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REVIEW

Allergy in an Evolutionary Framework

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Abstract
Respiratory allergy including bronchial asthma and food allergy have gained epidemic character in the last decades in industrialized countries. Much has been learned with respect to the pathophysiology of allergic disease and this has facilitated specific therapies. Allergy is a chronic disease, and being so prevalent claims to search for evolutionary causes of the general susceptibility of humans as a species to react to environmental antigens in a Th2 type immune reaction with IgE production. In an evolutionary analysis of Allergy, necessary questions addressed in this review are "Why does IgE exist or why did IgE evolve?" as well as from the point of view of the mismatch hypothesis, "Why is there an Allergy epidemic?" Recent studies on the possible biological and protective role of IgE against parasites, arthropods, venoms or toxins are challenging the widely accepted definition of allergens as generally innocuous antigens. Combining the immunologic danger model and the toxin hypothesis for allergies, the allergic response could have evolved with an adaptive value and allergens could be proxies for other putative noxious agents. The last decades yielded with vast molecular data of allergens. With available bioinformatics tools, we therefore also describe that evolutionary theory could be applied to prevent allergy, estimate cross-reactivity, to design allergen-specific immunotherapy and to assess the risks of novel foods.

Keywords Hygiene hypothesis · Toxin hypothesis · Allergy · IgE · Parasites · Evolutionary medicine

The Adaptive Immune System

The adaptive immune system evolved in vertebrate ancestors as a means to adapt to local disease ecology. Within an individual's lifetime B and T cells follow Darwinian principles for survival (McDade and Worthman 1999). Once necessary B and T cells have been selected, intergeneration times can match those of pathogenic microorganisms. The specificity of cell and antibody production comes with energetic trade-offs, but also with the fact that generally 2 to 4 weeks are necessary to mount an effective primary immune response. In the case of a repeated exposure to pathogens, a secondary response is faster due to production of memory cells, but still in the order of a few days (Straub 2012). Allergy belongs to a specialized type of adaptive immune response, which probably evolved for a very sensitive and faster response together with a rapid tissue repair response (Allen and Wynn 2011).

Allergens, IgE Antibodies and Mast Cells

Here we refer to allergy only to those features associated with specific IgE production. Type I hypersensitivity involves the generation of IgE antibodies against antigens, such as proteins, drugs or venoms. After sensitization (primary immune response), in a secondary reaction, IgE reactive epitopes of the allergen bind to IgE molecules on the surface of mast cells and basophils, which then leads to the release of multiple chemicals. Histamine, together with other substances (heparin, leukotrienes, prostaglandins, etc.), produces vasodilation erythema and edema, as well as pruritus, and along with ongoing inflammation eventually the clinical features of allergy. These depend on the localization of the response, as mast cells are localized in all tissues, which have contact with the external world, and thus allergy affects tissues that interface with the environment. Broadly, affliction of the respiratory tract produces asthma

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and rhinoconjuctivitis, food induced local symptoms produce oral allergy syndrome and gastro-intestinal complaints, whereas generalized symptoms with urticaria, angioedema and or anaphylaxis can also be triggered by ingestion of allergens. Thus, allergens, IgE and mast cells are part of the same immune response, which have the proximate function of triggering a rapid effector response, to respond to sometimes minute quantities of the offending allergen/antigen and from the clinical view to behave in an apparently disproportionate or exaggerated clinical response. This last concept will be challenged below.

Application of Evolutionary Theory to Allergy

Evolutionary medicine describes the application of modern evolutionary theory to the understanding of health, symptoms and disease (Williams and Nesse 1991) (See also Box 1 in the Appendix). One focus is as a complement to the analysis of proximate causes, physiology or pathophysiology, searching for evolutionary explanations. An ultimate causation interpretation emphasizes the biological origins of the allergic response patterns, selected over evolutionary timescales because of putative adaptive values in the past and possible adaptive values in the present. Thus, mismatch hypotheses claim that humans respond with disease when environmental input does not fit to the expected range of possibilities and response features (Okin and Medzhitov 2012).

All organisms are exposed to chemicals and other living beings. Allergic disease as an immune disorder is always initiated by exogenous environmental stimuli. With few exceptions allergens are proteins and thus of biological origin. Figure 1 summarizes some of the taxa, which are addressed within the text in an estimated phylogenetic relationship. It will be shown that allergic responses have evolved against antigens, whose presence is potentially associated with reduced biological fitness and that chemicals can also be targets of type I hypersensitivity reactions.

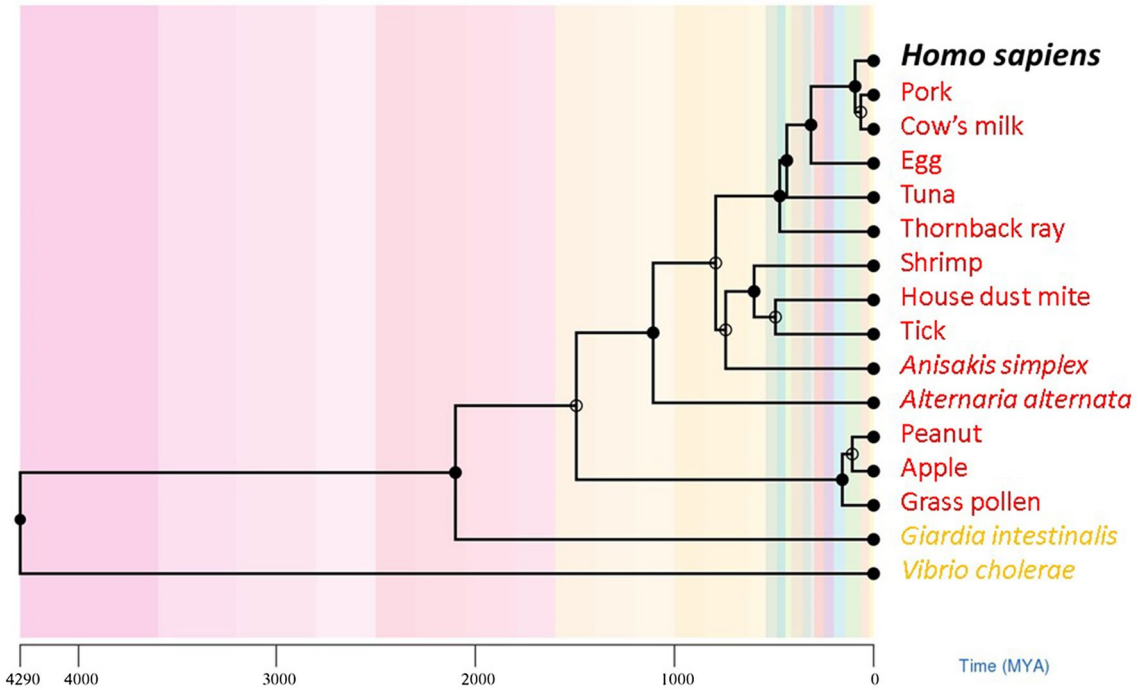

Fig. 1 Phylogenetic relationships of species associated with human IgE production. Phylogenetic relationships are shown from the human host point of view with estimated time to common ancestors in million years (MYA). Examples are given of major allergen-relevant taxa, as well as bacteria and unicellular parasites, for which allergenicity has only rarely been postulated, for comparison. Cow's milk and hen's egg (birds) allergy are common food allergies in children, whereas meat allergy (e.g. pork, mammals) is very rare, although pet allergy is a frequent respiratory allergy. Shellfish allergy is a frequent food allergy as well as house dust mites, which are predominant respiratory allergens. Two examples of fish are given [tuna (*Actinopterygii*); thornback ray (*Chondrichthyes*)] and evolutionary distance make it plausible that they behave with higher allergenic potential than mammals in pan-allergen examples. Ticks and *Anisakis simplex* are examples of invertebrate exoparasites or helminth parasites, respectively, and are able to induce evolutionary conserved IgE immune responses in all mammals. *Alternaria alternata* as example of mold and grass pollen are frequent respiratory allergens. Peanut and apple are examples of food allergens from the plant kingdom

Origins and Biological Role of the IgE Response

In the clinical setting, IgE has been interpreted as a bothersome immunoglobulin isotype, associated with disease and likewise allergens are still defined as generally innocuous, only giving problems in susceptible atopic individuals. But an evolutionary perspective searches directly for the possible role of the existence of IgE. In this first approach, a phylogenetic comparison should therefore analyse the origin of IgE. IgE production and specific mast cell activation are concomitant features in a wider immune Th2 type response, with further participation of CD4 T cells and eosinophils.

Interestingly, the Th2 immune response has long been known to occur not only in allergic disease but as a typical immunity against extracellular parasites. Especially metazoan parasites and insects are too big to be attacked or constrained by or within single cells by other immune type reactions (Allen and Wynn 2011). IgE is produced only in mammals and it is straightforward to suspect a selective advantage that has been maintained for more than 300 million years. Mast cells, on the other side, seem to have a more ancient origin predating the emergence of the chordates more than 500 million years ago, even before the development of adaptive immunity (Wong et al. 2014). Mast cells perform important sentinel roles against numerous pathogens, such as bacteria, virus, uni- and multicellular parasites and have several central roles in innate as well as adaptive immunity. The IgE triggered mast cell degranulation is thus a newer acquired feature of these ancient cells.

Parasites, Insects and "Innocuous" Antigens

Helminth parasites, such as intestinal nematodes, share with allergies the typical Th2- activated responses with production of cytokines such as IL-4, IL-13 and IL-9. Mast cells, but also eosinophils and other immune cells of the Th2 type immune response contribute to the release of mediators. By their effects on smooth muscle, epithelial and goblet cells of the respiratory, gastro-intestinal tract or skin a 'weep and sweep' response is elicited: local inflammation with mucus production, bronchoconstriction, intestinal peristalsis or pruritus are only some of the effector mechanisms and renders inhospitable the environment for the helminth parasite (Anthony et al. 2007). Thus, this response has been claimed to be protective against a high parasite burden or re-infection (Urban et al. 1992; Cooper 2009). Interestingly, ubiquitous specific allergies nowadays could have their evolutionary counterpart in specific parasite responses. As an example, tropomyosin, which is one of the most frequent causes of shellfish allergy, has been implicated in host protective responses to microfilariae in onchocerciasis or schistosomiasis (Jenkins et al. 1998; Silas et al. 2014).

However, an important feature of a Th2 type response is that IgE production could also be triggered for the interest of the parasite. Host-parasite co-evolution produces an arms race, and the net effect of evolved immune responses over long time periods is difficult to ascertain. High polyclonal production of IgE is characteristic of helminth disease and has been proposed to diminish the effector effect of specific IgE against the invading parasite.

The adaptive role of IgE against unicellular parasites is controversial. The involvement of IgE in malaria remains unclear, but mast cells could have a role influencing multiple stages of malaria infection (Mecheri 2012; Mukai et al. 2016). Interesting is that mast cells are abundant in the skin. As malaria is transmitted by mosquito vectors, their reaction to mosquito saliva during blood feeding may have a "gatekeeper" effect on the initial stage of malaria transmission, ensuing by IgE mediated (and non-IgE mediated) mechanisms a local inflammatory response (Mukai et al. 2016).

Other important human infectious diseases that are widespread and should have witnessed an important selective pressure are also transmitted by blood-feeding arthropod vectors. Filariasis, trypanosomiasis, leishmaniasis or Lyme's disease need mosquitoes, tsetse flies, sandflies or ticks for propagation of infective stages. Therefore co-evolution between arthropods, pathogens and hosts cannot be ruled out (Gillespie et al. 2000). Insect bites and arthropods are also Th2 type immunity inducers. IgE production and cutaneous hypersensitivity has been reported after repeated exposure to ticks with associated itch. This anti-tick immune response seems to protect people from Lyme disease through several effector mechanisms (Burke et al. 2005). Mast cells located in the skin are here responsible for both allergic and non-allergic urticaria. Interestingly, patients with chronic urticaria, which is not an IgE mediated disorder, has been associated with a differential helminth-arthropod related atopy phenotype with higher sensitization to *Anisakis simplex* or house dust mites than to other more frequent inhalant allergens (Daschner et al. 2010).

The idea that insects and other arthropods could have promoted the evolution of type I hypersensitivity with IgE production is not so new but has not been a research priority because of the 20th Century Allergy epidemic (see below). In an early hypothesis, Stebbings proposed hypersensitivity reactions due to insect bites to elicit an avoidance behaviour. The proposed effector mechanisms would however not be aimed at reducing probability of morbimortality by transmitted pathogens, but because of otherwise important immune reactions against major source of antigens in saliva (Stebbings 1974). In this line, arthropods can produce venoms and other potentially harmful substances.

A recent breakthrough of the role of IgE and the ensuing allergen definition comes from animal studies addressing in experimental studies the possible protective role of IgE

production against insect venoms. In this evolutionary scope, IgE antibodies and specific mast cell receptors have been found to be essential for an acquired resistance to honeybee venom, enhancing the survival of mice after repeated exposure of potentially lethal amounts of this venom (Marichal et al. 2013). An important allergen phospholipase A2 (PLA2) is present in large quantities in many animal venoms, such as hymenoptera, arachnids or snakes, and can induce inflammatory reactions. Interestingly, in order to induce an adaptive acquired immunity, the host needs only to generate an IgE response against one or some of the components of a complex venom. Allergens behave as signals to elicit a protective response against other toxic substances and can thus be interpreted as proxies.

The fact that parasite infection does not induce this response only in atopic people, but potentially in all humans (and mammals), reveals that IgE production in evolutionary and contemporary scenarios is a conserved mechanism. A recent example is to be seen with *Anisakis simplex* and *A. pegreffii*, cosmopolitan fish-nematodes, which induce IgE production in any individual if larvae enter in contact (after eating raw or undercooked fish and thus viability of the larva is ascertained) with the immune system (Daschner and Cuéllar 2010; Daschner et al. 2012). Further, in beekeepers or individuals with repeated hymenoptera stings, irrespective of clinical overt allergic symptoms, IgE production is encountered more frequently than expected from atopic predisposition prevalences (Müller 2005). An important feature of IgE producing, but clinically tolerant individuals is that they produce simultaneously high specific IgG_4, which could be one of the reasons for the prevention of anaphylaxis (Meiler et al. 2008).

Combining the Toxin Hypothesis and the Danger Model

In the last decades several models have been proposed to be the raison d'être of immune responses. Self and non-self considerations have been challenged by the danger model proposed by P. Matzinger, who clarifies that foreignness of a pathogen is not the important feature that triggers the response and selfness is no guarantee of tolerance (Matzinger 2002). With respect to antigenic proteins, their signalling properties would not so much be a matter of foreignness, but of possible associated danger signals. In the last years several alarm signals, such as DNA, RNA, heat shock protein, uric acid or hyaluronic acid breakdown products, have been revealed. Pathogen associated molecular patterns (PAMPs) induce different signalling pathways via pattern recognition receptors. Allergens have not been found to behave as PAMPs. Otherwise, if allergens signal their association with potentially harmful agents, these could be interpreted as alarm signals. Again, allergens behave as proxies of noxious substances and thus mimic alarm signals. The immediacy of the allergic reaction and the triggering by minute quantities confers IgE mediated allergy an outstanding significance within the danger model.

Taken together, Th2 immunity, which includes IgE and specific mast cell activation, enhances host defenses against parasites, arthropods or arthropod associated pathogens, venoms and probably also toxins from other sources. Recent exploration into biological origins of IgE production challenges the current definition of allergens as "generally innocuous antigens".

Rescuing Early Hypotheses

Margie Profet, an evolutionary biologist, published her toxin hypothesis in 1991 and constitutes one of the first published proposals of the evolutionary significance of allergy (Profet 1991). As IgE is able to elicit symptoms such as vomiting and diarrhoea, but also a drop in blood pressure in anaphylaxis, she proposed these effector mechanisms to serve expelling the allergen and slowing down of the circulation, respectively. Therefore, the mechanisms could correspond to a defense mechanism preventing putative toxins reaching the different organs. Since one of the characteristics of the allergic response is the speed of action, the hypothesis proposes that this immunoglobulin and ensuing allergic response have evolved to protect from some kind of immediate danger. She questioned the definition of allergen as a generally innocuous agent, since these substances have a toxic potential. Proposed examples are pollens containing phenolic acids and alkaloids or hay dust containing toxic spores, fish or shellfish may be contaminated by toxins from algae or plankton. Vegetable foods often contain toxins, which are secondary metabolites frequently produced as defense mechanism. IgE generally recognizes proteins and glycoproteins. It would thus be possible that natural selection has favoured the production of IgE against proteins associated to the presence of possible toxins. Initially her hypothesis was not generally accepted, but in recent years Profet's ideas have been rescued by data, which propose IgE to play a crucial role in the defense against venoms and toxins, as described above (Palm et al. 2012; Mukai et al. 2016). There are now reports, which indicate that IgE antibodies, induced by venoms, such as from Russell's viper or honeybee can increase the resistance of mice when rechallenged and that Th2 immunity can be beneficial rather than detrimental (Tsai et al. 2015). However, these data contrast with the overall impression that hymenoptera venom allergy can cause anaphylaxis in humans and has raised concern about the possible different immunological effects on different species (Gutierrez and Rodewald 2013).

Marc Lappé published as a toxicologist in 1994 a book on various aspects of Evolutionary medicine. One chapter is

devoted to the possible origin of asthma (Lappé 1994). Like Profet, he also described the allergic reaction attributing a possible benefit to it if by this means the immune reaction is able to prevent the entry of toxic molecules into the tissues of the lung. Listing several substances most frequently involved in the induction of asthma, he asserted in most cases that these are of natural origin, such as insects and their derivatives, bread making products, grains and seeds. He proposed the often inherent allergenicity of these substances to respond to a defense against some secondary consequence associated with their exposure. Lappé described asthma to be connected with agriculture. House dust mites, which represent one of the most important ubiquitous and asthma inducing allergens, are related to storage mites, which in turn have been frequently present in grain stores. Likewise, several epidemics associated with soybean flour, could be due to contamination by fungi. An example is the *Aspergillus* spp., which are simultaneously allergens and in turn highly toxic. Lung infection, especially in immunosuppressed patients, can be severe, and can be invasive in 90% of cases. The asthma association with agriculture is further highlighted by the fact that in asthmatic patients, sensitization against fungi is often due to species such as *Alternaria* and *Cladosporium*, fungi related to silos. For all these reasons, Lappé situated the evolutionary response of asthma in the domestication of cereals. The asthmatic response in humid environments and/or against fungi would prevent the inhalation of spores and reduce the probability of serious or lethal infection. Finally, these ancient reactions would eventually have facilitated the path towards a response to allergens associated with similar growth conditions, such as house dust mites.

His early hypothesis proposed therefore bronchospasm (frequently elicited by IgE production and recognition of allergens), to have evolved to reduce the inhalation of toxic air transported substances such as those produced by fungi.

In this sense a later publication, in which Spanish scientists studied an epidemic related to a discharge of soybeans in a port (García-Ortega et al. 1998), described how out of 15 patients studied, who presented an asthmatic crisis during the days of the soybean discharge, 13 were sensitized to soybean (specific IgE against soy). But more interestingly all the patients were atopic and most of them had positive skin tests against house dust mites. It is interesting to note here that it is known that house dust mites not only need ideal moisture conditions and epidermal remains for their growth, but they need environmental fungi that perform predigestion of nutrients (Arlian and Platts-Mills 2001).

If asthma is connected with prevention of lung-damage by fungi, one can predict more frequent appearance of bronchospasm in humid environments. Indeed, epidemiological studies confirm the association of asthma with humid environments. This association is known for patients who are sensitized to moisture-dependent allergens such as mites or fungal spores, although humidity is also one of the nonspecific triggers of asthmatic crisis in non-allergic asthmatic patients. Dampness and mold hypersensitivity syndrome (DMHS) fits thus well in this situation, where different immunologic (including IgE production and allergy), but also other mechanisms, such as sickness avoidance behaviour could be explained by the selective pressure of mold and fungi and defense mechanisms in mammals (Casadevall 2012; Daschner 2016). In fact, sensitization to fungi is associated with asthma, but more interestingly with severe forms of asthma (Del Giacco et al. 2017). Otherwise, Lappé's hypothesis that asthma could have evolved to protect against invasive fungal disease should still be tested and epidemiologic studies could evaluate those patients, who are at risk to acquire fungal disease and search not only for an exposure history, but also for symptoms or lack of symptoms associated with asthma or DMHS (Daschner 2016).

An Evolutionary View of the ALLERGY Epidemic

Allergy has gained epidemic character during the last decades and is one of the leading chronic inflammatory conditions (Prescott 2013; Platts-Mills 2015). Knowledge about the origin of high allergy prevalences and possible explanations comes from epidemiological observations and recapitulates the above described association with parasites. In several studies in different regions, a negative association between parasitism and allergy has been documented, giving rise to one section of the hygiene hypothesis (HH). These studies describe how patients with filariasis, schistosomiasis or subjects parasitized with *Necator* or *Trichuris* show a reduced prevalence of skin tests against cockroach or house dust mites (Yazdanbakhsh et al. 2001; Flohr et al. 2006). In addition, during anti-helminthic treatment of Gabonese children, an increase of positive skin tests against house dust mites was ascertained (van den Biggelaar et al. 2004). The HH postulated initially that lack of exposure to infectious agents increases the susceptibility to allergic diseases (Strachan 1989). The revised form of the HH proposes that in chronic parasitism the regulatory immunological pathway would be activated, paralleling production of the anti-inflammatory cytokines IL-10 and TGF-β. These anti-inflammatory cytokines would be associated with a decrease in the allergy phenotype and would thus explain that despite high levels of IgE there is no clinical manifestation of allergy. On the contrary, sporadic acute or accidental parasitism, such as from studies from China or Germany, where parasitism was positively associated with allergy, could increase the clinical manifestation of allergy, since it would stimulate the (pro-inflammatory) Th2 response

pattern, but without enough stimulation to produce an anti-inflammatory response (Yazdanbakhsh et al. 2002). Genetic studies have also helped to clarify the relationship between parasites and allergy. It is interesting to remark that many genes associated with asthma have similarly been associated to susceptibility to parasites such as *Ascaris*, *Schistosoma* or *Leishmania* (Barnes et al. 2005; Vercelli 2008).

The HH has suffered several modifications in the last two decades. With the advent of the microbiome era, it is now describing a model, in which chronic inflammatory disease in westernized populations is associated with a diminished environmental contact with microorganisms and parasites. This leads eventually to changes in microbiome diversity and risk of chronic pro-inflammatory events (Hanski et al. 2012). Allergic disease is but one of the possible chronic inflammatory disease outcomes and genetic predisposition leads immune deviation to a specialized type 2 immune response.

What Makes an Antigen an Allergen? An Evolutionary View

An antigen is any molecule that can bind specifically to an antibody and allergens are antigens that elicit hypersensitivity or allergic reactions. The antigen word arises from its ability to generate antibodies. However, some antigens do not generate antibodies by themselves; those antigens that can induce antibody production are called immunogens (Janeway 2001). Thereby, the question is why an antigen is able to respond in the individual evading the Th2 suppressive mechanisms (Th1 T cells, CD8+ T cells, Treg cells and IL-10 or TGF-β) and thus to induce IgE production.

This question was addressed by different researchers in the last five decades. An initial article reviewed publications about the hypersensitivity reaction, incidence, non-immunological and structural factors that make an antigen allergen, predicting the future synthesis of peptides with linear epitopes (Aas 1978). In 2000, Aalberse updated the classification of protein folds in allergens and defined some concepts like major allergen, cross-reactivity and linear *vs* conformational epitopes (Aalberse 2000). In 2004 Bannon, focused on food proteins, reviewed all the properties which must have a protein present in food to elicit an IgE response and, on subsequent exposures, to trigger an allergic reaction (Bannon 2004). In the last years, a renaissance of studies of the innate immunity highlights its feature and importance in the relationship to allergic reaction, offering a better understanding of the molecular and cellular substrates of allergenicity (Karp 2010; Scheurer et al. 2015).

Physicochemical Aspects

There are some hypothetical factors likely to affect allergenicity such as size, solubility, enzymatic/binding properties, protein sequence, 3D surface (post-translational modifications, electrostatic potential and compactness) (Aalberse 2000; González-Fernández et al. 2017a, b). These aspects affect the transport over mucosal barriers or susceptibility to proteases. Further the molecule in question must be bivalent or carry more allergenic determinants easily accessible for the IgE molecules accessible on the mast cell surface (Aas 1978).

Moreover, there are other factors extrinsic of the allergen as the presence of other immunoglobulin isotypes, food processing, digestibility and other clinical co-factors such as intestinal permeability, chronic parasitism or autoimmune diseases (González-Fernández et al. 2017a, b).

Clinical and Biological Significance

The clinical relevance of IgE antibodies can only be assessed in clinical observations or studies. Allergic children can have low IgE levels but evident clinical symptoms. In the case of allergenic tropomyosin of tilapia (Ore m 1), the amount of the anti-tropomyosin IgE did not significantly correlate with severity of symptoms of the patients studied. After a double-blind placebo-controlled food challenge with tilapia, the clinical relevance depended on the administration route or concomitant protective IgG_4 or IgA (Liu et al. 2013) In fact, oral food challenges of 603 patients were studied retrospectively and related with their specific and total serum IgE. The research revealed that patients with higher total serum IgE levels were significantly less responsive to the challenge (Horimukai et al. 2015).

Karp reviewed the question of possible intrinsic allergenicity of proteins, but concluded that a general molecular basis of allergenicity at the epitope level would not be expected, such as in the case of pattern recognition receptors. Otherwise widely diverse allergens seem to be linked to a common ability to drive innate immune activation (Karp 2010). Whereas no common structural characteristics are found among allergen epitopes, it is possible that intrinsic adjuvant activity are associated with allergenicity by biochemical features such as hydrophobic cargo of lipid-binding allergens, highly cross-reactive carbohydrate structures of glycoproteins or protease activity of a high number of allergens.

Evolutionary Distance

In addition to general features affecting IgE recognition, evolutionary distance from human homologues has been used to explain allergenicity of proteins (Jenkins et al.

2007; Platts-Mills 2012). Applying foreign and non-self recognition criteria, allergenic mammalian proteins lie at the limits of the capability of the human immune system to discrimination (Jenkins et al. 2007). One example is tropomyosin, where mammals, birds and fish share at least 90% identity with at least one human tropomyosin. This protein is a typical pan-allergen of invertebrates and it has been thought that vertebrate tropomyosin is not allergenic in vertebrates. However, by applying evolutionary thoughts and phylogenetic relationships, this view has recently been challenged on clinical data (Liu et al. 2013; González-Fernández et al. 2018). As can be seen in Fig. 1, evolutionary distance to fish compared to mammals makes it plausible that their proteins are recognized in food allergy. Another interesting example is parvalbumin a major allergen and pan-allergen in fish-allergic patients. Levels of IgE to α-parvalbumin from cartilaginous fish have been detected in lower quantities than to β-parvalbumin from bony fish and were so expectedly due to evolutionary distance and thus lower amino acidic sequence identity (Kalic et al. 2019). Other scenarios are IgE sensitization to fungi where a close relationship between fungal phylogenetics and fungal sensitization has been demonstrated (Soeria-Atmadja et al. 2010), or a highly studied area of food plant allergens: structural as well as evolutionary relationships have allowed the concept of allergenic plant protein families, such as prolamin superfamily, cupin superfamily or profilins (Mills et al. 2004). Also in the animal kingdom, three major food allergen families with high cross-reactivity potential are tropomyosins, parvalbumins and caseins (Breiteneder and Ebner 2000). Otherwise, similar sequence from phylogenetically related species is only a necessary, but not a sufficient factor for proteins to behave as pan-allergens, as observed for vertebrate IgE tropomyosin recognition (González-Fernández et al. 2016, 2018).

An interesting example is haemoglobin. *Anisakis* haemoglobin is an allergen (Ani s 13) but *Ascaris* haemoglobin not (González-Fernández et al. 2015). The tertiary and quaternary structures of haemoglobins, experimentally determined by x-ray crystallography, are significantly similar adopting a common classical globin fold (Hardison 1996). Although haemoglobin sequences have billions of years of evolution, and their three-dimensional structure is conserved, surface of IgE binding epitopes seems to be modified in *Ascaris* haemoglobin, to avoid the host IgE binding during co-evolution with host. In addition, mice immunized with rAni s 13 did not generate IgG1 antibodies against epitopes from *Ascaris* haemoglobin, which confirms the specificity of Ani s 13 immunogenic epitopes (González-Fernández et al. 2017a, b).

Evolutionary Knowledge and the Clinical Setting

Cross-reactivity occurs when the originally induced IgE production against a particular antigen causes reactivity to other antigens. Phylogenetic considerations are important in cross-reactivity. All cross-reactive proteins have a similar fold but proteins with a similar fold are not necessarily cross-reactive. In addition, protein fold is conserved allowing punctual amino acidic changes in the protein sequence, which happen during evolutionary time but they may be modifying the epitope surface reducing or increasing the antibody recognition. It is difficult that they are cross-reactive with an identity below 50%. Generally more than 70% of sequence identity is necessary to cross-react (Aalberse 2000).

The FAO establishes that IgE cross-reactivity between a newly expressed protein and a known allergen should be considered a possibility when there is more than 35% identity in a segment of 80 or more amino acids, or shares at least six consecutive amino acids in its amino acid sequence with another protein which is a food allergen (Ladics and Selgrade 2009). This rule is programmed on the server of the Structural Database of Allergenic Proteins https://fermi.utmb.edu/SDAP/sdap_who.html which is useful to compare the protein sequences with the registered allergens of the database.

Using this method, a negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. However, in special cases with proteins of similar fold sequence identity could be as little as 25% being cross-reactive if relevant epitopes are shared (Aalberse 2000).

Is There Room for a Personalized Allergen Cross-Reactivity Prediction?

In the clinical setting it would be ideal for the allergist to have personalized information about future allergic episodes, especially in food allergic patients. Performing clinical challenge test is often not feasible. Allergists have learned to classify allergens in botanic or animal families, but specificities vary in the range that specific antibodies can vary from patient to patient. Clinical and laboratory studies are now facilitating component resolved diagnosis. However, the question arises, how much can evolutionary knowledge help.

With the current detection methods of specific IgE against different allergens, the physician knows the family of the allergens against which the patient is reactive.

If a patient is allergic to a specific food, cross-reactivity between this specific food "species" A and another B may decrease with evolutionary distance. Amino acid sequences of relevant epitopes are expected to differ paralleling evolutionary distance. Otherwise, clinical evidence has not always demonstrated linear predictions. In a study examining cross-reactivity to tree nut and seed allergens, no convergence could be suggested between distantly allergenic proteins at the level of amino acid sequences (Fisher 2015). Another phylogenetic analysis of cross-reactivity in allergic rhinitis and oral allergy syndrome (with plant food) demonstrated that sequence-similarity can occur with less related species as well (Platt et al. 2014).

Bioinformatics prediction tools are based on available retrospective data, where phylogenetic relationships can be found but are not introduced in the initial prediction algorithm. With this information, the 3D models may be constructed from the amino acidic sequence, and the prediction of their 3D binding epitopes may be carried out. Using 3d surfer (La et al. 2009) with the epitope cut, it could be used to search similar epitopes on proteins from different organisms and explore possible cross-reactive proteins even from evolutionary distant organisms (González-Fernández 2017).

Allergen Tree of Life

Our first approach using tropomyosin, because of its simple alpha helix fold, confirmed the aminoacidic sequence as an evolutionary marker. But this sequence based tree is not necessarily translated to clinical reality, because any aminoacidic changes may suppose important variations on the flexibility of the molecules (González-Fernández et al. 2014). This reason gave us the idea of using a 3D approach because IgE binding is conformational. By cutting the experimental IgE binding epitopes of shrimp tropomyosin (Ayuso et al. 2010) and comparing 3D similarity with orthologous epitopes of other tropomyosins, we were able to establish a tree of risk of cross-reactions (González-Fernández 2017). This methodology was used to confirm the 3D similarity of the domains I of the haemoglobin of *Anisakis, Pseudoterranova, Toxocara* and *Ascaris* and their respective host's alfa globin domains, which could be an example of molecular mimicry with the host homolog protein to evade the host immune response (González-Fernández 2017).

With the current information from the databases, it could be feasible to select all characterized allergens in order to elaborate a multi complex tree based on the 3D similarity useful to predict cross-reactions.

Application, Prospection and Possible Research Agenda

If Allergy is a costly trade-off reflecting an inappropriate response to rapidly changing environments, a thorough analysis could yield preventive or therapeutic proposals applying evolutionary considerations. "What expected environment are we supposed to be adapted?" could be translated to lifestyle considerations, as are reflected by the different forms of the Hygiene Hypothesis. Obtained lessons with evolutionary scope include treatment options, which have widened to microbiome oriented therapies or even helminth therapy (Maizels 2016; Kahl et al. 2018). Specific treatment options are to be seen in specific immunotherapy, where tolerance is induced by repeated allergen challenge, where the immune system is educated not to recognize the allergen as a putative danger. The discontinuity theory of immunity proposes that the immune system responds to sudden changes in antigenic stimulation and is rendered tolerant by slow or continuous stimulation (Pradeu and Vivier 2016). Applying this theory, immunological studies have shown the induction of a specific anti-inflammatory response when immunotherapy is administered in scenarios of very rapid administration of high doses or progressively increasing doses of allergen (Pradeu and Vivier 2016; Daschner 2018). Interestingly the rationale is being applied in the context of oral tolerance induction in food allergic patients (Perezábad et al. 2017). Knowledge of differential Th2 versus Th1 type response of allergens is used by immunotherapy manufacturers and adjuvant assessment, but also for intended allergen modification. Evolutionary insights are now even applying microbiome science (Pascal et al. 2018).

The possible role of IgE production in the context of an evolved danger model could be implemented in future studies assessing epidemiological research comparing allergic and non-allergic individuals with respect to other long-term outcomes and evaluation of (novel) exposure to environmental agents or chemicals. In this respect, some studies have addressed the possible protective function of Th2 type responses or allergies against cancer. There is still controversy in this topic, but some data are in accordance with a negative association between some type of cancer and some type of allergies (Sherman et al. 2008; Kozłowska et al. 2016). As food allergy is still increasing within the overall Allergy epidemic, future studies can investigate specific food allergy and cancer associations. Environmental pollutants have been shown to increase allergic disease by inducing increased allergen expression, which eventually leads to higher allergen exposure. One early study showed how chitinase, the pan-allergen responsible for the latex-fruit syndrome, is induced by ethylene

treatment (Sánchez-Monge et al. 2000). The biological rationale of these mechanisms is to be seen in the fact that the majority of plant pan-allergens are plant defense proteins (Shahali and Dadar 2018), which respond to environmental hazards and could thus serve for humans as (intermediate) hazard signals. A thorough review provides an overview of chemicals able to enhance allergen upregulation (Seo et al. 2012). Likewise, this scenario could only partially explain the (food-) allergy epidemic, but should thus make possible to monitor increase in allergen-specific IgE in humans and animals in order to identify hazards of adjuvant chemical effects. Future studies could make use of this model for food safety evaluations. Also for interest for the food industry and food safety agencies are allergenicity prediction programmes, which are mainly based on sequence homology and thus are based not only on known motifs or epitopes (Kim et al. 2014; Fu and Lin 2017), but should also construct on phylogenetic relationships. Bioinformatics evaluation of genetically modified foods has already been implemented (Dunn et al. 2017).

Appendix

Box 1: Some Evolutionary Principles Addressed in This Work

For reviews see (Williams and Nesse 1991; Nesse and Stearns 2008; Stearns 2012).

Proximate explanations are related to physiology and pathophysiology, those mechanisms, which all medical students learn. **Evolutionary explanations** deal with the question why concrete traits have evolved or why humans are **vulnerable** to certain diseases from an evolutionary point of view.

Co-evolution between parasites and hosts has shaped immune features and is thought to explain the anti-inflammatory power of chronic parasitism and species living within our microbiota. The new versions of the **Hygiene Hypothesis** give clear relevance to possible depletion or reduction of diversity of our microbiome causing vulnerability to chronic inflammatory disease.

Symptoms can be interpreted as **defenses** or **defects**. Defects are annoying, but their presence can be of survival value. This is interesting when analysing allergic symptoms. From an evolutionary perspective vulnerability to allergic symptoms could reflect evolved mechanism to get rid of parasites or noxious substances.

The thresholds for defense expression are set by the **smoke-detector principle:** When the cost of expressing a defense is low compared to the potential harm it protects against, false alarms are predicted to evolve. Allergic hypersensitivity leads to exaggerated symptoms, but these remember some of the defense mechanisms elicited by contact with pathogens or irritant, noxious substances.

Trade-offs are intrinsic to all designs and deal with evolutionary constraints and compromises. The allergic response comes with costly trade-offs nowadays but an evolutionary interpretation could give clues to increased biological efficacy in past or other environmental situations.

Mismatch between design and environment: Genetic design has evolved to cope with an expected environment. Rapid environmental changes produced by human activity are thought to be one of the reasons for the increasing prevalence of chronic inflammatory diseases and Allergies.

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