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Commentary

Early prevention instead of mending late damage in allergy?

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Immunoglobulin E (IgE)-associated allergy is the most common hypersensitivity disease affecting almost 30% of the population worldwide [7]. The symptoms of IgE associated allergy such as asthma, chronic rhinoconjunctivitis, skin inflammation, food allergy and life-threatening anaphylactic shock severely affect the quality of life of allergic patients, are often disabling and eventually life-threatening. Accordingly, IgE-associated allergy is a heavy economic burden for the health care systems [10]. The analysis of the development of IgE-sensitization towards multiple allergen molecules by chip technology in longitudinal population-based birth cohorts has demonstrated that IgE-associated allergy often starts as clinically silent IgE sensitization without associated symptoms and, after repeated allergen exposure, progresses towards symptomatic allergy when children get older [9]. This finding is reminiscent of several other major diseases affecting mankind such as cancer, cardiovascular diseases, autoimmune diseases, infectious diseases and metabolic diseases which develop from pre-stages of disease without clinically visible pathological symptoms towards severe disease manifestations. It is common to all these diseases that early interventions in a pre-stage have the potential to stop the march towards severe disease manifestations. Thus, early prevention is usually relatively simple and inexpensive and preventive measures are usually much more effective than mending damage occurring at late stages of disease.

Wang et al. in *EBioMedicine* have conducted an analysis of antibacterial IL-2 responses in peripheral blood mononuclear cells obtained from children within the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) mother-child cohort and studied how this is associated with serum IgE responses and clinical indicators of allergy in the children at age 7 [8]. They found a reduced IL-2 response from PBMCs exposed to common pathogenic airway bacteria at age 6 months which was associated with elevated levels of total IgE and symptoms of allergy at school age. This finding is interesting because it is known that IL-2 can be used to expand T regulatory cells [6] and it has been recently shown in a humanized model for IgE-associated allergy that the *in vivo* expansion of regulatory T cells with IL-2 immune complexes was effective in preventing the development of allergy in a humanized mouse model [5]. Wang et al. indeed suggest considering the use of low-dose IL-2 therapy to prevent the development of allergy in childhood. The current study is therefore in line with several strategies for early prevention of allergy in childhood which include the early induction of immunological tolerance by oral tolerance induction [2], early active allergen-specific immunotherapy (AIT) or passive antibody-based treatments [3,4], gene therapy with genetically-modified stem cells [1] to name a few.

Early preventive strategies clearly would have many advantages over interventions performed in late-stage, severe disease but many issues need to be clarified. When using the approach of early low dose IL-2 treatment as proposed by the authors, many questions remain. First of all, there is the question of whom to treat? How can we determine with certainty what children have an increased risk of developing an IgE-associated allergy? A next question is when to initiate and how long to give treatment. Is it necessary to prevent allergic sensitization or would the treatment be also effective once IgE sensitization has already occurred? Another question is of course what would be the right dose and could there be any harmful effects? According to the fundamental principle in medicine "*primum nihil nocere*" (ie, above all do not harm), one must be particularly careful not to induce harm. In the current scenario IL-2 overdosing could lead to overshooting expansion of regulatory T cells and cause immune deficiency but also over-activation of T cells leading to autoimmunity could be a potential threat.

Since recent data suggest that there is a rather narrow window for allergic sensitization early in childhood, preventive approaches would need to target infants very early in life and consequently safety is an absolute pre-requisite if one intends to translate preventive concepts such the one proposed by Wang et al. into clinical practice.

Disclosure

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