Trends in Parasitology

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Forum

Salivary Prostaglandin E2: Role in Tick-Induced Allergy to Red Meat

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Tick-induced allergy to red meat is associated with anti-α-Gal IgE antibody levels. We propose that tick salivary prostaglandin E2 triggers antibody class switching in mature B cells, increasing the levels of anti-α-Gal IgE antibodies. Immune tolerance to α-Gal in blood type B individuals might reduce the risk to this allergy.

Tick-induced allergy to red meat is becoming a global problem with increasing prevalence in the USA, Australia, and Europe, and several tick species have been implicated in these disorders [1]. Remarkably, most of the patients that become allergic, had tolerated red meat for many years before being sensitized by tick bites [1]. This finding suggests that anti-Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal) IgE antibodies induced by tick bites, break the oral tolerance to food allergens. This tick-induced immune response is antigen-specific and results in gut-related but not lung-related allergy.

Tick saliva is a complex mixture of pharmacologically active compounds. Tick saliva and/or tick salivary gland extracts were shown to inhibit almost every defensive mechanism and affect leukocyte populations through immunomodulatory, antihemostatic and anti-inflammatory molecules [2]. Transcriptomics studies of tick salivary glands discovered clusters of related proteins that are referred to as multigene families and usually contain tens or even hundreds of more or less similar proteins, with protease inhibitors being the most abundant group of tick salivary secreted proteins in *Ixodes scapularis* [2]. Interestingly, the genes coding for these proteins are usually expressed sequentially throughout tick feeding, bringing up the question of whether this phenomenon could be a form of antigenic variation [2].

Apart from proteins with immunomodulatory activity, ticks also produce nonprotein molecules such as prostaglandin E2 (PGE_2), which is synthetized in the tick salivary glands and secreted via the saliva into the feeding lesion [3]. Several tick species from major genera such as *Amblyomma*, *Ixodes*, and *Rhipicephalus*, which have been involved in tick-induced allergies, were found to secrete PGE_2 in their saliva [3,4]. Tick salivary PGE_2 was reported to have an immunomodulatory effect [3,4]. In particular, PGE_2 inhibited cytokine production by inducing cyclic AMP-proteins kinase A (cAMP-PKA) signaling in dendritic cells [3]. While attention has been paid to the immunomodulatory effect of tick salivary PGE_2 on dendritic cells [3,4], the effect of PGE_2 on B cells has been overlooked. However, recent reports showed that PGE_2 has a major impact on B cell function with implications in allergy [5]. Specifically, PGE_2 induces class switch recombination (CSR) on mature B cells [5].

Anti-α-Gal IgM and IgG antibodies are exclusively produced in humans in response to antigenic stimulation by α-Gal antigens produced by gut microbiota [6]. Several gut-dwelling bacterial species were suggested to induce anti-α-Gal response. These include several

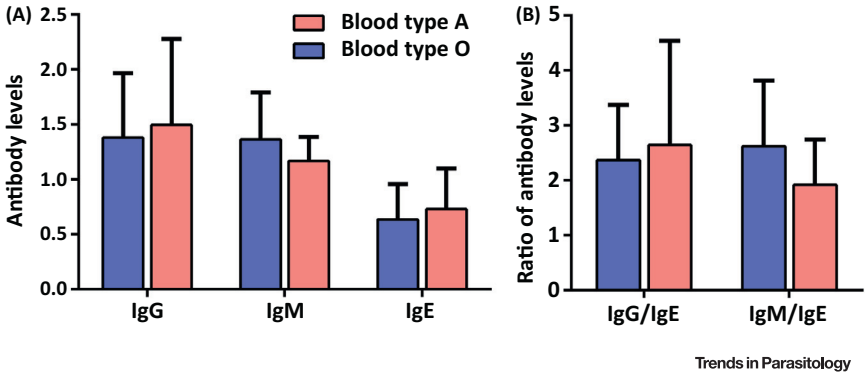

Figure 1. ABO Blood Types and Antibody Response to α-Gal: A Case Report. The ABO blood types are important self-antigens with implications in immune tolerance and xenotransplantation [6]. Humans have antibodies against missing A/B blood type antigens. As shown in a series of studies, the levels of anti-α-Gal antibodies are lower in individuals with blood type B [8]. This finding may be related to the fact that monoclonal and polyclonal anti-α-Gal antibodies show strong interaction with both galactose residues of α-Gal [11]. Therefore, the presence of galactose residues in blood type B antigen may be sufficient for the binding of anti-α-Gal autoantibodies to blood type B antigen, resulting in total or partial tolerance to Gal–Gal blocks in individuals with blood type B. The figure shows the analysis of anti-α-Gal IgG, IgM, and IgE ratios in healthy individuals with blood types O and A, which should have similar levels of anti-α-Gal antibodies. The dataset containing the anti-α-Gal antibody levels in healthy adults from the Iberian Peninsula was published by Cabezas-Cruz *et al.* [12]. (A) Anti-α-Gal IgG, IgM and IgE antibody levels (O.D. 450 nm) were determined by ELISA in sera from healthy individuals [12]. Anti-α-Gal IgE levels are lower than anti-α-Gal IgG and IgM levels in healthy individuals with blood types A and O. (B) Anti-α-Gal IgG/IgM/IgE ratio analysis shows that no significant differences ($P > 0.05$) exist between IgG/IgE and IgM/IgE ratios in healthy individuals with blood type A or O. These results support our hypothesis that tick bites may induce class switch recombination (CSR), which will result in an increase in anti-α-Gal IgE in individuals with blood types A and O. Subsequently, IgG/IgE and IgM/IgE ratios are expected to decrease below the values shown in the Figure (i.e., for blood type O individuals, IgG/IgE<2.36 with SD ± 1.0 and IgM/IgE<2.61 and SD ± 1.2, and for blood type A individuals, IgG/IgE<2.64 and SD ± 1.9 and IgM/IgE<1.92 and SD ± 0.8).

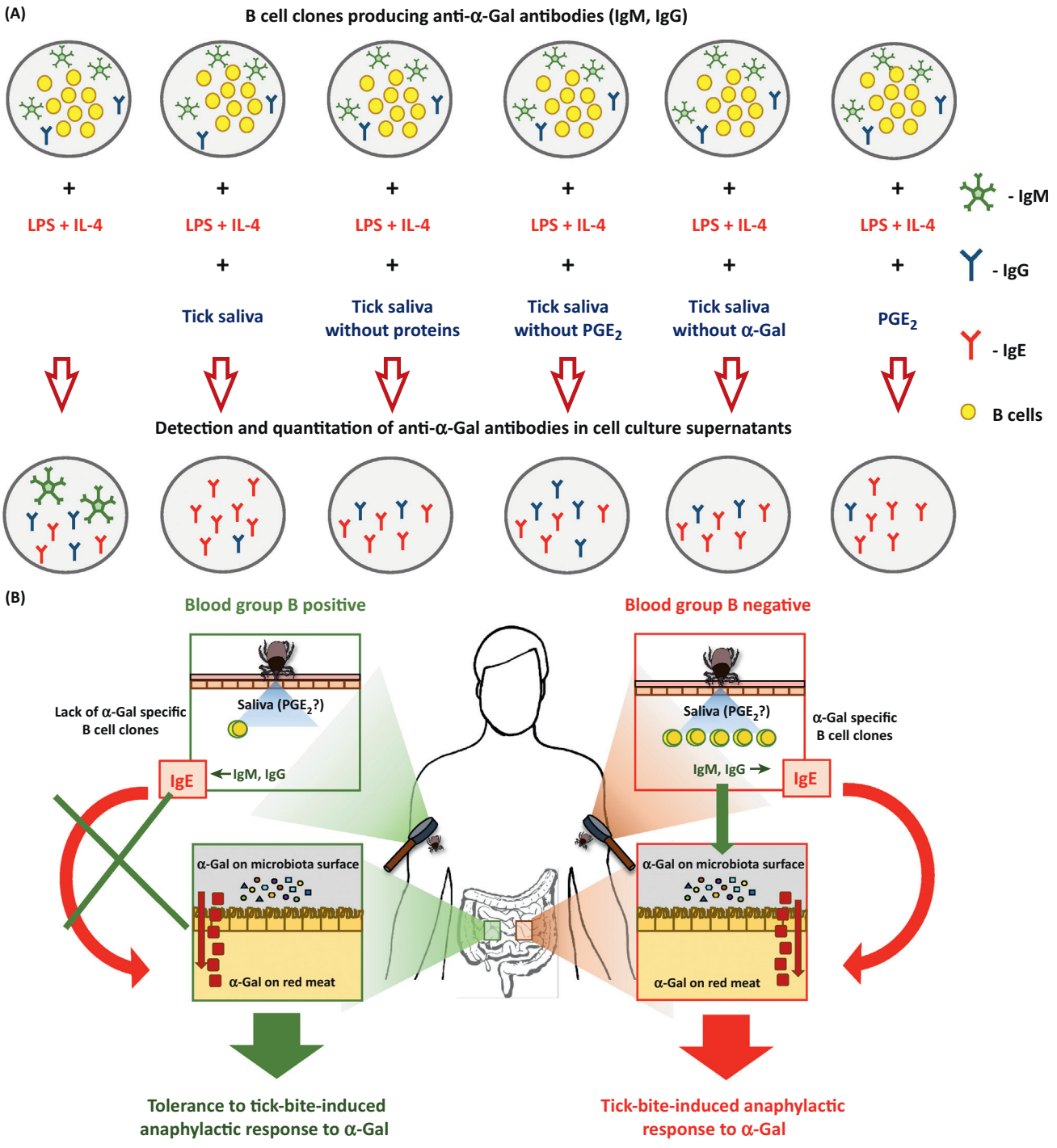

Figure 2. Immunological Basis of Tick-Induced Allergy to Red Meat. (A) Our hypothesis is that tick salivary PGE_2 induces class switch recombination (CSR) towards IgE production on pre-existing anti-α-Gal IgM- and/or IgG-specific mature B cell clones, and blood type B-negative individuals will be more susceptible to develop α-Gal-related allergy to red meat after tick bites. To test this hypothesis, tick saliva can be added to B cell culture in combination with other established isotype switch inducers such as lipopolysaccharides (LPS) and IL-4. PGE_2 would serve as a positive control, as it was shown to enhance the quantity of IgE produced by LPS/IL-4-stimulated B cells [5]. To exclude the influence of tick salivary proteins, saliva could be dialyzed against a 3 kDa semipermeable membrane. To confirm the role of α-Gal, tick saliva could be depleted of α-Gal by removing the galactose epitope by α-galactosidase enzyme and added with and without synthetic α-Gal. To support the conclusions of this experiment, several genetic tools such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9

(Figure legend continued on the bottom of the next page.)