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REVIEW ARTICLE

Allergy for a Lifetime?

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ABSTRACT

As the key molecule of type-I-hypersensitivity, IgE provides specificity for the allergen and links it to the allergic effector functions. Antibodies are secreted by plasma cells and their precursors, the plasma blasts. The fate of plasma cells is a subject of controversy, with respect to their lifetime and persistence in the absence of allergen. In general, plasma cells were for a long time considered as short-lived end products of B-cell differentiation, and many of them are short-lived, although already for more than 20 years evidence has been provided that IgE-secreting plasma cells can persist over months. Today long-lived, "memory" plasma cells are considered to represent a distinct cellular entity of immunological memory, with considerable therapeutic relevance. Long-lived plasma cells resist current therapeutic and experimental approaches such as immunosuppression, e.g. cyclophosphamide, steroids, X-ray irradiation, anti-CD20 antibodies and anti-inflammatory drugs, while the chronic generation of short-lived plasma cells is sensitive to conventional immunosuppression. The seasonal variation in pollen-specific IgE can be suppressed by immunotherapy, indicating that component of the IgE response, which is stimulated with pollen allergen is susceptible to suppression. Targeting of the remaining long-lived, allergen-specific plasma cells, providing the stable IgE-titers, represents a therapeutic challenge.

Here we discuss recent evidence suggesting, why current protocols for the treatment of IgE-mediated allergies fail: Memory plasma cells generated by inhalation of the allergen become long-lived and are maintained preferentially in the bone marrow. They do not proliferate, and are refractory to conventional therapies. Current concepts target plasma cells for depletion, e.g. the proteasome inhibitor bortezomib, BAFF and APRIL antagonists and autologous hematopoietic stem cell transplantation.

KEY WORDS

IgE memory, long-lived IgE, mucosal challenge, plasma cells, therapy

INTRODUCTION

IgE-B CELLS IN ALLERGY

IgE Develops by Class Switch of Antibody Genes

B lymphocytes develop in the bone marrow. They leave it as mature B cells, expressing IgM and IgD on their surfaces. These IgM or IgD B cell receptors recognize antigen specifically and thereby activate the B cell. If the mature B cell binds its processed antigen presented on a T helper (Th) cell it is activated. Co-activation by cytokine signals and signals from membrane-proteins is the prerequisite for B cell activation followed by Ig class switch recombination. Ig class switching occurs by a directed loop-out-and-deletion-recombination between two highly repetitive switch regions (S_H), resulting in switch transcripts that are composed of 5' and 3' parts of the donor and acceptor regions, respectively.[1] These hybrid switch regions can serve as donor regions in further switch recombinations. Although all murine switch regions have been shown to be involved in sequential switch recombination, Jung and coworkers report that for Sε sequential switching via S'γ1 appears to be dominant over direct switching.[1] The frequent observation of Sγ1 sequences in the chromosomal and excised circular products of IgE switch recombinations, and the fact that in vitro, the appearance of IgE$^+$ cells in *LPS/*

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IL-4 cultures can be largely suppressed by anti-IgG1 antibodies, led to the suggestion that most IgE^+ cells are generated by sequential switching. Interestingly, functional deletion of γ1 membrane exons by gene targeting showed that switching to downstream Ig isotypes was not affected, indicating that direct switching occurs in vivo.[2] Direct switching to IgE was also suggested by Luger and coworkers, as antigen-specific sequence motifs found in IgE antibodies differed from those found in IgG1 antibodies. This argues against the notion that consecutive switch recombination via γ1 is a major operational mechanism in the generation of IgE-expressing B cells in vivo.[3]

The isotype to which the B cell is switching to depends on the cytokine present during activation. For instance, interleukin 4, secreted by Th2 cells induces the immunoglobulin class switch to IgE. Thereby the B cell keeps its specificity for the antigen, while the function of the antibody is altered.

From Membrane-Bound IgE to Secreted IgE

During differentiation of activated B cells to plasma blasts and plasma cells, not only immunoglobulin class switch takes place but also a change from membrane expression to the secretion of antibody molecules.[4] Antibodies, together with the accessory molecules Igα und Igβ are expressed by B cells as membrane-bound antigen-receptors controlling activation of the B cell. The constant regions of the immunoglobulin heavy chain are encoded by 5 or 6 exons, depending on the antibody class. All antibody classes express the last exons alternatively. One codes for the transmembrane domain of the membrane bound antibody, expressed on naïve and memory B cells. The other one codes for the last domain of the secreted antibody. In B cells transcription ends after the "membrane-exon", while in plasma cells it is terminated after the "secretion-exon". The "membrane-exon" is spliced out of the transcript in plasma cells.[5] Although IgE—as well as all other antibody isotypes can exist in both forms, evidence for IgE-positive memory B cells is rare.[6] At any rate—the frequencies of IgE-positive memory B cells are a thousand fold lower than IgG-expressing memory B cells. Though, IgE-positive plasma cells can differentiate from IgG-positive memory B cells after consecutive immunoglobulin class switch recombination.[1,4]

MAINTENANCE OF MEMORY LYMPHOCYTES

It is a matter of debate in the field of immunology whether specialized memory cells do exist at all, branding the term "immunologic memory" for the cell by cell amplification of antigen-specific lymphocytes.[7,8] The discussion is based on the present lack of markers distinguishing between long-lived effector cells and professional memory cells.[8] One may understand this debate, as it is technically highly sophisticated to differentiate between the maintenance of a pre-existing pool of memory cells and a slow proliferation-rate.

It is discussed as to what extent effector cells are maintained by repeated antigen-contact as in e.g. chronic immune reactions, as compared to "memory" in its strict sense, i.e. the "maintenance of information in the absence of effective antigenic instruction".[9]

Chronic immune reactions can be driven (i) antigen-specifically by e.g. residual antigen or (ii) unspecifically as shown for cross-reactivities. Here, due to shared T cell epitopes, B cells specific for e.g. birch pollen major allergen Bet v 1 can be activated by Th cells recognizing an epitope on apple allergen Mal d 1.[10]

Memory in the absence of effective antigenic instruction has been demonstrated for B cells, for memory T cells and for long-lived plasma cells, which no longer respond to antigen, and rest in terms of proliferation.[11]

BIOLOGY OF SYSTEMICALLY INDUCED PLASMA CELLS

In systemic immune responses analysed so far, antigen-specific antibody-secreting cells are generated in secondary lymphoid organs. Most of these cells then migrate into the bone marrow as plasmablasts.[12-14] Essential for this differentiation is the expression of the transcription factor Blimp-1, which downregulates the B cell transcription factor Pax-5 (in: [9]).

Plasmablasts are proliferating precursors of plasma cells and can therefore be depleted from the system by cytostatic drugs such as e.g. cyclophosphamide. In the bone marrow, migratory plasmablasts apparently differentiate into resident plasma cells and survive as such over extended periods of time.[3,15-18] Although this differentiation and survival has so far only been shown for IgG-secreting plasma cells, it is assumed that IgE-secreting plasma cells behave similarly. Still, long-lived plasma cells have stopped proliferation and are refractory to antigen.[17] As a result, conventional immunosuppressive therapy is ineffective as it is aiming at suppression of the development of plasma cells. Survival of these long-lived plasma cells is likely to be due to signals from their environment,[19-21] forming a plasma cell survival "niche". Plasma cells relocated from their survival niches will probably die, because they are no longer migratory and are deprived of their survival signals.[13,19]

CLASSICAL PLASMA CELL SURVIVAL NICHES AND "HOT SPOTS" IN PERIPHERAL TISSUES

Niches for plasma cells have been described extensively in the bone marrow but there is also evidence for survival in other tissues, in particular in secondary lymphoid tissues.[22] It was also reported, that long-lived plasma cells can be maintained in inflamed tissues for long time periods, suggesting that such tis-

sues provides niches for these cells as well.[23] Peripheral niches for plasma cells provide an elegant way to bring antibody-secreting plasma cells close to the antigens they are specific for, and to provide high local concentrations of antibodies there. It is also a sophisticated way to contract the numbers of plasma cells after the acute immune reaction, when the inflamed tissue is regenerated and the plasma cells are no longer migratory and cannot move to other niches anymore (in: [19]) They are prone to die, since the signals required for survival are no longer provided.

THE INFLAMED LUNG AS TEMPORARY SURVIVAL NICHE: LYMPHOCYTES MIGRATE INTO THE LUNG DURING AEROSOL INHALATION BUT DO NOT PERSIST THERE

It has been reported that after allergen uptake via the mucosa, airway-dendritic cells migrate to the draining lymph nodes of the lung, up-regulate the expression of costimulatory ligands, and interact with naïve T lymphocytes, inducing an immune response (in: [24]). Airway inflammation induced by repeated allergen-in-aerosol exposure leads to the immigration of leukocytes into the lung.[3,25] Plasmablasts have been reported to be able to migrate from secondary lymphoid tissue into inflamed tissue and survive there,[19] but they also could be generated within inflamed tissue from precursors in ectopic immune reactions.[26] We could show that already after the second allergen-aerosol inhalation, not only B cells, T cells, kappa/lambda-positive B and antibody-secreting cells but also IgE- and IgG1-positive B and plasma cells are detectable in the lungs, suggesting that these cells had immigrated rather than developed there.[3] Their persistence in the lung provided high local titers of allergen-specific antibody. We could show, however, that persistence of these plasma cells is dependent on continued allergen-aerosol stimulation of the lung; after termination of aerosol treatment these plasma cells disappear, while they are still detectable in spleen and bone marrow where they continue to secrete allergen-specific antibodies.

THE DEPENDENCE OF PLASMA CELLS ON BAFF AND APRIL SIGNALS

Members of the TNF family of ligands, specifically BAFF (B cell activating factor of the TNF family) and APRIL (a proliferation-inducing ligand), have been implicated in B cell subset survival but their precise roles in supporting post-germinal center B cell differentiation and survival are still unresolved.[27] Both of these ligands bind to the receptors TACI (transmembrane activator and calcium modulator ligand interactor) and BCMA (B cell maturation Ag), with BAFF additionally and exclusively binding the BAFF receptor (BAFF-R) while APRIL can also bind to heparin sulphate proteoglycans. Randolph Noelle and coworkers have investigated whether BAFF, APRIL or both support plasma cell survival. In their recent study they show, that either BAFF or APRIL is sufficient to support plasma cell survival, but bone marrow plasma cells cannot survive in the absence of both of these ligands. Their data provide important new insights into the role of BAFF and APRIL on long-lived humoral immunity.[28] BAFF and APRIL are probably not the only signals for plasma cell survival.[23]

ORGANIZATION AND MAINTENANCE OF IMMUNOLOGICAL MEMORY IN ALLERGY: LONG-LIVED IgE PLASMA CELLS—KEY PLAYERS IN CHRONIC IMMUNOPATHOLOGY

Plasma cells play a central role in infection and vaccination, because they are responsible for the secretion of protective antibodies. Most plasma cells generated in a given immune reaction die within the first week. This is reflected by the rapid decrease of antibody titers. In secondary systemic immune responses, antibody titers rise and then decrease till they reach a low but stably maintained plateau, often about 10-20% of the peak response. These antibody-titers are maintained for years after immunization (in: [29]).

As the product of systemic T-cell-dependent activation of B cells, long-lived plasma cells can be an essential component of immunopathology. This is particularly evident for IgE-mediated allergy, since the half-life of IgE in serum is only about 12 hours.[30] Persistent production of specific IgE in the apparent absence of the corresponding antigen remains a hallmark of type 1 allergies in humans.[31] To some extent, allergen-specific IgE production can be transferred by bone marrow transplantation from allergic donors to non-allergic recipients[32] although it has not been shown unambiguously that this transfer is due to long-lived plasma cells.

Allergies are also prolonged over extended periods of time because secreted IgE arms basophils and mast cells through binding via the FcεR. Immediately after crosslinkage of FcεR-bound IgE with allergen, basophils and mastcells secrete IL-4, thereby multiplying the allergic reaction.

More to the point is the demonstration of Holt and collaborators, that IgE- (and IgG-) secreting cells in allergic rats survive X-irradiation, which is sufficient to eliminate memory B cells but not long-lived plasma cells—an early demonstration of long-lived plasma cells secreting pathogenic IgE antibodies.[33]

However, long-lived plasma cells may not be the only source of allergen-specific IgE. Mucosal immune responses may play an important role in IgE-responses to antigenic challenges in the lung and gut, and so far we do not know whether the mucosa-associated lymphoid tissue generates long-lived plasma cells. Local production of allergen-specific IgE in inflamed tissue and the presence of allergen-specific B cells has been described by several groups,

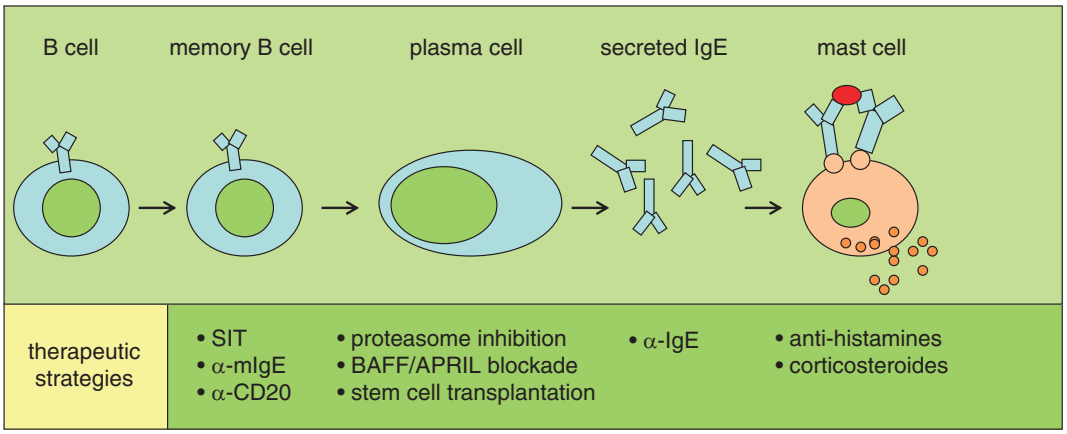

Fig. 1 Current intervention strategies to treat IgE-mediated allergic disease.

but the lifespan and persistence of these cells was unclear, as is their origin, which could be from a local immune reaction or an immune reaction in adjacent lymphoid organs.[34-36] Indicative of a substantial contribution of long-lived plasma cells to IgE-mediated allergy is the resistance of such diseases to immunosuppression, and the persistence of allergen-specific IgE titres despite such therapy,[37,38] since it is known that long-lived plasma cells are resistant to immunosuppression.[39-41]

INDUCTION OF LONG-LIVED, ALLERGEN-SPECIFIC PLASMA CELLS BY MUCOSAL ALLERGEN CHALLENGE

Recently, we have analyzed whether inhalation of allergen can lead to the formation of long-lived, allergen-specific plasma cells.[3] We followed the generation and persistance of allergen-specific plasma cells after ovalbumin-aerosol inhalation in a murine model of type-I-hypersensitivity, the ovalbumin asthma model.[25] We showed that ovalbumin-specific antibody-secreting cells, generated during systemic sensitization, homed to and survived preferentially in the bone marrow, but also in the spleen. Inhalation of ovalbumin-containing aerosol in already sensitized animals induced a profound boost of IgE, but also IgG1 and IgA secretion. The mucosal allergen challenge induced ovalbumin-specific PC in the lung, cells which vanished rapidly after termination of aerosol treatment. However, numbers of ovalbumin-specific IgE, IgG 1 and IgA secreting, cyclophosphamide-resistant cells in the bone marrow increased upon aerosol treatment, indicating that aerosol-delivery of allergen induces long-lived specific plasma cells. We have provided evidence showing, that inhalation of aerosolized allergen generates long-lived, allergen-specific IgG1-, IgA- and IgE-secreting plasma cells which survive cytostatic treatment in spleen and bone marrow.

A NEW VIEW ON THE ORGANIZATION OF ALLERGEN-SPECIFIC IMMUNOLOGICAL MEMORY

In light of our data we believe that pathogenic plasma cells are generated in the early lifetime of an individual. This has been shown in various animal models for human disease for e.g. lupus prone NZB/W mice, where pathogenic plasma cells were detected before the clinical onset of disease. After disease onset, only a few of these plasma cells generated *de novo* become long-lived (in: [29]).

THERAPEUTIC IMPLICATIONS TARGETING ALLERGY

Novel approaches to treat IgE-mediated diseases are required since present intervention concepts can not cure allergy[42] (see Fig. 1). These strategies should be safe, provide long lasting protection and avoid the risk of anaphylactic reactions.

A. SPECIFIC INTERVENTIONS

Allergen-specific Immunotherapy: Reprogramming the Immune System for Induction of Tolerance to Allergen?

The only current treatment of allergic disease, besides the use of symptom-based interventions such as anti-histamines and corticosteroids to treat the inflammation, is specific immunotherapy (SIT). However, this treatment is transient, time consuming, expensive and may even result in life threatening reactions. Immunotherapy is now performed for more than 100 years, but still bears the risk of severe adverse reactions. More importantly, many patients experience only an insufficient or just a short term remission. Still, hymenoptera venom allergy can be treated successfully in approximately 90%. Recently, sublingual application of the allergen (SLIT) has gained interest and compliance among the patients. SLIT explores a novel route of administering an allergen, to induce mucosal tolerance to inhaled allergens. Studies of SLIT in allergic rhinitis demonstrate

that it reduces symptoms and use of medication and is associated with a low incidence of systemic allergic reactions.[43,44]

To date, no long term causal treatment for allergic diseases is available and the development of new, safe and convenient treatment protocols are urgently needed. As the allergic immune response is characterized by a dangerous deviated cellular response such new therapies need to target the involved cell types and their cellular products specifically.

Anti-IgE Antibody Therapy: Omalizumab

A more specific therapeutic approach for asthma is based on decreasing the levels of circulating and cell-bound of IgE: The one drug that has so far entered clinical practice is a humanised monoclonal antibody to the Fc portion of the IgE molecule, omalizumab. It is highly effective in reducing IgE blood levels and its established mode of delivery is by subcutaneous injection. Published data claim its efficacy in clinical practice.[45] The target group of omalizumab treatment are severe asthmatics who are still symptomatic after being administered with high-dose inhaled corticosteroids plus long-acting β-agonists. However, such therapy is limited by high costs and the requirement of permanent or repeated application.

Combination of Omalizumab and Specific Immunotherapy Is Superior to Immunotherapy Alone

SIT and IgE depletion in theory could complement each other. To determine whether combined therapy provides better efficacy than either treatment alone, the efficacy and safety of subcutaneously administered anti-IgE in children and adolescents with seasonal allergic rhinitis (grass- and birch pollen) was investigated.[46] The authors could show, that anti-IgE therapy achieved a protective effect independent of the type of allergen. Additional clinical benefit of anti-IgE antibodies was demonstrated in pollen seasons, with or without SIT. This combination might prove useful for the treatment of allergic rhinitis, particularly for polysensitized patients.[46,47] Still, the treatment of allergic asthma by SIT is hampered by potential side-effects. Kopp and coworkers reported the effect of omalizumab in combination with SIT in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma incompletely controlled by conventional pharmacotherapy.[48] To this end, the efficacy and safety of omalizumab in combination with SIT during the grass pollen season was assessed. Omalizumab or placebo was started 2 weeks before SIT. The entire treatment lasted 18 weeks. Primary endpoint was daily 'symptom load', the sum of daily scores for symptom severity and rescue medication use. Combination therapy reduced the symptom load by 39% over SIT monotherapy. This difference was mainly due to reduced symptom severity, while rescue medication use did not change significantly. Combination therapy also improved asthma control and quality of life in the case of asthma and rhinoconjunctivitis. The authors have concluded, that the combination of omalizumab with SIT was safe and reduced the symptom load significantly.

These data show that the combination of anti-IgE plus SIT may be beneficial for the treatment of allergic diseases, offering improved efficacy, limited adverse effects, and potential immune-modifying effects. Still, the cause of disease, the memory IgE B cell, and the memory IgE-secreting plasma cell are not addressed.

Regulation of the IgE Response at the Molecular Level: Cellular Anti-IgE Therapy Concepts Targeting IgE Memory B Cells

The classical allergic immune reaction starts seconds or minutes after antigen contact and is committed by IgE antibodies produced by differentiated B cells. Treatment of IgE-mediated diseases with humanized anti-IgE antibodies leads primarily to a decrease of serum IgE. (in: [49,50]). As a consequence, the number of high-affinity IgE receptors on mast cells and basophils decreases, leading to a lower excitability of the effector cells. IgE bount to the high-affinity receptor remains unaltered. The underlying biological mechanism remains speculative, an effect of the therapeutic anti-IgE antibodies on membrane IgE (mIgE) expressing B cells can not be excluded. Feichtner and co-workers investigated this assumption by producing mouse antibodies exclusively directed against the extracellular membrane-proximal domain of mIgE aiming at a specific depletion of mIgE-positive B cells. By this approach, circulating IgE memory B cells would be eliminated from the system hindering these cells from differentiation into IgE-secreting plasmablasts and plasma cells. The interaction between the monoclonal anti-IgE-mIgE antibody and mIgE on B cells induced receptor-mediated apoptosis *in vitro*. Signals generated by the antigen receptor are needed not only for the maturation process but also for the expansion of antigen-specific B cells. Antigen binding by the antigen receptor is considered the first signal in B cell activation. Without a second signal, consisting of physical contact with the specific Th cell and the interleukins it produces, the activation is abortive. Such activated B cells disappear, either by an apoptotic mechanism or after a short anergic state, in which the B cell cannot be further activated. In passive immunization experiments they could show a block of newly synthesized specific IgE during allergen encounter. The authors conclude, that the decrease of allergen-specific serum IgE might be related to tolerance-inducing mechanisms stopping mIgE-displaying B cells in their proliferation and differentiation into plasma cells (in: [50]).

B. ALLERGEN- AND IgE- INDEPENDENT INTERVENTION STRATEGIES

Hinderance of the Reproduction of Plasma Cells by Antiproliferative Immunosuppressive Therapy

Memory plasma cells secreting allergen-specific IgE antibodies are the cells of humoral memory.[51] They represent an unmet therapeutic challenge, because they are resistant to conventional treatment, in particular to immunosuppression and anti-inflammatory drugs. Once in their survival niches, antibody-secreting plasma cells are resistant to environmental threats and to immunosuppressive treatment. As Hoyer and coworkers could show in the murine model of systemic lupus erythematosus, treating the mice with cyclophosphamide did not reduce long-lived autoreactive plasma cell numbers. The plasma cells were extremely resistant even to high-dose treatment and continued antibody secretion.[3,29]

Cure of Allergy by Destruction of Memory for the Allergen

Rituximab—Anti-CD20 Treatment

CD20 is a cell surface protein expressed on B cells from the pre-pro B cell stage through memory cells, but not on either pro-B cells or plasma cells. It is the target of the monoclonal antibody Rituximab. CD20-targeted B cell depletion therapy in humans has been met with success in the treatment of autoimmune and malignant B cell disorders. However, this treatment eliminates CD27+ B cells for up to 6 months. These cells express CD20. Bone marrow plasma cells do express little or no CD20. Accordingly, Rituximab only induces a minor decrease in serum immunoglobulin levels of the patients. Autoreactive and protective antibodies are reduced to different degrees, indicating that some of the cells secreting pathologic antibodies are generated before the clinical onset of disease, whereas others are secreted by newly generated, and probably short-lived plasma cells,[29] (in: [51]).

BAFF/APRIL Blockade Using TACI-Ig

Because simultaneous BAFF and APRIL blockade depletes bone marrow plasma cells in mice, this might be an option to treat patients with malignant or autoimmune diseases. It has recently been reported that BAFF and APRIL blockade ablates multiple myeloma cells *in vivo* more effectively than BAFF blockade alone (in: [28]). BAFF blockade does not deplete memory B cells. Thus, even upon BAFF or BAFF and APRIL blockade, a patient's memory B cell compartment should persist and provide reactive immunological memory.

The Biology of the Plasma Cell Determines its Fate: Proteasom-blockade?

Recently, Voll and coworkers showed that the sensitivity of myeloma cells toward proteasome inhibitors directly correlates with their immunoglobulin synthesis rates.[52] They hypothesized that normal plasma cells are also sensitive to proteasome inhibition. They could show that the proteasome inhibitor bortezomib, which is approved for the treatment of multiple myeloma, a plasma cell neoplasia, eliminates both short- and long-lived plasma cells by activation of the terminal unfolded protein response. Apart from plasma cells, rapidly proliferating lymphocytes such as thymocytes and germinal center B cells were depleted by proteasome inhibition. Resting B and T cells, monocytes, dendritic cells and antigen presentation by dendritic cells were not affected or only moderately affected, particularly after prolonged treatment, indicating selectivity for plasma cells.

Treatment with bortezomib depleted plasma cells producing antibodies to double-stranded DNA, eliminated autoantibody production, ameliorated glomerulonephritis and prolonged survival of two mouse strains with lupus-like disease, NZB/W F1 and MRL/lpr mice.

Whether proteasome blockade would also successfully stop allergic symptoms by depletion of long-lived IgE plasma cells, secreting pathogenic IgE, needs to be investigated in the near future.

Depletion of Autoreactive Immunologic Memory Followed by Autologous Hematopoietic Stem Cell Transplantation

Immunoablative chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) has emerged as a promising experimental therapy for severely affected patients, achieving treatment-free, long-term remission in about 50% of patients refractory to conventional treatments.[53] Alexander and coworkers report the long-term reconstitution of T- and B cell subsets and serologic changes in 7 patients with SLE for up to 8 years after receiving immunoablation and ASCT.[53] They show that immunoablation with high-dose chemotherapy, methylprednisolone, and anti-thymocyte globulin efficiently depletes naive and memory T and B cells and long-lived plasma cells, including those that are autoreactive. In addition, immunoablation plus ASCT reactivated the thymus, leading to the development of a tolerant, "juvenile" adaptive immune system, which is reflected by long-term, treatment-free, clinical remissions, essentially a reset of the immunesystem with efficient depletion of autoreactive plasma cells.

Addressing the T Cell Compartment to Combat Allergic Diseases

Various populations of regulatory T (Treg) cells have been shown to play a role in the maintenance of peripheral homeostasis and the establishment of protective immune responses. Both, naturally occurring $CD4^+CD25^+$ Treg cells and inducible populations of allergen-specific, IL-10-secreting Treg type 1 cells in-

hibit allergen-specific effector cells in experimental models. Skewing of allergen-specific effector T cells to a protective, regulatory phenotype appears to be a key event in the development of a healthy immune response to allergens and a successful outcome in allergen-specific immunotherapy (in: [54]).

Still, it is debated, whether allergen-specific immune reactions can develop because regulatory B and T cells do not function correctly, or whether allergen-specific cells withdraw themselves from effective control by regulatory cells. Further it is possible, that the physiologic control for the allergen is leaky.

We could show, that the transcriptional repressor twist1, as an antagonist of nuclear factor kappa B-dependent cytokine expression, is involved in the regulation of inflammation-induced immunopathology. Ectopic *twist1* expression reduced the frequencies of cytokine-expressing reactivated Th1 or Th2, or of Th cells that had been stimulated without addition of polarizing cytokines, to 40-50% of the controls.[55]

CONCLUSION

Summarizing clinical therapeutic interventions and experimental data obtained so far we have to realize, that cure of allergy is more complex than probably assumed.

Still, the most promizing approaches are aiming at the pathogenic, symptom-causing IgE antibodies although this is not curative at all.

Therefore, addressing the IgE-secreting allergen-specific plasma cell, or the IgE memory B cell is the only curative concept, which has to find its way into the clinics in the coming future.

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