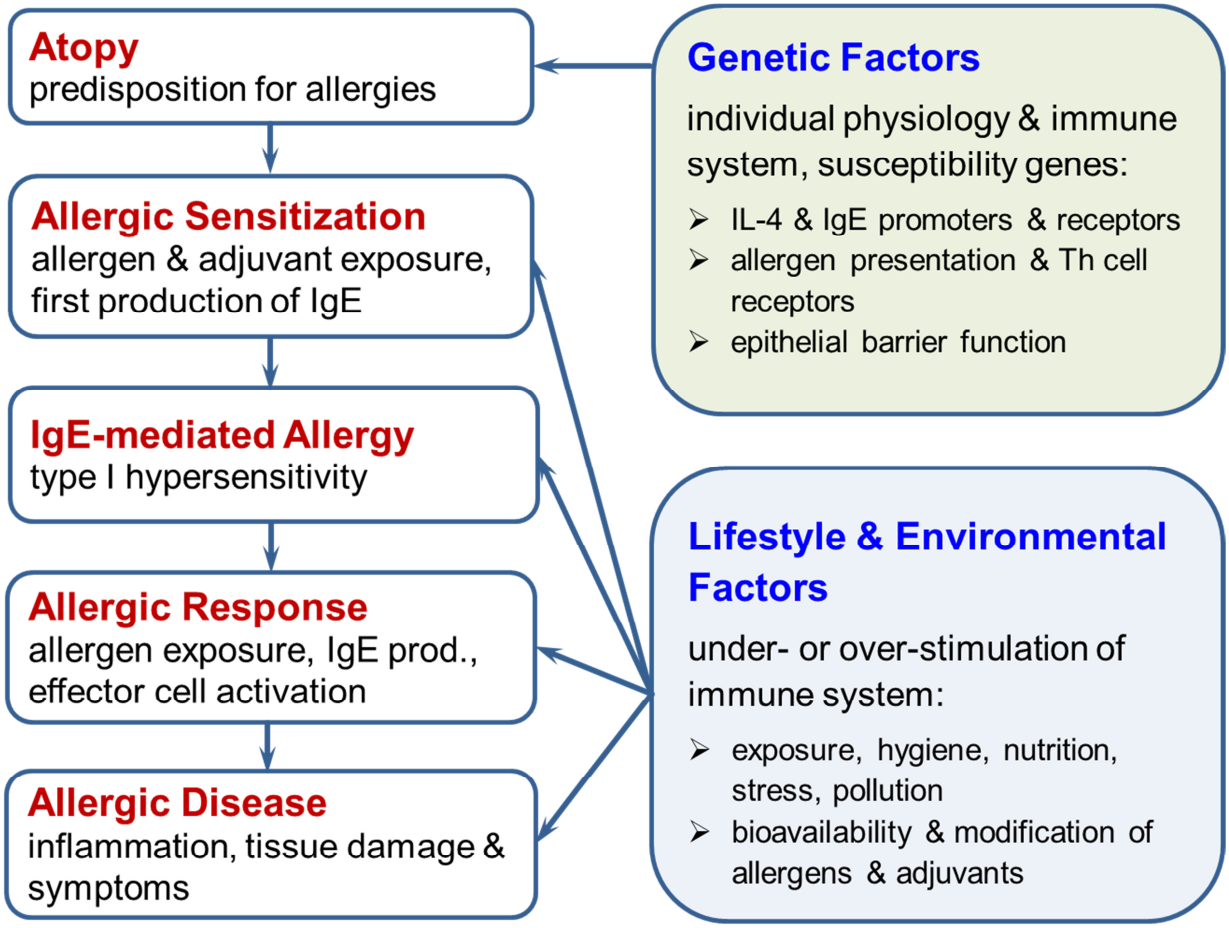

Figure S1.

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

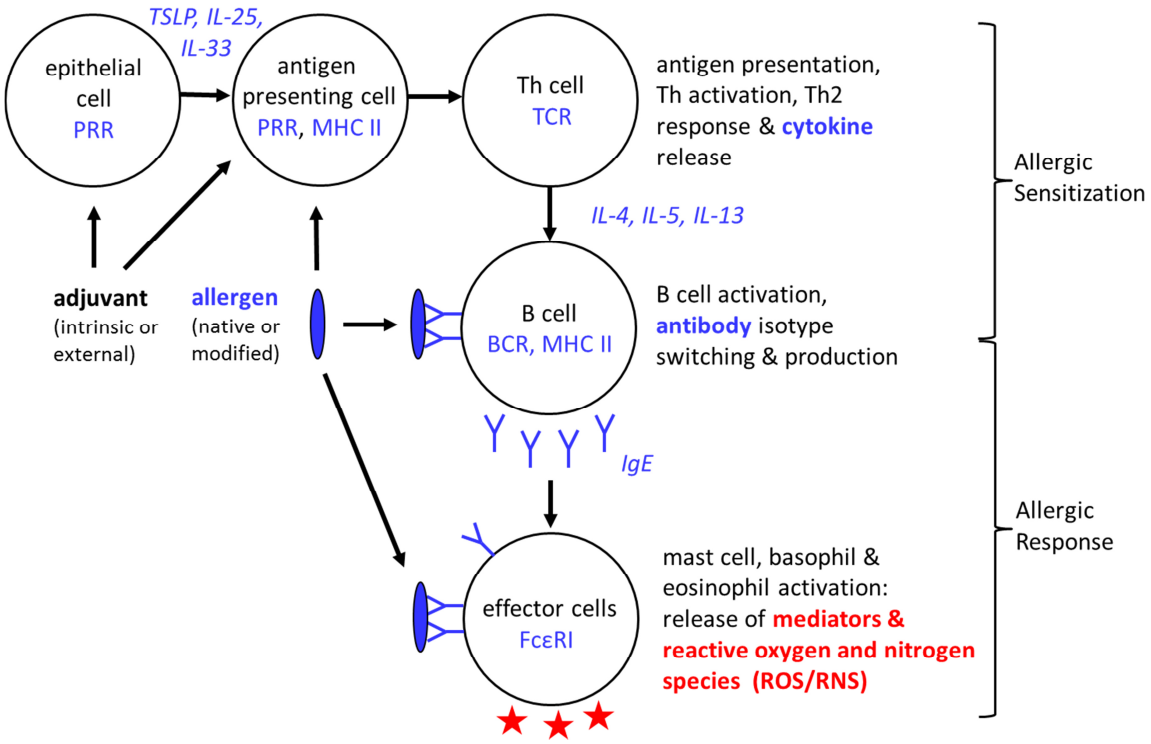

Figure S2.

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).

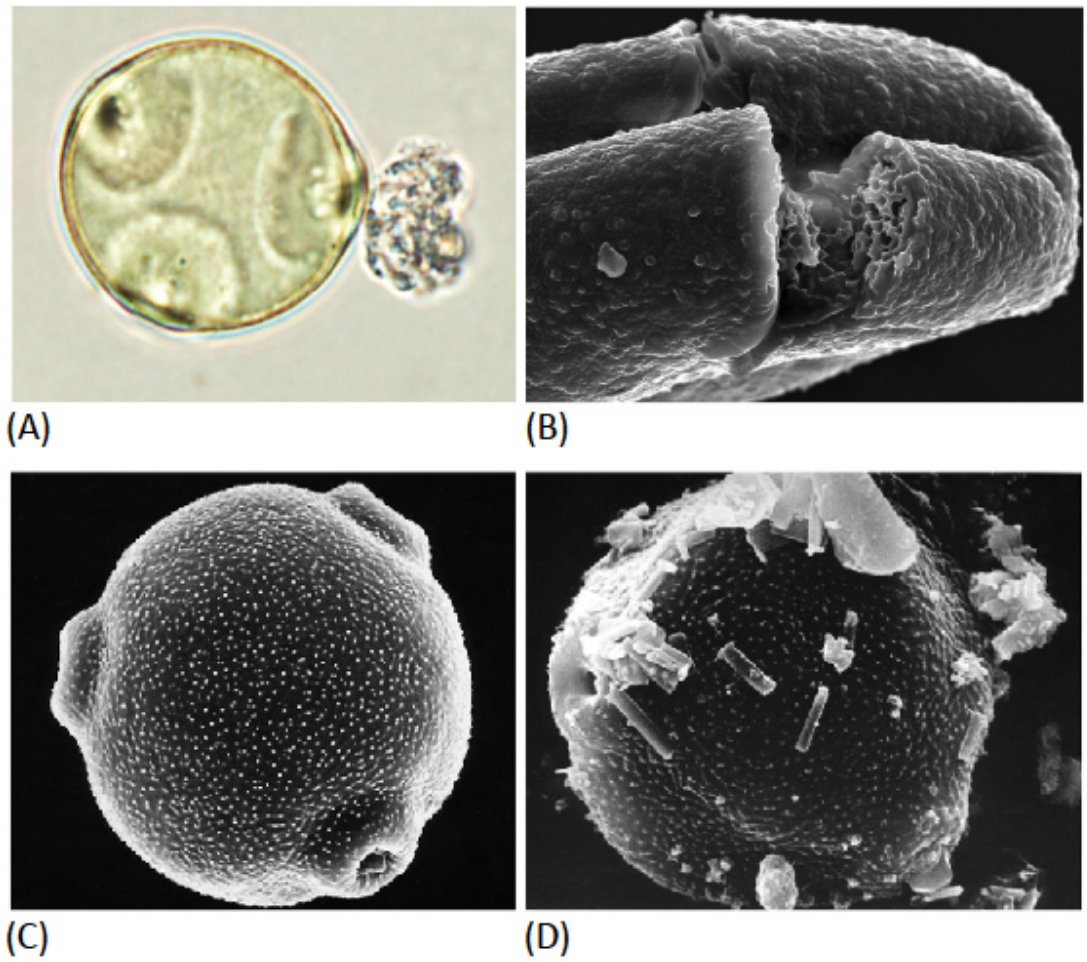

Figure S3.

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]

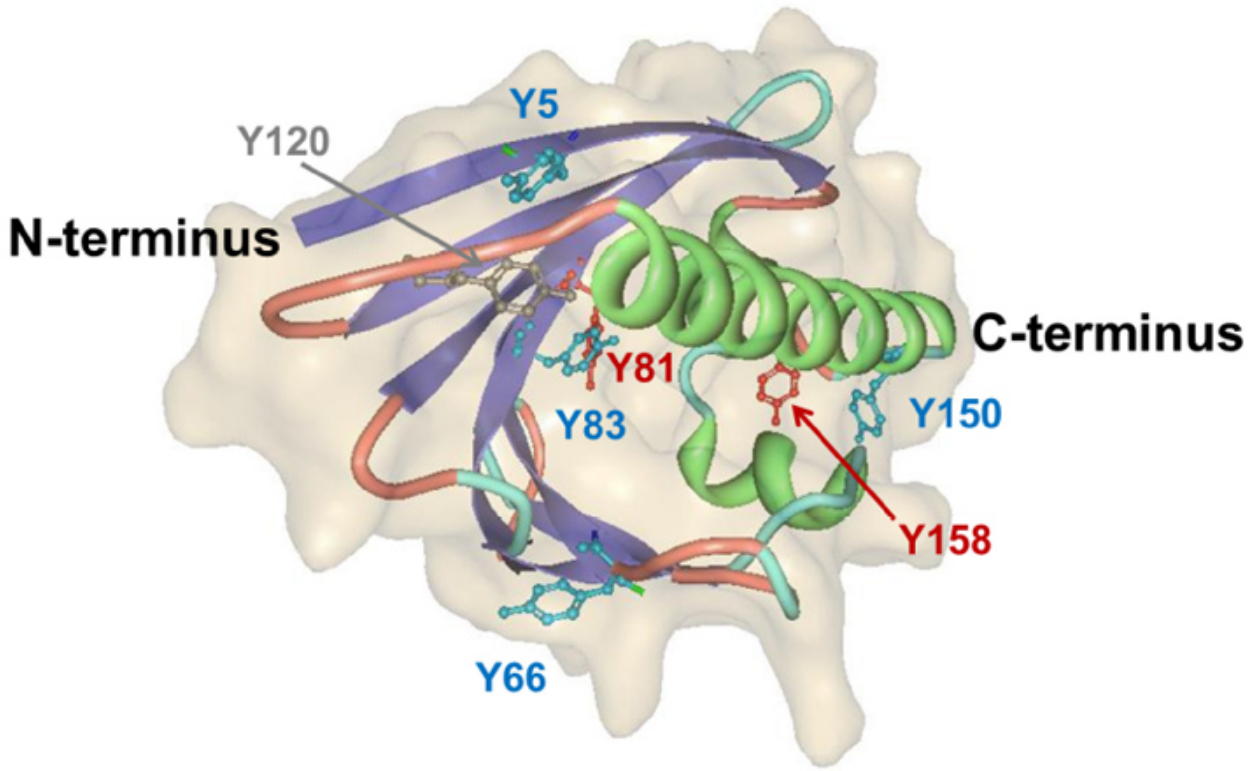

Figure S4.

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).

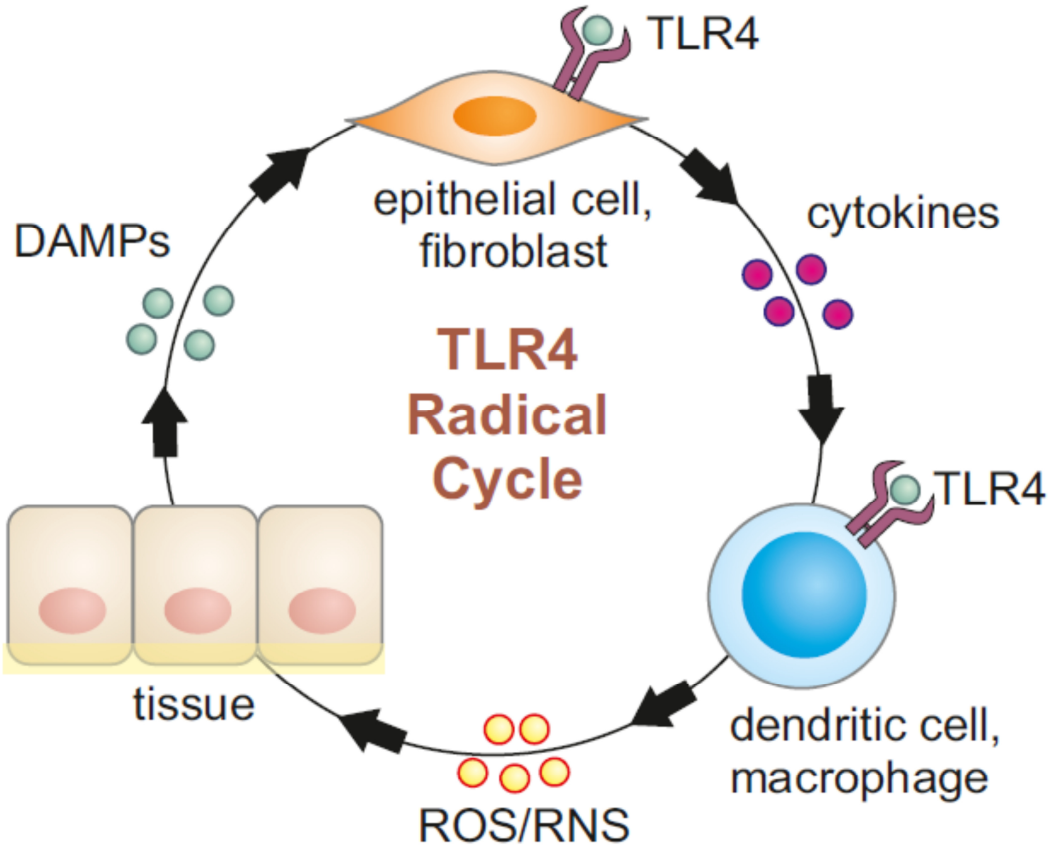

Figure S5.

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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