

# The evolution of IgE-mediated type I hypersensitivity and its immunological value

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## Abstract

The allergic phenotype manifests itself in a spectrum of troublesome to life-threatening diseases, from seasonal hay fever, through the food allergies, atopic eczema, asthma, to anaphylaxis. Allergy, that is an overreaction to allergen in hypersensitive individuals, results from the production of IgE, mast cell and basophil sensitisation and degranulation, requiring a range of medications to manage the conditions. Yet it is highly likely that allergy evolved for a purpose and that allergic diseases are accidental consequences of an insufficiently regulated immune response. This article presents a viewpoint from which to restore the immunological reputation of the allergic phenotype. We consider the evolutionary origins of potential allergens, toxins and parasites, and how they might have influenced early-mammal species in existence when IgE first developed. We conclude that the allergic phenotype has likely saved the lives of many more mammals than have ever died from allergy, so justifying the positive role of IgE in our evolution.

## KEYWORDS

basophils, evolution, IgE, mast cells, parasites

## 1 | INTRODUCTION

Allergic reactions begin with the exposure of the skin and mucosal surfaces to allergens. This results in the activation of characteristic immunological pathways, initially through the innate production of molecules such as IL-33,<sup>1,2</sup> which is released by activated mast cells or damaged epithelial cells. IL-33 plays an important role in initiating an allergic response, functioning as an alarm signal, and has therefore been called an “alarmin.”<sup>3</sup> The allergic phenotype is also closely associated with the so-called Th2-like response, involving the production of cytokines such as IL-4, IL-5 and IL-13.<sup>4</sup>

This Th2 phenotype is further characterized by the subsequent production of immunoglobulin E (IgE) following facilitated antigen

presentation (FAP),<sup>5-7</sup> eosinophilia, the sensitisation of leucocytes and, in the case of mast cells and basophils, pharmacologically powerful mediator release on further allergen exposure. IL-4 and IL-13 are key Th2 cytokines, as they induce antibody isotype switching from immunoglobulin G (IgG) to immunoglobulin E (IgE),<sup>8</sup> another characteristic of Th2-skewed immune responses.

The resultant type 1 hypersensitivity affects a large section of the world's population, with those reporting allergy steadily increasing from the 1960s and 1970s. Today, an estimated 40% of the population are sensitized (ie have specific IgE) to environmental proteins.<sup>9</sup> Therefore, IgE-dependent type 1 hypersensitivity remains medically problematic.

In this review, we give particular attention to the context in which the IgE response first arose in our mammalian ancestors, then

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present our view that the allergic phenotype, despite its apparent high cost, offers evolutionary value through a range of benefits. These range from protection against parasitic infection for a large proportion of the world's population, to accelerated wound healing, protection against venoms and possibly tumours.

## 2 | EVOLUTION OF IgE

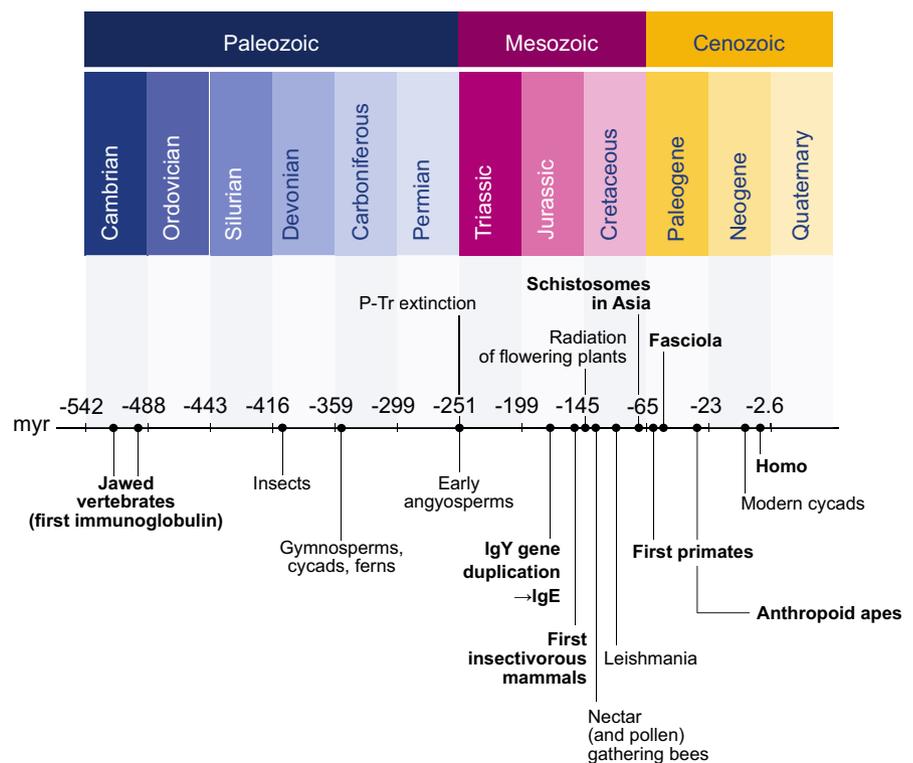
The ability to produce IgE is a unique mammalian trait; therefore, it is likely that the IgE repertoire was available for engagement on the first appearance of insectivorous mammals during the Triassic period, approximately 195 million years ago (see Figure 1).<sup>10</sup> That IgE occurred early during evolution of mammals, probably due to an IgY gene duplication event, is supported by the observation that this immunoglobulin occurs in all mammals, that is before their separation into the three extant branches (monotremes, marsupials and placental mammals), more than 200 million years ago.<sup>11</sup> It is thought that a genetic event leading to duplication of the full-length IgY gene, still found in amphibians, birds and reptiles,<sup>12</sup> resulted in both IgG (with the loss of the C<sub>2</sub> domain) and IgE (with conservation of all 4 domains in the constant chain) in early mammals. A truncated IgY form, lacking two heavy chain domains C<sub>3</sub> and C<sub>4</sub>, is found in some turtles and birds.<sup>12</sup> The structure of IgE appears well conserved throughout mammals, pointing to strong evolutionary pressures to maintain its full functionality intact.<sup>13</sup>

While it is clear that mast cells and basophils are found throughout the animal kingdom, including avians and reptiles<sup>14,15</sup> and thus are phylogenetically older than IgE, a number of fascinating

questions arise. Did these cells already possess the high-affinity IgE receptor FcεRI, which mediates the most salient effects of IgE? If not, did the primordial IgE in our small, warm-blooded, insectivorous ancestors have any beneficial effects in the absence of FcεRI? Or did the high-affinity IgE receptor predate the appearance of IgE, and in this case, what was its original physiological ligand? Which of the protective effects of IgE, in the absence of FcεRI on mast cells and basophils, could not be exerted by IgM, IgG, IgD, IgY or other immunoglobulins? As all those early mammals are extinct, at present there is no clear way to answer these questions. What is known about the evolution of IgE receptors was summarized in the recent review by Hellman and co-authors.<sup>11</sup> Phylogenetic evidence suggests that the IgE receptor evolved from Fc receptor-like (FcRL) molecules early during mammalian evolution.<sup>16</sup> It is interesting to note that humans still have 8 genes encoding these poorly understood FcRL molecules in their genome.<sup>11,17</sup> Mast cells and basophils, in all likelihood, precede the advent of both IgE and its high affinity receptor, as does the protease content of their granules.<sup>11</sup>

It is important in the context of this investigation to stress that while IgE is unique to mammals, other components of the allergic phenotype, such as the aforementioned basophils and mast cells, or the Th2-type cytokine response in itself, are not. For example, chickens have been shown to respond with a similar polarized immune Th1- or Th2-like response to viruses and helminth parasites, respectively.<sup>18</sup> Here, we discuss the evolution of type 1 hypersensitivity. Our discussion will be restricted to the effector arm of the allergic response, that is the last portion of the immune response leading to IgE-dependent mediator and cytokine release by high-affinity IgE

**FIGURE 1** Approximate timeline of key events related to allergenic sources (normal font) or evolution of mammals (bold font) described in this paper. The timeline highlights how potential sources of archetypal allergens (insects and plants) preceded the evolution of IgE and its receptor in mammals, while other sources of allergens (such as venom from bees and human parasites) arose well after the evolution of IgE, putatively increasing its evolutionary value, thus leading to its preservation and consolidation across all mammals



receptor FcεRI bearing mast cells and basophils, usually after activation by cognate allergens.

What were the ancestral allergens present around the time IgE appeared for the first time, and which sources of allergens existed at the time of the primordial mammals? We will attempt to answer this question by reviewing the status of three major potential sources of allergens at the time of early mammals some 195 million years ago: plants, insects (in our context, haematophagous exoparasites) and endoparasites.

### 3 | WHAT WERE THE FIRST ALLERGENS?

By the time small insectivorous mammals appeared (see Figure 1), many plants, which reproduced using wind-borne pollens and spores, such as gymnosperms, cycads and ferns, had been around since the Carboniferous—a geologic period beginning at the end of the Devonian some 360 million years ago. Considering today's importance of pollen as a source of allergens, it is tempting to suggest that the first allergens emerged from these pollens and spores, and similarly, from insects, which formed part of the diet of ancestral mammals. Parasites, widely believed to be closely associated with the IgE arm of the immune response, are also ancient. Coprolites, fossilized faecal matter, recovered from Early Cretaceous dinosaurs such as the Bernissart Iguanodons in Belgium,<sup>19</sup> contain evidence of protozoan and helminth parasites. Blood-feeding ectoparasites, such as sand flies and biting midges, and their protozoan parasites such as early *Leishmania*, already existed in the Early Cretaceous, more than 100 million years ago, as documented by organisms preserved within amber.<sup>20</sup> In other words, by the time our mammalian ancestors made their first appearance on Earth, and as will be explained in more detail below, the IgE isotype, plus all ingredients implicated in the IgE response and the allergic phenotype, already existed. On the environmental/allergen side, plant pollens, spores and invertebrates, such as insects, parasitic helminths, protozoan parasites and ectoparasites, while on the immunological side, mast cells, basophils, Th2 cytokines, IgE and its high-affinity receptor FcεRI, were all present during early mammalian evolution.

If airborne allergens were the original sensitizers, these probably impacted on the skin, the mucosal surfaces of the airways and gastrointestinal tract, possibly resulting in cross-sensitisation of the mucosal immune system through antigens shared between insects, pollens and fungal spores. While the molecular identity of such hypothetical, ancestral cross-reactive allergens will in all likelihood remain unknown, structural similarities, shared within large families of allergens, suggest that wide cross-reactivities across kingdoms (plants, fungi, animals) are possible (see Table 1). Examples are EF-hand proteins (AIIFam AF007), widely shared between insects, helminth or other parasites, and plants, or peritrophin A-type chitin-binding domains (AF077), also shared between insects and plants. Perhaps the most promiscuous Allergen Family (in terms of allergenicity across kingdoms) is the heat shock protein 70 family (HSP70; AF002), which is shared between several haematophagous

insects, cestode and trematode parasites, moulds, skin colonizing yeasts, dust mites and plants. Further examples of allergens shared between parasites, plants and nonparasitic animals are found in the CRISP/PR-1/venom group 5 (AF044) and glutathione-S-transferase (AF010) allergen families, see Fitzsimmons et al for more details.<sup>21</sup> Two more issues may be of relevance here: first, it has been suggested that fungal spores are even more ubiquitous in the atmosphere than plant pollen.<sup>22</sup> Secondly, many fungal allergens also have cross-reactive counter parts in nonfungal organisms: enolases, manganese superoxide dismutases (MnSOD), cyclophilins, glutathione-S-transferases, thioredoxins, transaldolases, serine proteases, heat shock proteins, ribosomal or peroxisomal proteins from fungi have all been found to be cross-reactive (listed in detail by Twaroch and her colleagues).<sup>23</sup> Several of these molecules are also known allergens in parasitic helminths, for example glutathione-S-transferases in *Schistosoma haematobium*<sup>24</sup> and cyclophilin in *Echinococcus granulosus*.<sup>25</sup> Moreover, due to the increasing worldwide interest in insects as a source of food, more and more new allergens from insects are being described.<sup>26,27</sup> The resulting image is of an environment rife with allergenic sources, such as fungal spores, plant pollen, animal toxins and parasites (see Figure 2), with little reason to assume that the environment would have been radically different at the time of our mammalian ancestors.

Possibly, the allergic phenotype would have been operating at mucosal surfaces at this time in a gate-keeper capacity, to expel noxious material from the body. But was this material noxious, considering that pollen, and other allergenic materials found today, are not toxic?

Is it possible that some of the pollens, spores and insect-derived allergens at the time of first mammal appearance were more toxic than those currently experienced, giving a selective advantage to individuals with an allergic phenotype? The dominant plants at the time mammals first appeared would have been cycads. Cycads are gymnosperms, that is their naked seeds are unprotected by an ovary or fruit. These ubiquitous plants are seen as representative of the most primitive seeds-plants living today.<sup>28</sup> Whether ancient cycads were anemophile (ie requiring winds for pollination) or entomophile (ie using insects as pollinators), or both, is difficult to ascertain retrospectively. Modern cycads certainly use pollinators, for example certain beetles and tiny thrips.<sup>29</sup> Due to its widespread occurrence, early insectivorous mammals would have been constantly exposed to pollen, either directly, or via the insect pollinators upon which they preyed. Did the ancient cycads possess potentially toxic pollens, and did these have the ability to elicit an IgE-dependent elimination response (see "toxin hypothesis" below)? Only one allergen from cycads, Cyc c I from *Cycas circinalis*, is described in the Allergome database.<sup>30</sup> This appears to be a 20.7 kDa protein,<sup>31</sup> but its molecular identity remains to be described; neither is anything known about its potential toxicity. In other words, there is not much evidence for toxic ancestral allergens in modern cycads.

There are, however, two important caveats to this statement. First, modern cycads are not directly related to Mesozoic cycads. In fact, it is now thought that modern cycads may have originated

**TABLE 1** Table showing known allergens classified based on their structural motifs, separated in parasitic proteins, animal (nonparasitic) proteins, plant and fungal allergens. The table was compiled from the following sources: the Allergome database (2020),<sup>30</sup> the AllFam database (2020),<sup>117</sup> Fitzsimmons et al,<sup>21</sup> Tyagi et al,<sup>118</sup> Caraballo et al,<sup>119</sup> Daschner et al,<sup>112</sup> Farnell et al,<sup>120</sup> Cramer et al<sup>121</sup> and Díaz-Perales et al.<sup>122</sup> Not included was the large Prolamin superfamily (AF050), which is only found in plants, or several small AllFam families with only a few members. Allergens whose allergenicity has been predicted computationally, but not verified experimentally (as a minimum requirement, binding of IgE in ELISA or immunoblot experiments) have not been included. Parasitic allergens do not follow WHO/IUIS nomenclature<sup>122</sup>

Animal (parasitic)	Animal (nonparasitic)	Plant	Fungal
<b>Structural motif</b> (AllFam Accession; Pfam domain) <i>Common names/representatives</i>			
<b>EF-Hand proteins</b> (AF007; PF00036, PF01023, PF13202, PF13405, PF13499, PF13833) <i>Calmodulin, parvalbumin</i>			
Ani s Troponin C; Sch ma Sm22 (SmTAL-1); Sch ma Sm21 (SmTAL-2); Sch ma Sm20 (SmTAL-3); ShTAL-1; SjtAL-1; SmTAL-4; SmTAL-5; SmTAL-13	Aed a 5; Art fr 5; Bos d 3; Bla g 6; Bla g 8; Clu h 1; Cra c 4; Cra c 5; Cra c 6; Cyp c 1; Der f 26; Evy j parvalbumin; Gad c 1; Gad m 1; Gal d 7; Gal d 8; Hom a 3; Hom a 6; Hom s 4; Lat c 1; Lep w 1; Lit v 3; Lit v 4; Mac m parvalbumin; Mac n parvalbumin; Merl a parvalbumin; Merl b parvalbumin; Merl c parvalbumin; Merl g parvalbumin; Merl m parvalbumin; Merl pa parvalbumin; Merl po parvalbumin; Merl pr parvalbumin; Onc m 1; Pen m 3; Pen m 4; Pen m 6; Per a 6; Pon l 4; Ran e 1; Ran e 2; Ras k 1; Sal s 1; Salv f parvalbumin; Sar sa 1; Schi j tegumental CaBP; Sco j parvalbumin; Sco s parvalbumin; Seb m 1; Syr v 3; The c Parvalbumin; Thu a 1; Tra j parvalbumin; Tyr p 34; Xip g 1	Aln g 4; Amb a 10; Amb a 9; Art v 5; Bet v 3; Bet v 4; Bra n polcalcin; Bra r 5; Che a 3; Cup a polcalcin; Cyn d 7; Fra e polcalcin; Hom a 3; Hom a 6; Hom s 4; Jun o 4; Ole e 3; Ole e 8; Ory s polcalcin; Par j 4; Phl p 7	-
<b>Tropomyosin</b> (AF054; PF00261) <i>Tropomyosin</i>			

(Continues)

TABLE 1 (Continued)

Animal (parasitic)	Animal (nonparasitic)	Plant	Fungal
Ani s 3; Asc l 3; Bru m 3; Onc v 3; Onc o 3; Sch ma 3; Sm Tropomyosin-1	Aed a 10; Bal r tropomyosin; Bla g 7; Blo t 10; Cha f 1; Chi k 10; Chio o tropomyosin; Cho a 10; Cra c 1; Cras g tropomyosin; Cras v tropomyosin; Der f 10; Der p 10; Eri s tropomyosin; Erim i tropomyosin; Eup p tropomyosin; Eup s tropomyosin; Ful m tropomyosin; Hal d tropomyosin; Hal di tropomyosin; Hal l 1; Hel as 1; Hom a 1; Lep d 10; Lep s 1; Lit v 1; Mac r 1; Mel l 1; Met e 1; Mim n tropomyosin; Nep p tropomyosin; Oct v tropomyosin; Omm b tropomyosin; Onch v tropomyosin; Ora o tropomyosin; Ore m 4; Pan b 1; Pan s 1; Para c tropomyosin; Pen a 1; Pen i 1; Pen j tropomyosin; Pen m 1; Per a 7; Per f tropomyosin; Pern v tropomyosin; Por p 1; Por s tropomyosin; Por t tropomyosin; Proc c tropomyosin; Pse s tropomyosin; Sca b tropomyosin; Scy s tropomyosin; Sep e tropomyosin; Sepi l tropomyosin; Sino c tropomyosin; Sole s tropomyosin; Tod p 1; T re k tropomyosin; Tur c tropomyosin; Tyr p 10; Ven p tropomyosin	-	-
<b>Paramyosin</b> (AF100; PF01576) <i>Paramyosin, Myosin heavy chain</i>			
Ani s 2; Sch ma PM; Sch j PM (Sj97)	Blo t 11; Der f 11; Der p 11; Hal d paramyosin	-	-
<b>Calreticulin</b> (AF055; PF00262) <i>calreticulin</i>			
Nec a calret; Sm calret	-	-	Pen ch 31
<b>Glutathione-S-Transferase (GST)</b> (AF010; PF00043, PF02798, PF13410, PF13417, PF14497) <i>Glutathione-S-Transferases</i>			
Asc l 13; Asc s 13; Bru m 13; Onc v 13; Sarc s GST; Sm GST; Sch j 13; Wb GST	Bla g 5; Bla g GST; Blo t 8; Der f 8; Der p 8; Per a GST	Tri A GST	Alt a 13; Asp f GST; Pen c 24

(Continues)

TABLE 1 (Continued)

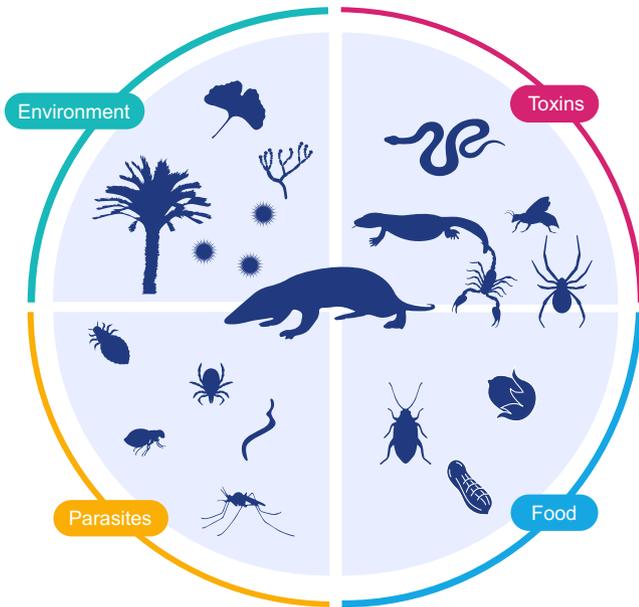
Animal (parasitic)	Animal (nonparasitic)	Plant	Fungal
<b>CRISPR/PR-1/venom group 5/CAP family</b> (AF044; PF00188) <i>Venom-Allergen Like, Pathogenesis-related protein PR-1, group 5 insect venom allergens, Cysteine-rich secretory protein family</i>			
Na asp 2; SmVAL-4; Sm VAL-26; Cte f 2	Dol a 5; Dol m 5; Glo m 5; Pac c 3; Pol a 5; Pol d 5; Pol e 5; Pol f 5; Pol g 5; Pol m 5; Poly p 5; Pol s 5; Sol g 3; Sol i 3; Sol r 3; Sol s 3; Str s venom group 5-like; Tab y 5; Ves f 5; Ves g 5; Ves m 5; Ves p 5; Ves s 5; Ves v 5; Ves vi 5; Vesp c 5; Vesp m 5; Vesp ma group 5	Art v 2; Cuc m 3; Cyn d 24	-
<b>Lipocalin</b> (AF015; PF00061, PF08212) <i>Lipocalins, Cytoplasmic Fatty acid binding proteins, <math>\beta</math>-Lactoglobulins, mammalian dander allergens</i>			
E. granulosus FABP-1; Sm FaBP; Sm Lipocalin; SmBv1L	Aca s 13; Arg r 1; Bla g 4; Blo t 13; Bos d 1; Bos d 2; Bos d 5; Can f 1; Can f 2; Can f 4; Can f 6; Cav p 1; Cav p 2; Cav p 3; Cav p 6; Cyn sp; Der f 13; Der p 13; Equ as BLG; Equ c 1; Equ c 2; Fel d 4; Fel d 7; Lep d 13; Mes a 1; Mer un 23 kDa; Mus m 1; Ory c 1; Ory c 2; Ory c 4; Per a calycin; Per a 4; Phod s 1; Phos 21 kDa; Rat n 1; Sus s 5; Tria p 1; Tyr p 13	-	-
<b>Cyclophilin</b> (AF038; PF00160) <i>Cyclophilin, Peptidyl-prolyl Isomerase</i>			
E gra cyclophilin (EA21)	Der f 29; Der p 29	Bet v 7; Bet pu 7; Cat r 1; Cuc ma CYP; Dau c cypn; Hev b cyp; Lol p CyP; Ole e 15; Pla or CyP; Rub i CyP; Sola l 5	Asp f 11; Asp f 27; Cand a Cyp; Mala g 6; Mala sl 6; Mala j 6; Mala n 6; Mala o 6; Mala p 6; Mala r 6; Mala s 6; Mala y 6; Psi c 2; Rhi o 2; Sac c CyP
<b>Heat Shock Protein 70 (HSP70)</b> (AF002; PF00012) <i>Heat shock protein 70</i>			
Aed a 8; Cul n HSP70; E gra HSP70; Tox g HSP70; Sm HSP70	Blo t 28; Der f 28; Der f HSP70; Der p 28; Sim vi 70kD; Tyr p 28; Vesp a HSP70	Cor a 10; Cic a 10	Alt a 3; Cla h Hsp70; Mala g 10; Mala s 10; Pen c 19
<b>Superoxide Dismutase (SOD)</b> (AF019, AF020; PF00080, PF00081, PF02777) <i>Cu/Zn Superoxide dismutases, Fe/Mn Superoxide dismutases</i>			
Sm superoxide dismutase	Dro m MnSOD	Hev b 10; Ole e 5; Phl p Fe/Mn SOD; Pis v 4; Sola l SOD	Alt a 14; Asp f 6; Cand a MnSOD; Mala s 11; Mala f 11; Mala y 11; Neo fi 6; Sac c MnSOD
<b>Thioredoxin</b> (AF023; PF00085, PF13848) <i>Thioredoxins</i>			

(Continues)

TABLE 1 (Continued)

Animal (parasitic)	Animal (nonparasitic)	Plant	Fungal
Sm Thioredoxin	Plo i 2	Hev b Trx; Tri a 25; Tri a Trx; Zea m 25	Alt a 4; Asp f 28; Asp f 29; Cop c 2; Fus c 2; Mala s 13
<b>Trypsin inhibitors</b> (AF003, AF013, AF018, AF046; PF00014, PF00050, PF00079, PF14625) <i>Kunitz-Type Trypsin inhibitors, Kazal-Type Trypsin inhibitors, Serine protease Inhibitors, Serpin serine protease inhibitors</i>			
Ani s 1; Ani s 6; Sm serpin-like protein	Api ml 7; Bos d T1; Der f 27; Gal d 1; Gal d 2; Hir me Hirudin; Lop cu 1; Lop sp 1; Neo ju 1; Pha ca 30; Sim vi 2	Ara h 3; Cuc ma 4; Fag e 10 kD; Fag e Tl; Gly m Tl; Hev b 15; Hor v 15; Hor v BTI; Hor v 39; Ory s 17 kD; Ory s aA Tl; Sola t 2; Sola t 3; Sola t 4; Tri a 30; Tri a 33; Tri a 39; Tri A 40; Tri a CMX; Tri tu 30	-
<b>Alpha-amylase</b> (AF033; PF00128, PF02806, PF09260) <i>Alpha-amylases</i>			
Aed a 4	Aca s alpha-amylase; Asp o 21; Bla g 11; Blo t 4; Der f 4; Der p 4; Eur m 4; Per a 11; Sus s Amylase	-	-
<b>Profilin</b> (AF051; PF00235) <i>profilins</i>			
Sm profilin; Sj profilin	Der f profilin; Tyr p 36	Aca f 2; Act d 9; All c 4; Aln g 2; Ama r 2; Amb a 8; Amb t 8; Ana c 1; Ant o 12; Api g 4; Ara h 5; Ara t 8; Art h 4; Art v 4; Aspa o 4; Ave s 12; Bet pu 2; Bet v 2; Beta v 2; Bra n 8; Bra ni 8; Cap a 2; Car b 2; Car mi 2; Car m profilin; Cas s 2; Cat r 2; Che a 2; Cit cl 2; Cit s 2; Citr l 2; Coc n 5; Cor a 2; Cro s 2; Cuc m 2; Cuc ma 2; Cuc p2; Cuc s 2; Cum c 2; Cup s 8; Cyn d 12; Dac g 12; Dau c 4; Dio k4; Fag s 2; Fic c 4; Foe v 2; Fra a 4; Fra e 2; Gly m 3; Hel a 2; Hev b 8; Hor v 12; Hum j 2; Jug r 7; Koc s 2; Lig v 2; Lil l 2; Lit c 1; Lol p 12; Lup a 5; Mal d 4; Mal g 4; Man i 3; Mer a 1; Mor a 4; Mus a 1; Mus xp 1; Nic t 8; Ole e 2; Ory s 12; Pap s 2; Par j 3; Pers a 4; Pet c 2; Phl p 12; Pho d 2; Pho ro 2; Phr a12; Pim a 2; Pis s 5; Pla l 2; Poa p 12; Pro j 2; Pru av 4; Pru du 4; Pru p 4; Pyr c 4; Que a 2; Ric c 8; Rob p 2; Sal k 4; Sec c 12; Ses i 8; Sin a 4; Sola l 1; Sola m 1; Sola t profilin; Sor h 12; Spi o 2; Syr v 2; Tri a 12; Vac fa 2; Vig r 5; Vit v 4; Zea m 12; Zyg f 2	Sac c Profilin

Note: The following abbreviations are used for parasitic allergens: Aed a: *Aedes aegypti*; Ani s: *Anisakis simplex*; Asc l: *Ascaris lumbricoides*; Asc s: *Ascaris suum*; Bru m: *Brugia malayi*; Cte f: *Ctenocephalides felis*; Cul n: *Culicoides nubeculosus*; E. granulatus, E gra: *Echinococcus granulatus*; Nec a, Na: *Necator americanus*; Onc o: *Onchocerca ochengi*; Onc v: *Onchocerca volvulus*; Sarc s: *Sarcoptes scabiei*; Sch j, Sj: *Schistosoma japonicum*; Sch ma, Sm: *Schistosoma mansoni*; Sh: *Schistosoma haematobium*; Tox g: *Toxoplasma gondii*; Wb: *Wuchereria bancrofti*.



**FIGURE 2** Schematic illustration attempting to reconstruct the putative “allergenic environment” which may have been present during the early Jurassic, at the time when the first mammal ancestors are thought to have arisen. The centre of the picture shows early mammal *Morganucodon* in an environment which consists of early plants (dominated by cycads, ferns, giant horsetail-trees and conifers), but would also have included early angiosperms (indicated by the pollen), as well as fungal spores, which would also have been omnipresent. Many exo- and ectoparasites would also have been present, such as ticks, fleas, lice and haematophagous dipterans (mosquitoes) as well as an array of intestinal and other worm parasites. Other sources of allergens might have been found in food, such as insects, nuts and seeds. Finally, allergens would also have been present in venomous animals, some of which originated in the Paleozoic era (scorpions, spiders), well before the first mammals existed, while others (bees) arose later. Some of these may also have played a role as a source of food, suggesting the interplay between early mammalian protection against the venoms of their prey (as a source of food) as a possible driving force underlying the evolution and preservation of the IgE response. The increased incidence of sensitization to insect-derived proteins in the context of the rising popularity of entomoculture and entomophagy also illustrates the potential link between insects and food as a source of ancestral allergens

as recently as 5–12 million years ago.<sup>32</sup> Therefore, it is not clear to which extent the ~ 300 species surviving today are representative of their older Mesozoic ancestors, particularly in terms of their biochemistry and potential allergenicity. Secondly, the noxious agents do not need to be proteinaceous, and do not have to be found in pollen.

Taken together, there is insufficient evidence to suggest cycads as an early source of ancestral allergens. As angiosperms were not yet widespread when the first mammals arose, this would appear to rule out plants as the original sources of allergens. If plants are not “at the root” of the evolution of the IgE response, are perhaps animals, and/or their toxins, better candidates as the source of ancestral allergens?

To continue our speculative palaeohistory of allergy, the first primates appeared in the Palaeocene epoch, some 53 million years ago, which followed the appearance of angiosperms and their associated pollens in the Middle to Late Mesozoic era (250 to 65 million years ago), with their main radiation occurring during the Cretaceous.<sup>33</sup> With the appearance of angiosperms, however, also came the need for pollinators, as the gametes in angiosperms are produced in separate organs. It is probably not a co-incidence that pollen-gathering bees appeared soon after angiosperm plants, 110–140 million years ago,<sup>34,35</sup> and with the bees, also their sting and venom would have become widespread.

## 4 | THE TOXIN HYPOTHESIS

The appearance of venomous stinging insects leads us to the so-called “toxin hypothesis” of allergy, formulated by Margie Profet in 1991.<sup>36</sup> This followed on from the work of Higginbotham<sup>37</sup> and Stebbings<sup>38</sup> who considered this idea in a much more restricted way before her, and was later expanded and re-proposed by Ruzlan Medzhitov<sup>39</sup> and Stephen Galli.<sup>40</sup> In fact, the toxin hypothesis can even be traced back all the way to the original discovery of sensitization and anaphylaxis, to the “hypnotoxin” from *Physalia* (a.k.a. Portuguese man-of-war), by Paul Portier and Charles Richet in 1901—for a detailed history of the discovery, see May.<sup>41</sup>

The main tenet of Profet’s “toxin hypothesis” is that the allergic response has evolved to “defend against some sort of immediate danger”,<sup>36</sup> that is a multitude of toxins from plants and animals, but also (and this is where Profet becomes less focussed) toxins from ingested mushrooms, or toxic substances contained in pollen (“eg phenolic acids, sesquiterpene lactones and alkaloids”), or fungal spores, or carcinogenic nickel. Profet sees allergy as the “last line of defense against toxins” when “other mechanisms prove insufficient, either because of a defect in one of the mechanisms or because of the ability of a particular toxin to evade these defensive mechanisms.”

In support of Profet’s toxin hypothesis, it can be noted that most physical responses elicited during IgE-mediated immune activation, such as sneezing, vomiting, diarrhoea, tear production or coughing, are all responses which can help expel a toxin that has triggered an IgE-mediated response. Also, a moderate decrease in blood pressure induced by histamine could “slow the rate at which toxins are circulated to target organs”<sup>36</sup> Taken together, Profet’s toxin hypothesis suggests that IgE acts as a sensor for low levels of toxic proteins, inducing an immediate protective response to expel the (eg ingested or inhaled) toxin.

However, it could be easily argued that, for example, the occurrence of lethal anaphylactic reactions to bee venoms speaks against such a postulated beneficial role of IgE, at least as far as humans are concerned. These suggestions can be reconciled if we remember that histamine is not the only mediator released by mast cells or basophils after IgE-crosslinking. In particular, mast cells are richly endowed with potent, preformed proteases such as tryptase, chymase and carboxypeptidase A, which have been shown to at least

in part break down powerful poisons of insects such as bees,<sup>42,43</sup> scorpions<sup>44</sup> or reptiles (gila monster, snakes).<sup>44</sup> These aspects have been recently reviewed by Galli and colleagues.<sup>40,45</sup>

While important correlations have been found by these authors, which appear to lend support to some of Profet's hypotheses, it can also be argued that such correlations only attempt to justify a posteriori the evolution of IgE in a context which may not have been as relevant at the time this immunoglobulin evolved, that is in early mammals. Some might feel that Profet's toxin hypothesis may have been influenced by a degree of anthropocentrism. From an evolutionary point of view, the question is less whether IgE can confer protection against metals such as nickel and arsenic, aflatoxins from moulds, or other toxic secondary metabolites contained in food. The key question is, which of the factors present during early mammal evolution were sufficiently powerful to confer IgE-producing animals a strong evolutionary advantage, leading to the consolidation and preservation of this new trait in all mammals?

## 5 | WHERE THE FIRST ALLERGENS ANIMAL-DERIVED?

Our small mammalian ancestors will certainly have been affected by venomous animals, as their prey (eg snakes, large spiders), predators (eg scorpions),<sup>46</sup> or through accidental exposure, for example to bees, wasps or other (not hematophagous) stinging insects. As mentioned earlier, a fast immune response operated by the immunological IgE/mast cell/protease axis has the potential to provide protection against venomous predators or accidental exposure to venoms.

Galli and colleagues have provided very compelling evidence that mast cell-derived proteases can degrade individual venom components, as well as protect against the lethal effects of whole venom.<sup>42,44</sup> It needs to be borne in mind here that animal venoms are usually complex mixtures, with several components acting on different targets (eg antihemostatic, neurotoxic and cytotoxic). To name just one example, a recent proteomic study of *Heloderma suspectum* (a.k.a. gila monster) venom has identified 19 new venom components from a total of 39 proteins contained in 58 spots, which are the major constituents of gila monster venom.<sup>47</sup>

Clearly, mast cells are ideally positioned to effect such a protective role, as they are found in large amounts in the skin, in particular in proximity of blood vessels, and through the release of histamine and other mediators can promote vascular permeability and access of other protective molecules to the tissues affected by a venomous bite.<sup>48</sup> Galli et al's work also provided important evidence regarding the role of IgE in this process. Specifically, they showed that (a) a single exposure to honeybee venom was sufficient to induce an IgE response, (b) that protection was indeed dependent on IgE (shown by heat treatment and depletion experiments) and (c) that the effects were mediated via the high-affinity IgE receptor.<sup>40</sup> This suggests that mast cells and IgE could play a central role in anti-venom protection.

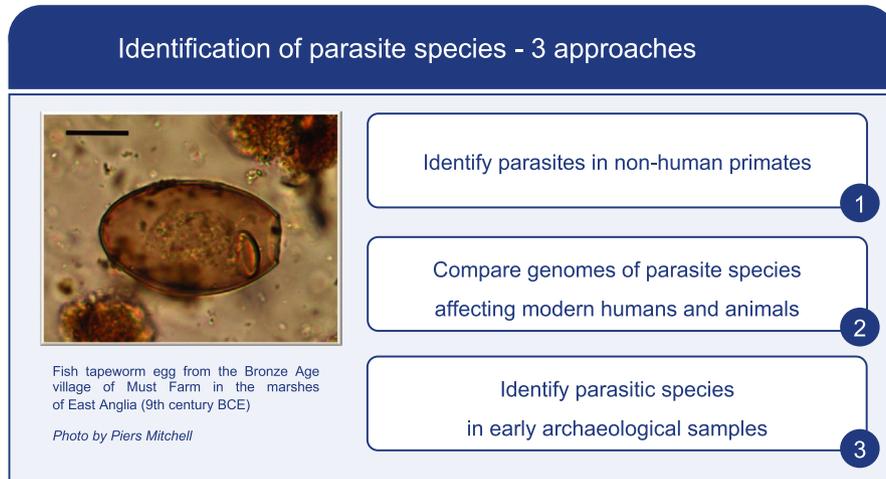
There certainly are also examples of protective factors that are not related to IgE, or mast cells, or mast cell-derived proteases.<sup>49</sup> For example, the honey badger *Mellivora capensis* has amino acid substitutions in the muscular nicotinic cholinergic receptor (nAChR) protecting them against the effects of  $\alpha$ -neurotoxins. Similar mutations, resulting from convergent evolution, are found in hedgehogs, mongoose and pigs.<sup>50</sup> In the case of the woodrat *Neotoma micropus*, and other animals resistant to snake poison, protection is conferred by relatively large, acid antihemorrhagic proteins, none of which are proteases or mast cell-derived.<sup>51,52</sup> However, such examples rely on very specific adaptations to individual components in specific venoms. The key advantage of an IgE/mast cell/protease-dependent protection is that the mixture of proteases released during degranulation (chymases, tryptases, carboxypeptidase A)<sup>53</sup> is able to neutralize a wide range of polypeptide-based venoms, independently on their molecular interactions with their intended target, akin to pepsin providing nonspecific digestion of proteins ingested with food.

## 6 | PARASITE-DERIVED ALLERGENS—THE WORM HYPOTHESIS

Another important early source of allergens would have been parasites. As stated earlier, even dinosaurs had their parasites, and parasitic nematodes infecting blood-sucking arthropods have been found preserved in amber from the Cenozoic epoch and later periods.<sup>54</sup> Thus, early mammals would have been fed upon by a range of hematophagous parasites (eg ticks, mosquitos, midges, lice, sandflies and fleas), some of which might also have transmitted parasitic protozoa or helminths. An exact chronology is very difficult, due to the rarity of sufficiently well-preserved fossil finds (in amber) and their interpretation. Ticks, for example, appear to have arisen somewhat later than mammals, with their origin traced back to at least the Cretaceous,<sup>55</sup> or fleas, during the middle Jurassic.<sup>56</sup> However, the "dinosaur flea" hypothesis postulates that the earliest flea ancestors originally parasitized dinosaurs, and later switched to mammals, a view which is not devoid of controversies.<sup>57</sup>

Despite the difficulties in establishing a phylogenetic chronology of parasitic species, there is no reason to assume that early mammals would have been affected by parasites in any lesser way than today.

This brings us to the alternative hypothesis explaining the existence of allergy and the IgE response, which here we would like to call the "worm hypothesis." This hypothesis suggests that "most if not all environmental allergens can be related to helminth counter parts and that the IgE response against these allergens is associated with host protection."<sup>21</sup> This hypothesis has been reviewed extensively by Fitzsimmons and co-authors.<sup>21,58</sup> Therefore, we need to explore the parasitic burden of early humans, to assess whether helminth and other parasites would have been ubiquitous and so exerted a significant immunological, evolutionary pressure on health and fitness in our early ancestors, justifying the preservation of the IgE response which had arisen in early mammals.



**FIGURE 3** Infographic illustrating the three approaches that can be used for identification of parasites affecting ancestral hominids

## 7 | PARASITES IN EARLY HUMANS

The origins of many parasites that now infect humans have been investigated in order to see when and where they might have first spread to our species. *Taenia* spp. tapeworms have evolved to infect a broad range of mammals, and genetic analyses suggest the oldest originated many millions of years ago.<sup>59,60</sup> Schistosomiasis is thought to have evolved in rodents in Asia perhaps 60-70 million years ago, before being spread to Africa by animal migrations perhaps around 12 million years.<sup>61,62</sup> *Fasciola* (liver fluke) seems to have evolved in African proboscideans (elephant family) roughly 50 million years ago, before being spread to Asia around 18 million years ago.<sup>63</sup> While anthropoid apes appeared in the Oligocene epoch (around 26 million years ago), our own genus *Homo* can be traced back to the Pliocene around 2.8 million years ago, and *Homo sapiens* to the Quaternary period around 200 000 years ago.<sup>64-66</sup> Once our own species evolved in east Africa, all these parasites subsequently evolved species that infect humans. To understand the kinds of parasite to which humans have been exposed to throughout our evolution (sometimes referred to as heirloom parasites), three approaches have been helpful (see Figure 3).

The first is to look at the parasites present in nonhuman primates in Africa. When parasites identical to or very similar to those found in humans are identified in wild chimpanzees, gorillas or baboons, then this would suggest that such parasites affected ancestors of all these primates including humans. Examples of such parasites include hookworm (*Ancylostoma duodenale*, *Necator* sp), roundworm (*Ascaris* sp), whipworm (*Trichuris* sp), pinworm (*Enterobius* sp), dwarf tapeworm (*Hymenolepis nana*), threadworm (*Strongyloides* sp) and blood flukes (*Schistosoma mansoni*).<sup>67</sup>

The second approach is to use genetic analysis of modern parasites that affect humans to compare with related species that affect other animals, in order to determine when and where the human form diverged from the other species. For example, the forms of *Taenia* tapeworm that affect humans are pork tapeworm

(*T solium*), beef tapeworm (*T saginata*) and Asiatic tapeworm (*T asiatica*). Genetic analysis has shown that pork tapeworm is most closely related to *Taenia* species that infect hyenas, while beef tapeworm and Asiatic tapeworm are most closely related to *Taenia* species that infect lions.<sup>60</sup> This would suggest that the species of *Taenia* tapeworm that now infect humans probably evolved in Africa from the more ancient species that infected wild predators such as hyenas and lions, as they all hunted the same species of herbivores in east Africa, perhaps 1-2.5 million years ago.<sup>68</sup>

The third approach is to identify the parasite species infecting the human inhabitants of Africa in early archaeological samples, so showing the species of parasites that most likely evolved in that continent. Examples of such species include helminths such as roundworm, whipworm, fish tapeworm, pinworm, filarial worm, blood fluke, threadworm and *Taenia* tapeworm, and the protozoa responsible for visceral leishmaniasis (*Leishmania donovani*), malaria (*Plasmodium falciparum*) and toxoplasmosis (*Toxoplasma gondii*).<sup>67</sup>

Around 10 000-15 000 years ago, hunter-gatherer groups began to form more orderly social structures in the Near East, leading to the farming of crops and domestication of animals.<sup>69,70</sup> Before the introduction of farming and herding in the Neolithic period, the earliest archaeological evidence for parasite infection we have in humans are *Ascaris* sp eggs (roundworm) from a cave inhabited by humans in France dating to about 30 000 years ago.<sup>71</sup> Once farming and herding developed, human coprolites and pelvic soil from burials in the Near East dating to 7000-10 000 years ago have been found to contain a range of nematode and fluke ova.<sup>72,73</sup>

Studies of modern populations have shown that when nomadic hunter-gatherers settle and adopt farming, the prevalence of parasites spread by poor sanitation increases dramatically. Parasites most associated with this change include roundworm, whipworm, hookworm and pathogenic amoeba that cause dysentery.<sup>74</sup> Further support for such hypothesis comes from recent studies of foragers living in Amazonian Ecuador, which had dramatically lower helminth parasite loads than their neighbouring subsistence farming

populations.<sup>75</sup> This would suggest that over the last 10 000 years, the parasite burden experienced by many people around the world changed from a hunter-gatherer pattern to a settled farmer pattern. If we combine this with the absence of parasites in many people living in the high-income countries around the world today, this would suggest three broad patterns of parasite load occur: that of hunter-gatherers, of farmers, and absence of parasites in modern high-income countries.

## 8 | THE VALUE OF THE ALLERGIC PHENOTYPE TODAY

We can see that the allergic phenotype co-evolved in early mammals with a number of potent sources of allergenic material, ranging from venomous predators to hematophagous insects and parasites, possibly imparting a selective advantage to individuals best equipped to deal with the allergens present at the time. In the case of parasites, this was probably the beginning of an arms race, with parasites forced to evolve defence strategies against the immune system, possibly resulting in the appearance of the regulatory cell populations associated with immunological homeostasis in infected individuals today. Now we can start to consider examples that demonstrate the value of the allergic phenotype today (see Figure 4).

IgE in combination with both mast cells and basophils has been shown to play a host-protective role against ticks.<sup>76,77</sup> Another physical response to IgE-dependent activation of mast cells, scratching, might play a beneficial role in protecting against exoparasites. The itching sensation, induced by histamine released in response to tick bites, could be important in terms of alerting the host to the presence of parasites and inducing specific behavioural changes (eg the removal of ticks, before they can transmit pathogens). Ticks are related to spiders and scorpions (they are Arachnids), and it is therefore perhaps not surprising that many species of ticks also possess toxins,<sup>78</sup> which can induce paralysis, or other toxicoses. Furthermore, although this has possibly been overinterpreted,<sup>79</sup> there is an increased likelihood of transmission of potentially lethal pathogens by ticks with increased duration of feeding. Thus, fast detection and removal of ticks triggered by IgE-dependent histamine release or, which in the case of ticks remains entirely to be proven, inactivation of tick-derived toxins by mast cell proteases, would also point to beneficial roles of IgE.

At one time, in the context of gastrointestinal worm infections, the facilitated passage of plasma components to mucosal surfaces following vasodilation was termed "the leak-lesion" hypothesis. This hypothesis, originally formulated in the late 1960s, attempted to explain how IgE-mediated immune responses could lead to the expulsion of intestinal parasites. Examples of successful parasite expulsion mediated by IgE are infection of rats with *Trichinella spiralis*<sup>80</sup> or mice with *Heligmosomoides polygyrus*<sup>81</sup> (Figure 4). In this context, it is also interesting to note that mast cell-derived proteases are able to degrade collagens in the cuticle of nematodes.<sup>82</sup>

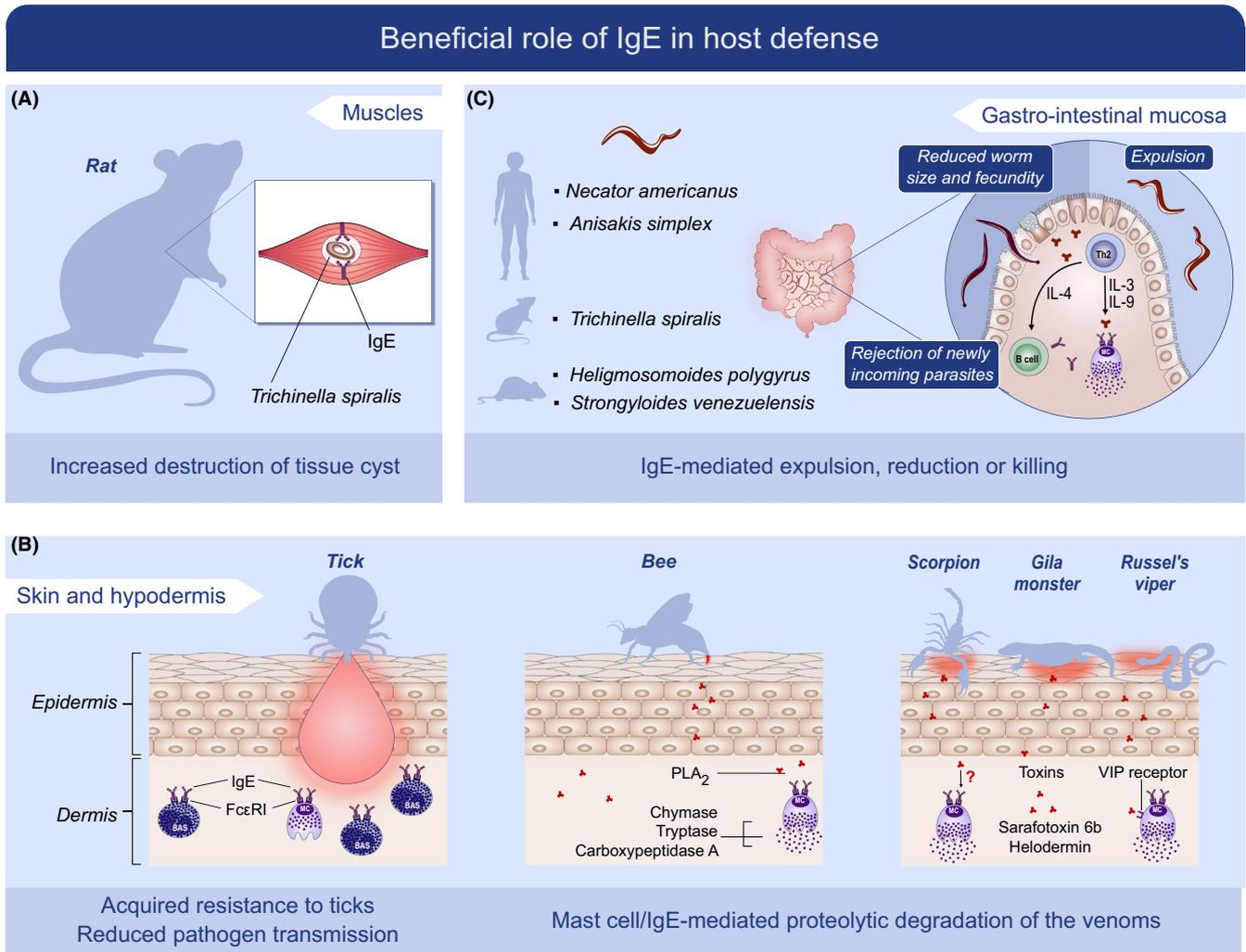
The allergic phenotype is also associated with immunity to re-infection with *Schistosoma haematobium*<sup>83,84</sup> and with reduced worm fecundity in necatoriasis.<sup>85</sup> In a seminal study, John Croese, Rick Speare and their collaborators<sup>86,87</sup> went on to show that resident hookworm (*Necator americanus*) infection supported a Th2 phenotype, which in turn provoked an eosinophilic enteropathy directed particularly at worms which had newly arrived in the gut following reinfection of the host. Using capsule and conventional gastrointestinal endoscopy, in volunteers inoculated with hookworms, these investigators showed (in their words, "seeing is believing") a distal drift of newly arrived parasites, which were unable to attach to the gut, in contrast to the comfortably attached resident primary population. The distal drift and expulsion of the potentially niche-threatening new arrivals was driven by an allergic response.

This is a truly fascinating observation, where a resident parasite population, which infects an estimated 500 million people worldwide, stimulates the allergic phenotype, which regulates the fecundity of that population without necessarily expelling it,<sup>85</sup> yet protects that population from competitive incursion. The investigators in the capsule endoscopy study have also argued that the primary infection induces a relatively benign (*nonatopic*) but evolutionarily effective allergic phenotype, compared to that seen in zoonotic infection with canine hookworm, which causes an overwhelming eosinophilic gastroenteritis.<sup>88</sup>

In support of our argument, it can be reported that the allergic phenotype has been positively implicated in further examples of protective immunity (Table 2). Associations of the allergic phenotype with immunity to protozoan parasites also exist, with malaria and leishmaniasis prominent targets.<sup>89,90</sup> Furthermore, allergists should be aware of the positive role the phenotype has also been demonstrated to play in immunity to viruses, bacteria and tumours.<sup>91-94</sup> Some published work supporting the value of the allergic phenotype in a variety of situations, ranging from association with protection against infectious diseases to cancer, is summarized in Table 2.

## 9 | LOSS OF VALUE: WHAT HAS GONE WRONG?

Most readers will have come across allergy in its clinical context. This is because the incidence of allergy has been reported to have increased fourfold in the past 20 years, with the United Kingdom's Department of Health stating that a third of people will suffer from allergy at some stage in their lives. Stephen Foster, writing in the *Pharmaceutical Journal*,<sup>9</sup> reported on the large number of hospital admissions for allergic conditions, highlighting the potential severity of this type of immune response. It has been estimated that 500-550 million people suffer from asthma or food allergies globally,<sup>95</sup> and another 400 million from allergic rhinitis.<sup>96</sup> Predictions are that this burden is going to rise further. Allergy UK has reported that 20% of children have asthma and that 85% of these are allergic to house dust mites.



**FIGURE 4** Chosen examples of tissues and immunological contexts where an IgE-dependent immune response provides advantages to the host. (A) Shows a muscular *Trichinella spiralis* cyst. In the rat, the presence of parasite-specific IgE around *T spiralis* larvae in muscle cysts has been demonstrated, together with an increased destruction of cysts.<sup>106</sup> (B) shows several examples of IgE-dependent host-protective immune responses against parasites or animal venoms. On the left, a tick lodged in the skin is shown. Elegant work by the Karasuyama group has shown how upon repeated exposure, mice develop acquired resistance characterized by strong infiltrations of IgE-bearing basophils, which can be detected in proximity of the tick mouth parts.<sup>76</sup> Mast cells, which are also shown in the picture, appear less essential in terms of acquired immunity to ticks. The importance of basophils had also been shown earlier by Brown et al<sup>77</sup> This immunity does not result in sterilising immunity but results in shorter feeding times and reduced engorgement weight of ticks, which is thought to reduce transmission of pathogens.<sup>107</sup> Further examples are venoms of bees (eg PLA<sub>2</sub>)<sup>43</sup> and other animal-derived venoms (Russell viper, Gila monster, scorpion), where an IgE-dependent degranulation of mast cells with the release of powerful proteases such as chymase, tryptase and carboxypeptidase A has been shown to provide protection by the Galli group.<sup>40,48,108</sup> Some toxins can activate mast cell directly by binding to receptors (eg helodermin to VIP-R), without the need for IgE. However, the presence of specific IgE may enhance this response<sup>44</sup> (C) Shows examples of intestinal parasites which have been shown to be expelled, reduced or killed IgE dependently in secondary immune responses, in a reaction which also involves Th2-driven mechanisms such as cell hyperplasia, increased mucin production and epithelial cell turnover. Such examples include *Strongyloides venezuelensis*,<sup>109</sup> *T spiralis* and<sup>80,109-111</sup> *Heligmosomoides polygyrus*.<sup>81</sup> *Anisakis simplex* is also listed as an interesting example of a parasite driving a strong IgE response, in its unique dual role as a zoonotic parasite but also as a common food-borne allergen.<sup>112-114</sup> To this day, anisakis is the best characterized nematode in terms of its allergenicity,<sup>113,115</sup> with 22 allergens listed on the Allergome database.<sup>30</sup> Also shown is the beneficial effect of elevated IgE in response to infection with the human hookworm *Necator americanus*, correlating with smaller size, number and reduced fecundity of adult hookworms, and the inability of new incoming parasites to establish in the gut

If the reader accepts what has been presented above, that the allergic phenotype evolved to be useful, a question arises.

Allergy is largely driven in the UK and many other countries by grass pollens such as Timothy grass (*Phleum pratense*), animal

dermatophagoides and allergens from faecal pellets of the dust mites *Dermatophagoides pteronyssinus* and *D farinae*. The allergy patient suffers because of the early release of the pollen grain, which should stay intact until it reaches the plant stigma, exposes

**TABLE 2** Examples of immunological situations where IgE and the allergic phenotype have been proposed to provide benefit

<b>Immunity to parasites</b>	
Schistosomes	83,84
Hookworms	85
Malaria	89
Leishmania	90
Ticks	76
<b>Immunity to other pathogens</b>	
Antiviral immunity	91
Septic peritonitis	92,93
<b>Immunity to tumours</b>	
	94
<b>Wound healing and tissue repair</b>	
Tissue damage induced during parasite migration	123
<b>Protection against venoms</b>	
Hymenoptera, snakes, scorpions	42

allergens such as expansins and profilins in the presence of water, for example during thunderstorms. This is contributed to indoors by pets, moulds and dust mites. The allergic individual has no hiding place.

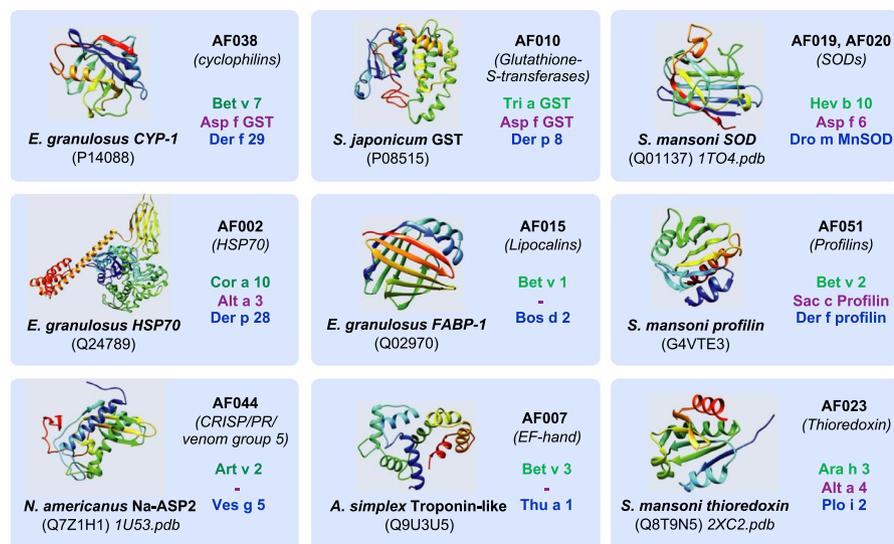
A key question is why those possessing the allergic phenotype, those who would be protected against infections as described earlier, should overreact to proteins from such diverse and relatively benign sources, causing clinical disease. As we have proposed here, it would seem that the allergic individual has an immune system geared to an ancestral existence, still finely tuned to react against infections that are no longer prevalent here and reacting instead to an alternative repertoire of allergenic material. We have previously described how nearly all known allergens from plants, moulds or invertebrates are shared with parasitic helminths,<sup>21</sup> also see Table 1 and Figure 5, for examples of parasitic allergens. The fact that not all known environmental allergens have matching counter parts in parasites does not mean that

these do not exist—they may still need to be discovered, perhaps in parasites of other mammals. *Vice versa*, the fact that some classes of helminth allergens do not have counter parts in plants (most do—see Figure 5), could be due to the fact that such proteins are simply not used in plants (eg tropomyosin, paramyosin), which in our view, validates rather than invalidates the anti-worm defence hypothesis.

Independently of the verdict regarding the toxin vs. worm defence hypotheses (arguments summarized in Figure 6), it can be argued that a large proportion of the world's population retains the benefit of this arm of the immune system. It would be interesting to compare the numbers of those infected with parasites, who benefit from the allergic phenotype, with the numbers of patients suffering from clinical allergy.

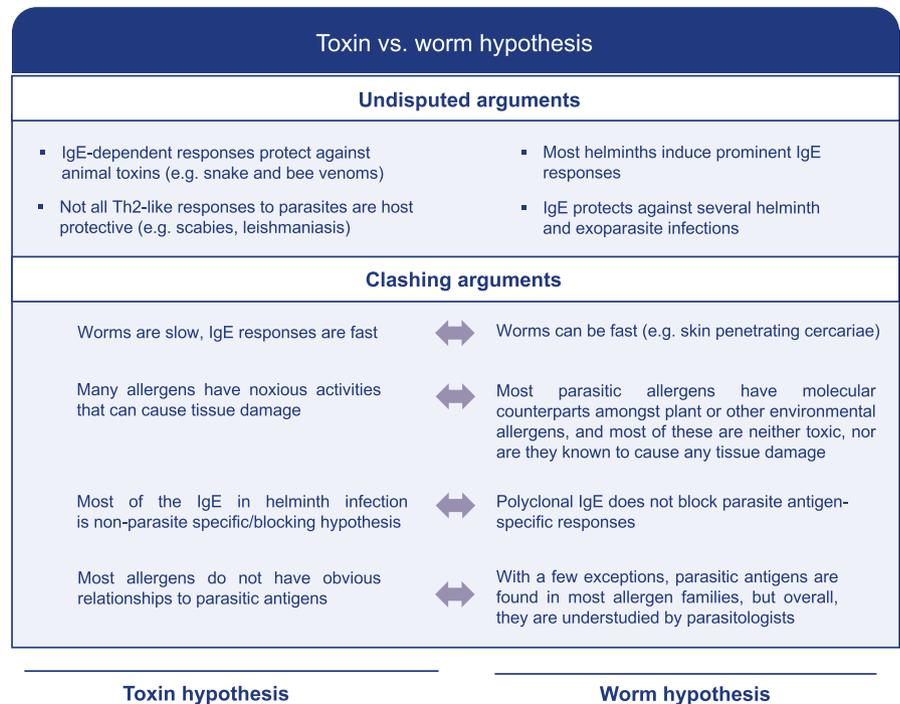
## 10 | HOW CAN THE EVOLUTIONARY ASPECT OF IgE HELP CLINICIANS DEVELOP FUTURE PERSPECTIVES IN MANAGING ALLERGIC DISEASES?

The key message of this review is that to fully understand its roles and potential benefits, it is important to assess IgE in the immunological context of when it first arose. Back in the Mesozoic Era, this antibody isotype would have conferred multiple layers of protection to our mammalian ancestors against ubiquitous parasites, venoms and other toxins. The advantages conferred by this immune response must have compensated its intrinsic costs (eg the risk of adverse reactions posed by the complex networks of structural similarities and cross-reactivities between allergens across phyla), leading to its preservation in all mammals until today for the last 200 Mio years. Can some of the past advantages, such as protection against (human) helminth parasite infection, be now considered obsolete, given the availability of safe and efficacious anti-helminthic drugs? Firstly, a large section of humanity does not have easy access to such drugs, for economic and other reasons. Drugs do not protect against re-infection. In the absence of truly successful measures for global eradication of parasitic (neglected tropical) diseases, which



**FIGURE 5** Three-dimensional structures of nine known parasite-derived allergens (UniProt accession number in brackets) together with the corresponding Allergen Family (AF) number and known representatives in plants (green), fungi (violet) or nonparasitic animals (blue). All structures were computed using Phyre 2,<sup>116</sup> except where a pdb accession number is given next to the UniProt accession number

**FIGURE 6** Infographic summarizing the key arguments and counter arguments underlying the two main hypotheses explaining the evolutionary benefits of the IgE response in mammals



need to combine mass drug administration with anti-helminth vaccinations (which still elude us), together with biological and other control measures, the IgE response to helminths will continue to provide benefits to many in the world's population, in spite of the availability of drugs. Secondly, the still under researched roles of IgE in viral immunity and cancer (see excellent recent review by Sutton and co-authors for the latter aspect)<sup>97</sup> suggest that any measures targeted at removing or reducing IgE-dependent immune responses must be approached with a degree of caution. Finally, assessing the overall balance of benefits versus cost of the IgE response also needs to consider the potential host-protective benefits associated with some helminth infections. In a nonconventional manner, clinical scientists are now even exploring whether allergy can in fact be controlled by the re-introduction of the ancestral and possibly anti-allergic immunological stimuli induced by parasites as a self-protective strategy.<sup>98,99</sup> The concept of helminth therapy has also been applied to treat other inflammatory disorders, such as inflammatory bowel disease (IBD) and Crohn's disease (CD) in humans, using eggs of *Trichuris suis*.<sup>100,101</sup> Such attempts have been recently reviewed by Helms,<sup>102</sup> Garg<sup>103</sup> or Wu and co-authors,<sup>104</sup> as have the underlying immunoregulatory mechanisms.<sup>105</sup>

## 11 | CLOSING REMARKS

It is likely that the allergic phenotype, which in its extreme manifestations causes allergic disease following an overreaction of this arm of the immune response (type 1 hypersensitivity), is not as immunologically imperfect as immunologists and clinicians have been led to believe. In this article, we have attempted to redress the balance somewhat in favour of the allergic phenotype. It is possible

that its development over mammalian evolution has saved the lives of countless mammals, and now humans, whether infected by parasites or injected with toxins. The challenge now is to develop strategies that allow us to fine-tune the allergic response of those who currently have difficulty autoregulating themselves.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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