The alpha-Gal syndrome (AGS) is an allergic disease triggered by an IgE antibody (Ab) response against the carbohydrate Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal), which is present in glycoproteins from tick saliva and tissues of noncarnivore mammals. Tick bites induce high levels of anti-α-Gal IgE Abs in humans that mediate delayed anaphylaxis to red meat consumption, and immediate anaphylaxis to tick bites, xenotransplantation and certain drugs such as cetuximab [1]. Old world monkeys, apes and humans evolved with the inactivation of the α-1,3-galactosyltransferase (α1,3GALT) gene, which resulted in the recognition of α-Gal to produce high antibody Ab titters against this antigen [2].

The evolutionary history of α-Gal synthesis has not been fully characterized, but evidence point at differences between species. Nevertheless, ticks have the galactosyltransferases (GALTs) with the capacity to synthesize this molecule with functional implications for tick biology and pathogen infection [3]. Therefore, the source of α-Gal modifications in tick salivary proteins is indeterminable.

Hypotheses

- Hypothesis 1: Tick salivary proteins including those present in the tick cement with α-Gal modifications are involved in modulating human immune response against this carbohydrate responsible for the AGS.

- Hypothesis 2: Tick salivary protaglandin E2 triggers antibody class switching in mature B cells, thus increasing anti-α-Gal IgG Ab levels [4].

- Hypothesis 3: Basophils and released histamine are implicated in IgE-mediated acquired protective immunity to tick infestations and chronic tick itch [5]. Consequently, basophil response to tick bites may be associated to α-Gal containing proteins and anti-α-Gal antibodies, possibly linking tick resistance to AGS.

- Hypothesis 4: The α-Gal producing gut bacteria can be used to develop a probiotic-based pan-vaccine to control multiple infections caused by pathogens producing α-Gal.

- Due to structural similarities between α-Gal and blood antigen B, individuals with blood type B are at lower risk of developing AGS but may be more susceptible to disease caused by pathogens with a α-Gal.

Molecular triggers of AGS (hypothesis 1 & 2).

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- The the tick salivary components that are involved in the immune response mechanisms leading to the AGS have not been identified. Recently, we demonstrated that ticks produce GALTs involved in the α-Gal synthesis and developed an experimental approach for the identification and characterization of proteins with α-Gal in tick salivary glands [3,7]. Tick saliva modulates host immunity to facilitate tick feeding and possibly pathogen transmission. Therefore, the identification of tick salivary proteins with α-Gal modifications and recognized by human sera is fundamental towards understanding the immune mechanisms involved in response to α-Gal, and the treatment and prevention of the AGS before it becomes a pandemic disease.

- Tick species such as Amblyomma americanum leads ricinus and Ixodes holocerus that has been associated with the AGS in the USA, Europe and Australia, respectively constitute a good model for these studies.

- The information generated from these studies will provide a fundamental understanding of the tick-host molecular interactions and mechanisms that lead to development of the AGS. These results will also advance the possibilities for evaluating the risks of developing AGS after tick bite, and targets for the diagnosis, treatment and prevention of these allergies.

- Tick-host-pathogen interactions evolved as conflict and cooperation [8]. In this context, the AGS evolved as a trade-off to benefit humans by providing immunity to pathogens containing α-Gal while increasing the risks to develop the AGS [2,9].

- Infectious diseases constitute a major health problem worldwide. Major infectious diseases include malaria, tuberculosis, Lyme disease and Aspergillosis caused by Plasmodium, Mycobacterium, Borrelia and Aspergillus spp., respectively. No effective vaccines exist against these pathogens. Remarkably, all these pathogens produce a common antigen, the carbohydrate α-Gal.

- Recent evidence showed that immunization with α-Gal induces a protective immune response against Plasmodium spp., Trypanosoma cruzi, and Leishmania spp. Humans produce anti-α-Gal Abs in response to gut microbiota bacteria producing α-Gal (reviewed by [8]). These bacteria can elicit a strong anti-α-Gal Ab response, resulting in “sterilizing immunity” against Plasmodium transmission by mosquitoes (reviewed by [9]).

- Gut bacteria with high α-Gal content selected from individuals with protective immune response against pathogens with α-Gal could be used to develop a probiotic-based easy to administer and low-cost vaccine that could be administered by different routes alone or in combination with α-Gal-containing tick proteins to provide protection against multiple pathogens causing major infectious diseases worldwide.

- Experimental approach

  Towards a pan-vaccine for the control of major infectious diseases.