Current Topics in Microbiology and Immunology

Volume 388

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IgE Antibodies: Generation and Function

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ISSN 0070-217X ISSN 2196-9965 (electronic)
Current Topics in Microbiology and Immunology
ISBN 978-3-319-13724-7 ISBN 978-3-319-13725-4 (eBook)
DOI 10.1007/978-3-319-13725-4

Library of Congress Control Number: 2014956362

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

IgE antibodies were discovered in the 1960s as "reaginic antibodies" (Ishizaka and Ishizaka 1967), defined at that time as a type of immunoglobulin that could transfer hypersensitivity to protein antigens. Since then, the genes and proteins of both IgE and its high-affinity receptor, FcεRI (Kinet 1999), have been fully characterized. The role of IgE in human chronic inflammatory allergic diseases was suggested by a large number of association studies and was more recently conclusively proven by the beneficial effects of anti-IgE therapy in severe asthma.

The study of IgE-producing B cells was nevertheless long hampered by their relative paucity in peripheral blood and lymphoid organs. The recent development of genetically modified mouse models to study IgE responses has enabled the tracking and isolation of IgE-expressing cells and has uncovered distinctive aspects of the IgE response. We now know that IgE cell responses are characterized by a transient IgE germinal center phase, a predominance of the IgE plasma cell fate, an absence of functional IgE memory B cells, and the co-opting of the sequential switching process to generate high-affinity IgE antibodies. These findings have suggested a link between sequential switching to IgE and the pathogenic potential of IgE responses. Recent advances describing unique features of IgE cell differentiation and of the mechanisms involved in the memory of IgE responses are discussed in this volume by He Jin-shu and collaborators ("Biology of IgE Production: Ige Cell Differentiation and the Memory of Ige Responses").

IgE antibody genes are generated through class switch recombination (CSR), a process whereby the DNA sequence encoding the constant region of the IgE heavy chain, Cε, is brought in close proximity to the VDJ gene through looping out, ligation, and excision of the intervening DNA sequences. Antibody genes can be further modified by somatic hypermutation (SH). Both CSR and SH are mediated by the enzyme AID (Muramatsu et al. 2000). Here Pei Tong and Duane Wesemann discuss the molecular mechanisms underlying the generation of antibodies, how the specific features of CSR to IgE regulate the production of IgE antibodies in immature and mature B cells, and the implications of this regulation for the roles of IgE in disease ("Molecular Mechanisms of IgE Class Switch Recombination").

The pathogenic potential of IgE antibodies lies mainly in its ability to bind to the high-affinity FcεRI on the surface of mast cells and to induce mast cell degranulation upon crosslinking by allergens. Accordingly, it is now well established that IgE is a valid therapeutic target for difficult-to-treat allergic inflammatory diseases, such as corticosteroid-resistant asthma. Stephanie Logsdon and Hans Oettgen ("Anti-IgE Therapy: Clinical Utility and Mechanistic Insights") review the latest clinical data on the treatment of asthma and other allergic diseases with Omalizumab, the first therapeutic anti-IgE antibody successfully used in chronic allergic diseases. Immunological studies in anti-IgE treated patients have also shed new light on the role of IgE in immune responses beyond mast cell activation, and the success of Omalizumab has reinvigorated the search for new approaches targeting IgE-FcεRI interactions.

The affinity of IgE for an allergen, the relative concentration of allergen-specific IgE in the total IgE pool, and IgE cross-reactivity, are all important determinants of the occurrence, or not, of allergic reactions. Ryo Suzuki and collaborators ("New Insights on the Signaling and Function of the High Affinity Receptor for IgE") review the mechanisms of IgE- and FcεRI-mediated mast cell responses, sharing new insights into their modulation: we now know that monomeric IgE can induce diverse signaling and activation responses in mast cells, even in the absence of cognate antigens. New concepts have provided a framework linking monomeric IgE polyreactivity and its ability to activate mast cells in the absence of known antigen; furthermore, the affinity of IgE has been identified as a key determinant in the type of signaling and inflammatory responses induced downstream of antigen recognition.

The pathogenic role of IgE in allergy has somehow eclipsed its valuable protective functions in the case of parasitic infection. Helminthes in particular induce the production of high levels of serum IgE, but their presence is, somewhat counterintuitively, associated with protection from allergic diseases, even in the presence of IgE antibodies against allergens. Firdaus Hamid and collaborators ("Helminth-Induced IgE and Protection Against Allergic Disorders") discuss how helminthes infections result in the formation of IgE antibodies that recognize both the parasite and the allergen, but have low pathogenic potential. Interestingly, there is evidence of important differences in the allergen epitopes recognized by IgE from parasite-infected patients compared to allergic patients, and further research in this area holds the promise of exciting advances in our understanding of the mechanisms of allergy in the near future.

The novel ideas emerging from these studies suggest new preventive and therapeutic approaches based on interventions that alter IgE concentration and its affinity for allergens.

Alongside protection from parasites, IgE-mediated mast cell responses appear to be an important component of our bodies' anti-tumor defenses. Lai Sum Leoh and collaborators ("IgE Immunotherapy Against Cancer") explain the rationale behind the innovative use of IgE rather than IgG antibodies in cancer treatment, and discuss the therapeutic IgE antibodies that are currently under development for treatment of

malignancies, as well as the possibility of prophylactic use of anti-tumor IgE and the challenges of effective delivery.

We hope this volume on IgE antibodies will help to disseminate current knowledge on the generation and function of IgE, and encourage further studies. It is also our aim to showcase the broad spectrum of IgE functions: in causing, as well as preventing, allergic diseases; in defense against parasites, and as a valuable component in protection from cancer. Only by taking all these facets of the complex biology of IgE into account can we hope to fully understand the workings of this intriguing biological molecule and so harness its potential to improve human health.

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