# Cancer research meets tick vectors for infectious diseases

Continuous human exploitation of environmental resources and an increase in human outdoor activities have led to more contact with arthropod vectors, promoting an emergence and resurgence of tick-borne pathogens. Clinical trials of cetuximab, a monoclonal antibody that inhibits epidermal growth factor receptor used for treatment of metastatic colorectal cancer, have shown that the drug produces more hypersensitivity than expected, with some fatal cases. Patients who developed these hypersensitivity reactions were deemed to have pre-existing IgE antibodies specific to the alpha-gal present in the variable portion of cetuximab. Further studies have shown that the frequency of anti-alpha-gal IgE in healthy adults from the US states Tennessee, Virginia, and North Carolina was higher than in individuals from Boston or California, or northern Sweden. This enigmatic increase in serum anti-alpha-gal IgE concentrations in some areas of the USA was due to the lone star tick, Amblyomma americanum. The presence of anti-alpha-gal IgE was strongly associated with maximum incidence of Rocky Mountain spotted fever (a lethal rickettsial illness caused by the A americanum transmitted bacterium Rickettsia rickettsii); distribution of A americanum; history of itching after tick bites; and an increase in IgE to tick protein concentrations after tick bites, supporting the implication of anti-tick immunity in the rise of IgE concentrations. Similar cases in Australia, France, Germany, Japan, Spain, and Sweden were associated with A americanum, Ixodes ricinus, and Ixodes holocyclus ticks. Clinical outcomes are immediateonset anaphylaxis during first exposure to intravenous cetuximab and delayed-onset anaphylaxis 3–6h after ingestion of mammalian food products (eg, beef and pork). One question arises from these findings: are human beings resistant or susceptible tick hosts? Ticks and other haematophagous arthropod vectors manipulate the host immune system to complete blood feeding, which, in turn, favours pathogen transmission. However, the balance between tick manipulation of host immunity and eff ective host response, and the implications of these responses on the onset of allergies in the host, have not been well established. For instance, the increase in IgE concentrations after successive tick infestations has been shown in susceptible hosts and associated with resistance to Haemaphysalis longicornis tick infestations in mice. Furthermore, results have suggested that the anti-tick IgE response, together with recruitment of basophils and mast cells to the tickbite site, play a relevant part in host resistance to tick infestation and pathogen infection. Simultaneously, tick toxins induce allergic sensitisation that triggers development of specific IgE that can bind to receptors present on tissue mast cells and blood basophils, causing the release of mediators of allergy and anaphylaxis. Protection against tick infestations therefore has the potential to induce an allergic reaction in human beings. The effect of ticks and other arthropod vectors on host immune response is mediated by proteins in their saliva that impair host haemostatic and immune defences. Protein families and biological functions of tick saliva are similar to those of other well known venomous organisms. Tick saliva has been suggested to be a specialised subtype of venom. Venom components are well known antigens that induce allergic reactions and have, like tick saliva, a strong intrinsic ability to induce a T-helper-2 (Th2)-type immune response.

Two independent groups have reported that immunisation with bee and snake venom produces IgE responses that increase host resistance to challenge with potentially lethal doses of venom through IgE receptors and associated mast cells. In summary, people who are able to develop an IgE immune response and recruit basophils or mast cells to the tick-bite site can show higher resistance to tick infestations and tick-borne diseases, but might face major risks of anaphylactic reactions to cetuximab and red meat. The implications of the strong Th2-type response induced by ticks in the development of host allergic reactions should be assessed to understand the balance between tick resistance and susceptibility and allergic clinical output. The carbohydrate alpha-gal seems to be a good model antigen. The use of tick salivary antigens to induce antivenom-like IgE Th2-type protective immune responses should be explored to develop anti-tick vaccines.

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