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Review article

Analysis of allergic immune responses in humanized mice

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ABSTRACT

Nowadays, more than 25% of the population in industrial countries are affected by IgE-mediated (atopic) allergic diseases such as allergic rhinitis, asthma and atopic eczema. Due to intensive research on basis of *in vitro* studies with human immune cells and different murine *in vivo* models of allergy fundamental mechanisms of allergic immune responses have been elucidated during the last years. However, human studies are restricted and the immune system of mice differs from the human immune system in several aspects so that the transferability of experimental results from mice to men is limited. Humanized mice represent a new tool to analyze the interaction of human immune cells under physiological conditions as far as possible, particularly to test novel therapeutic strategies. This review summarizes the impact of humanized mouse models for the investigation and treatment of allergic diseases.

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1. Introduction

Despite much knowledge has been gained in the last decades, the immunological mechanisms of IgE-mediated (atopic) allergic diseases, i.e. allergic rhinitis, asthma, atopic eczema as well as intestinal inflammation during food allergy, are still not completely understood. Allergen immunotherapy (AIT) as the only curative treatment of such diseases is very efficient for venom and pollen allergic patients, but it is not equally well established for IgE-mediated food allergy due to the risk of anaphylactic reactions [1–4]. Novel therapeutic strategies using regulatory T cells (Treg), anti-IgE, or blocking critical Th2 cytokines such as IL-4, IL-5, IL-9, and IL-13 have been successfully applied in several mouse models of allergy and asthma but sometimes failed to show convincing results in human clinical trials. One reason for this is that the immune system of humans and mice differs in several aspects [5–8]. Furthermore, mice do not express specific human therapeutic targets and the investigation of novel drugs in humans is limited by ethical and technical constraints. Therefore, humanized

Abbreviations: APC, allophycocyanin; DC, dendritic cells; GARP, Glycoprotein A Repetitions Predominant; IMDM, Iscove modified Dulbecco medium; NOD, non-obese diabetic; PAF, platelet-activating factor; PE, phycoerythrin; SCID, severe combined immunodeficiency; SIT, allergen-specific immunotherapy; Treg, regulatory T cells; Tr1, type 1 regulatory T cells.

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mouse models represent a very important tool to study such novel strategies *in vivo* without putting humans at risk [9–12].

2. Pathogenesis of IgE-mediated (atopic) allergic diseases

The pathogenesis of IgE-mediated type I allergies can be divided in several steps. During the sensitization phase the allergen is taken up by airway dendritic cells (DC) which mature due to secondary stimuli generated from epithelial cells such as IL-25, IL-33, TSLP, or GM-CSF and then migrate to lymphoid tissues, where they present the allergen to naïve T cells and activate them to develop into Th2 cells. Once an individual is sensitized to an antigen, re-exposure rapidly leads to an exacerbation of allergic airway inflammation initiated by crosslinking of allergen-specific IgE antibodies bound to FcεRI on mast cells and basophils leading to mediator release causing the so-called early phase response with typical allergic symptoms such as rhinorrhea, airway mucus secretion, bronchoconstriction, as wells as urticaria, vomiting and diarrhea in food allergies and even anaphylaxis. The late phase response, i.e. the recruitment of further mast cells and eosinophils, follows within hours. The allergen is also taken up by DC, which activate memory Th2 cells to produce cytokines and other mediators, leading to chronic allergic inflammation and tissue remodeling [13–15].

3. Modulation of IgE-mediated allergic immune responses

3.1. In vitro studies

During the last decades, many researchers including our own group have intensively analyzed the mechanisms and modulation of Th2-dominated allergic immune responses by tolerogenic DC or Treg [16–19]. We could demonstrate in an human *in vitro* setup, i.e. stimulation of $CD4^+$ T cells from allergic donors with autologous allergen-pulsed monocyte-derived DC [20], that IL-10-treated DC inhibited production of Th1 and Th2 cytokines by T cells, whereas hydrocortisone-treated DC inhibited production of IFN-gamma but induced an increased release of IL-4 and no change in IL-5 [21]. In the presence of TGF-β, IL-10-DC-stimulated T cells possessed regulatory properties (induced Treg) suppressing the function of Th1 and Th2 effector cells in the periphery [22]. In another project investigating the role of naturally occurring $CD4^+CD25^+$ Treg in allergic inflammation we could show that Treg from the majority of allergic donors were not generally impaired in their inhibitory capacity [23]. However, the regulation of allergic immune responses by $CD4^+CD25^+$ Treg was dependent on the concentration and stimulatory capacity of the respective allergen as well as the allergic/atopic status of the donor [24–26].

3.2. Allergen-specific immunotherapy (AIT)

Analyzing the mechanisms of subcutaneous allergen-specific immunotherapy (SCIT) of wasp-venom allergic patients we and others could demonstrate that SCIT resulted in a shift from Th2 to Th1 and more importantly induced IL-10- and TGF-β-producing Treg leading to decreases in allergen-specific IgE and increases in allergen-specific IgG_4 production in the long-term [1,27,28]. Inhibition of T cells after SCIT was further associated with a decreased induction of the costimulatory molecule ICOS, which, in turn, seems to be dependent on the presence of IL-10 [29]. Studies in murine models of asthma had already demonstrated that IL-10-producing regulatory type 1 (Tr1) cells prevented allergen-induced airway hyperreactivity (AHR) and inflammation and that this process was mediated by inducible costimulatory molecule (ICOS)-ICOS-ligand interaction and by IL-10 derived from pulmonary DC [30]. Additionally, SCIT led to an IL-10- and IFN-γ-dependent decreased release of histamine and leukotrienes from mast cells and basophils [1,31].

3.3. Murine models of allergy

The group of A. Reske-Kunz from our department focused research on the regulation of murine IgE production. They immunized mice with β-Gal encoding plasmid vectors adsorbed on gold microparticles under the control of the CMV promoter or the promoter of the fascin gene. Fascin is an actin-bundling protein which is restricted to neuronal tissues and DC where it is strongly induced during their maturation and is important for the formation of the dendrites [32,33]. This biolistic DNA vaccination led to the suppression of allergen-specific systemic Th2 responses and IgE production and to an inhibition of allergen-induced Th2-mediated airway inflammation but on the other hand induced Th1-mediated neutrophilic infiltration and Th1/Tc1-mediated AHR [34–36]. An inhibition of IgE production could also be observed by Barwig et al. and Raker et al. by sensitization of mice with high antigen doses. In transfer experiments $CD4^-CD8^-$ double negative T cells were identified to mediate this suppression [37,38].

Besides this model of high-dose tolerance, the mechanisms of low zone tolerance in allergic contact dermatitis were also investigated since many years by the group of K. Steinbrink from our department [39,40]. Recently, Luckey et al. could demonstrate that tolerance induction by epicutaneous application of low doses of haptens is mediated by interactions between $CD4^+CD25^+FoxP3^+$ Treg and tolerogenic $CD8^+CD11c^+$DC via gap junctions leading to the generation of hapten-specific CD8(+) Treg cells, which protect against contact hypersensitivity [41,42].

3.4. Humanized mouse models of allergy

However, as the immune system of humans and mice differs in many aspects, the transferability of experimental results from mice to men is limited. For example, although IL-10-treated autologous tolerogenic DC inhibited human Th2 immune responses *in vitro* [21], injection of IL-10-treated OVA-pulsed DC into OVA/alum-sensitized BALB/c mice did not inhibit IgE production and airway inflammation [43]. To overcome such limitations, immunodeficient mice engrafted with functional human cells and/or tissues, called humanized mice, have been developed. Engraftment was conducted either by injection of human peripheral blood mononuclear cells (PBMC), termed human peripheral blood lymphocyte SCID (Hu-PBL-SCID) model, hematopoietic stem cells (HSC), termed human SCID repopulating cell (Hu-SRC-SCID) model, or bone marrow, liver, thymus (BLT), termed BLT model. Humanized mice are an important preclinical tool for *in vivo* studies of human pathogens which do not infect mice, e.g. human immunodeficiency virus type 1 (HIV-1) or hepatitis B and C viruses [10,44].

First experiments have been performed with severe combined immunodeficiency (SCID) mice which lack mature T and B cells [12,45,46]. SCID mice have also been employed for the analysis of allergic inflammation mainly using the Hu-PBL-SCID model by several groups including the group of A. Reske-Kunz from our department (summarized in Table 1) [47–53]. In general, total as well as allergen-specific IgE, increased airway hyperreactivity, allergic-type-I skin responses and systemic anaphylaxis could be measured after engraftment of PBMC from allergic donors, but not after engraftment of PBMC from healthy controls [50,54–59]. Only one study reported functional human IgE production in SCID mice reconstituted with house dust mite-stimulated PBMC from healthy persons [60]. However, all these humanized mouse models focused on lung inflammation while allergen-induced inflammation of the intestine in the context of pollen-related or other food