Venom toxicity countered by allergic antibodies

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The production of immunoglobulins E (IgE), i.e. the antibodies responsible for allergic reactions, is generally considered as noxious and as the result of a dysfunction in the immune system. A study led by Thomas Marichal, a postdoctoral researcher in the laboratory of Professor Steve Galli at Stanford University, showed that these antibodies can have a protective effect against the toxicity of honeybee and snake venoms. It could therefore be possible that allergic immunity to different venoms and toxins has been maintained over the course of evolution as a major defence mechanism of the host. It might therefore be conceivable that, for a proportion of the population, an initial exposure to the venom and associated IgE may have a beneficial effect against the same venom upon subsequent exposure. Now, scientists would like to identify which factors determine whether the IgE antibodies are more likely to induce a noxious or a protective response.

In developed countries, almost one out of three people suffer from an allergic disorder. And this rate could well increase to one out of two people in coming years according to World Health Organisation (WHO) estimations. In fact, the WHO ranks allergies fourth in the list of chronic global diseases. The exact causes of increases in the number of allergies haven't been identified, although different reasons have been suggested to explain this development. On the one hand, the growing vigilance of health professionals has generated increased screening in the past few years. On the other hand, our food and our environment have changed. As regards to food, there is a correlation between easier access to exotic products and the increase in food allergies. Furthermore, industrial products can contain "hidden" allergens or more allergenic products as a result of the manufacturing process. As regards to babies, certain allergies can develop as a result of food diversification introduced too early into their diet.
In terms of the environment, two main guilty parties have been pinpointed as a source of the growing number of allergies: pollution and the increasing aseptic environment in which people live.

A dysfunction preserved over the course of evolution

An allergic reaction is considered as a dysfunction of the immune system. It is an exaggerated and unwanted reaction of the latter to foreign substances in the body, the majority of which are inoffensive. "In some people, contact with a particular allergen (for instance pollen, dust mite faeces, or peanut extracts) triggers a type 2 or Th2 response, i.e. a response involving immune cells capable of orchestrating the allergic reactions", explains Thomas Marichal, researcher at the University of Liège, and currently performing a postdoctoral training at Stanford University in California (USA) as a Marie Curie IOF fellow from the European Commission. "Th2 lymphocytes produce cytokines that promote the synthesis of immunoglobulin E antibodies, underlying the allergic reaction. This Th2 response can be induced by many different allergens but the antibodies that are produced are specific to the allergen that triggered this response", specifies Thomas Marichal. When they are produced, immunoglobulin E (IgE) antibodies circulate in the blood and the majority of them will bind to the surface of mast cells.

These immune cells are present at numerous places in the body such as the skin, the digestive tract and the airways. "If the allergic patient comes into contact with the same allergen again, the mast cells release a series of mediators such as histamine and prostaglandins, which are responsible for the allergic symptoms", the researcher continues. While the mechanisms associated with allergic reactions have been studied extensively and are well known, one fundamental question is yet to be answered: why has this type of reaction and, more precisely, the production of IgE been preserved over the course of evolution? "We still don't know why these antibodies, which make us ill and can even cause death in extreme cases, have persisted over the course of evolution", Thomas Marichal stresses.
Spotlight on allergies to venom

Thomas Marichal did his doctoral thesis while working in Fabrice Bureau’s team, in the GIGA Cellular and Molecular Physiology Research Unit. "Our objective was to understand which signals can initiate a type 2 reaction", the young researcher explains. "And we made a major discovery since we were able to show that tissue damage was inducing the release of danger signals that were then detected by the immune system as powerful triggers of a type 2 response", reveals Thomas Marichal. It was following this discovery, and within the framework of his work at Stanford University, that the scientist was particularly interested in the effect of certain venoms, especially those of the honeybee and a specie of viper. "We know that venom can induce a toxic response responsible for tissue damage while also being capable of causing an allergic reaction, as it is the case with people allergic to bees for instance", continues the researcher. As for any other allergen, someone who has developed IgE against bee venom following an initial sting can be subject to a potentially fatal allergic reaction if they are stung again. "We attempted to reproduce this in laboratory animals which were injected with physiological amounts of venom", Thomas Marichal points out. "We observed that mice resisted quite well to the initial amount of venom, even though it did cause tissue damage, a Th2 response
as well as the production of IgE in the majority of them", he adds. The scientists then exposed the mice that had developed IgE to a dose of bee venom, expecting them to develop an allergic reaction to the venom. Surprisingly, these animals were doing better than those that hadn't developed antibodies against the venom. "Their temperature didn't go down as much and they were able to survive better to a high dose of venom", Thomas Marichal points out. In this case, the Th2 responses therefore seem to have a protective effect against bee venom rather than a noxious effect as in the case of allergies.

**First experimental proof supporting the toxin hypothesis**

To verify the potential protective effect of IgE against honeybee venom, the researchers repeated the experiment with three types of transgenic mice: those incapable of synthesising IgE, those deficient in IgE receptors and those deficient in mast cells. "In all three cases, protection against honeybee venom had disappeared", Thomas Marichal reveals. "This shows that IgE, known for being noxious and considered as being the product of an immune dysfunction, can have a beneficial effect in the host's response to a well-known allergen in humans". These tests were also done with venom from a specie of viper and the same results - the same protective effects - were observed.

This is the first experimental proof of a controversial hypothesis that was already suggested in 1991 by Margie Profet, i.e. the toxin hypothesis. "Margie Profet suggested that allergic reactions were immunological defense mechanisms against toxins", explains Thomas Marichal. "This hypothesis was largely ignored by the scientific community. It was already known that the Th2 response could have a beneficial effect in defense against macroparasites such as intestinal worms. Consequently, many scientists believed that all allergies were the price to pay for defense against these parasites", the researcher continues. "But we have clearly demonstrated here that IgE help to protect against toxins!"

The scientists suggest a mechanism by which IgE exert their protective effect against the two types of venom tested. During a second exposure to these venoms, the mast cells may be rapidly activated by the IgE and may release substances (especially proteases) capable of degrading and neutralizing the toxins present in these venoms. Hence, a decrease in toxicity and, consequently, an increase in the survival of the animals.

**Changing our conception of IgE**

According to the authors of this study, published in the journal *Immunity*(1), acute and potentially fatal allergic reactions may be just a very small part of a spectrum of reactions mediated by IgE. In the case of allergies to venoms, a dysfunction of the immune system is indeed involved but, for the majority of people, after an initial exposure to the venom, the IgE might be able to produce a beneficial effect against toxic substances in the case of further exposure to them. This notion is supported by clinical observations showing that only a minority of people having developed IgE against honeybee venom develop acute and potentially fatal reactions when exposed to the venom again.
Scientists would like to identify which factors determine whether the IgE are more likely to induce a harmful or protective reaction. "From a fundamental point of view, this discovery answers a basic question associated with the usefulness and conservation of IgE and allergic responses over the course of evolution. It is the first direct evidence of the beneficial and protective role of IgE against toxins. This will certainly modify the way scientists think about allergies and, in the future, could lead to the development of vaccines in order to protect us against toxins and other environmental threats”, Thomas Marichal concludes.