Superantigens and Superallergens
Superantigens and Superallergens

Volume Editor

Gianni Marone, Naples

42 figures, 1 in color, and 5 tables, 2007
Chemical Immunology and Allergy
Formerly published as ‘Progress in Allergy’ (Founded 1939), continued 1990–2002 as ‘Chemical Immunology’

Prof. Gianni Marone
Department of Clinical Immunology and Allergy
Center for Basic and Clinical Immunology Research (CISI)
University of Naples Federico II, School of Medicine
Via S. Pansini 5
IT-80131 Naples (Italy)
To my late mother, Francesca Rita Marsella,
as a token of my gratitude for her love and support.
Contents

XIII Preface
Marone, G. (Naples)

1 Streptococcal Superantigens
Proft, T.; Fraser, J.D. (Auckland)

1 Abstract
2 Group A Streptococcal Superantigens
4 The Pregenomic GAS SAgs
6 The Postgenomic GAS SAgs
7 Superantigens of Group C and G Streptococi
8 Regulation of Superantigen Gene Expression
9 Protein Structure of Superantigens
10 Molecular Interactions of Superantigens with Receptor Molecules
10 MHC Class II Binding
13 T Cell Receptor Binding
14 Streptococcal Superantigens and Human Disease
14 Invasive GAS Disease and STSS
14 Epidemiological Studies
14 Animal Infection Models
15 Clinical Studies
16 Genetic Background of the Host
16 Acute Rheumatic Fever
17 Kawasaki Disease
17 Why Do Bacteria Produce Superantigens?
18 Acknowledgement
18 References
24 Diversity in *Staphylococcus aureus* Enterotoxins
Thomas, D.; Chou, S.; Dauwalder, O.; Lina, G. (Lyon)

24 Abstract
24 *Staphylococcus aureus* Enterotoxin Discovery
25 Description and Properties of Enterotoxins
25 Chemical Properties of Staphylococcal Enterotoxin-Related Toxins
29 Biological Properties of Staphylococcal Enterotoxin-Related Toxins
31 Distribution of Staphylococcal Enterotoxins in Humans
31 Staphylococcal Enterotoxin Production and Regulation
32 Clinical Significance of Staphylococcal Enterotoxins
32 Staphylococcal Food Poisoning
34 Toxic Shock Syndrome
35 Noninfectious Disease
36 Conclusion
36 References

42 The SaPIs: Mobile Pathogenicity Islands of *Staphylococcus*
Novick, R.P.; Subedi, A. (New York, N.Y.)

42 Abstract
43 Nomenclature
44 Superantigen and Other Accessory Genes
45 Staphylococcal Pathogenicity Islands and Their Genomes
50 Integration and Excision
51 Evolution: Staphylococcal Pathogenicity Island Insertion Sites and Integrases
53 Recombination?
53 Staphylococcal Pathogenicity Island Life Cycle
56 References

58 Protein Fv: An Endogenous Immunoglobulin Superantigen and Superallergen
Bouvet, J.-P.; Marone, G. (Naples)

58 Abstract
60 Possible Physiological Role of Protein Fv
62 Superantigenic Properties of Protein Fv
63 Superallergenic Properties of Protein Fv
64 Protein Fv Is an Endogenous Superallergen That Activates Human Basophils and Mast Cells
64 IgE Are Involved in the Activating Property of Protein Fv
65 Protein Fv Induces Mediator Release from FceRI+ Cells through the Interaction with IgE V\_H3+
66 Endogenous Superallergen Protein Fv Induces IL-4 from Human Basophils
67 Protein Fv Is an Endogenous Superallergen That Activates Human Heart Mast Cells
70 Closing Thoughts
72 Acknowledgements
72 References

Contents VIII


77 Yersinia pseudotuberculosis Superantigens
    Donadini, R. (Auckland); Fields, B.A. (Woden)

77 Abstract
77 Pathogenic Yersinia Species
78 *Y. pseudotuberculosis* Infection
79 Virulence Factors
80 *Y. pseudotuberculosis* Superantigens
83 Structure of *Y. pseudotuberculosis*-Derived Mitogen
88 References

92 B Cell Superantigens Subvert Innate Functions of B Cells
    Zouali, M. (Paris)

92 Abstract
93 *S. aureus* Protein A Targets B-1a Cells and Marginal Zone B Cells
95 *P. magnus* Protein L Impairs Innate-Like B Cell Immunity
100 Depleting Activity of B and T Cell Superantigens
101 Exploitation of Innate B Cell Functions by B Cell Superantigens
102 Conclusions
102 Acknowledgements
103 References

106 The Allergic March from *Staphylococcus aureus* Superantigens to Immunoglobulin E

106 Abstract
107 Association of *S. aureus* Superantigens with Allergic Disease
108 Targets of *S. aureus* Enterotoxin Activity
109 T Cell Superantigens
111 B Cell Superantigens
113 Mechanism of Antibody Class Switching to IgE
116 Class Switching to IgE and Synthesis of Allergen-Specific IgE
120 Effects of Topical Application of Superantigens in vivo
121 Additional Pathogenic Mechanisms of *S. aureus* Enterotoxins
121 Basophil Activation
121 T Regulatory Cell Inhibition
122 Confounding Steroid Therapies for Asthma
125 Local Class Switching to IgE
128 Local Somatic Hypermutation
130 Summary and Conclusions
130 References

137 Superantigen-Induced Regulatory T Cells in vivo
    Ivars, F. (Lund)

137 Abstract
138 The Superantigen-Induced Immune Response
Cytokine Production
Division Followed by Deletion
Anergy
In vitro versus in vivo Anergy
Regulatory T Cells
CD4+CD25+ Natural Tregs
Characteristics of Natural Tregs
Development of Natural Tregs
Functions of Natural Tregs
IL-10-Secreting Tregs
T Helper Type 3 Cells
Regulatory Cells in Superantigen-Induced Responses
CD4+ Tregs Induced by Repeated Immunization with bSAgs
CD4+ Tregs Induced by Repeated Exposure to vSAgs
Other SAg-Induced Regulatory Cells
What Cells Present SAggs in vivo?
Naïve DCs and B Cells Induce Tolerance
Similar in vivo T Cell Responses to SAggs and Conventional Protein Antigens
What Might Be the Role of Tregs in SAg-Induced Responses?
Concluding Remarks
Acknowledgements
References

T Cell Signalling Induced by Bacterial Superantigens
Bueno, C.; Criado, G.; McCormick, J.K.; Madrenas, J. (London, Ont.)

Abstract
Structural Biology of Superantigen Recognition by T Lymphocytes
SAg Interaction with MHC Class II Molecules
SAg Interaction with the TCR β-Chain
SAg-Mediated T Cell Activation Complexes
T-Cell-Receptor-Dependent Signalling in Response to Bacterial Superantigens
Alternative Coreceptors and Additional Receptors for Bacterial Superantigens
T Cell Effector Responses Induced by Bacterial Superantigens
Concluding Remarks and Future Avenues
Acknowledgements
References

Modulation of Chemokines by Staphylococcal Superantigen in Atopic Dermatitis
Homey, B.; Meller, S. (Düsseldorf); Savinko, T.; Alenius, H.; Lauerma, A. (Helsinki)

Abstract
Atopic Dermatitis
Chemokine Superfamily
Superantigens constitute a growing family of bacterial and viral proteins that share the capacity of inducing massive activation of the immune system. This concept was first introduced in the late 1980s by the group of Philippa Marrack to describe the ability of staphylococcal enterotoxin B to induce a remarkable expansion of T cells expressing T cell receptors with a specific subset of the T cell receptor β-chain variable region. The classical superantigens are the T cell superantigens. However, some naturally occurring proteins possess the properties of superantigens for B lymphocytes. B cell superantigens are proteins endowed with immunoglobulin-binding capacity. Protein A of *Staphylococcus aureus* is the prototype B cell superantigen. Other B cell superantigens are gp120 of HIV-1, protein L and the human gut-associated sialoprotein known as ‘protein Fv’. B cell superantigens, by interacting with membrane-bound IgE, activate human basophils and mast cells that express the high-affinity receptor for IgE. In this context, the definition of immunoglobulin superantigens has been transferred to superallergens.

In this volume, we have tried to cover novel aspects of T cell and B cell superantigens and some recent molecular and clinical findings generated by the superallergen concept. In particular, the recent completion of several genome projects and database mining led to the identification of a myriad of novel superantigens. We also focused on the possibility that certain superantigens can modulate regulatory T cells and that superantigens may stimulate or inhibit IgE synthesis depending on the conditions.

An important part of this volume is devoted to the significance of superantigens in a wide spectrum of clinical settings going well beyond the classical
superantigen-associated diseases. For instance, there is some evidence that superantigens/superallergens might play a role in certain aspects of HIV-1 infection and autoimmune diseases. In addition, there is growing evidence that staphylococcal superantigens and superallergens might be involved in certain diseases of the upper and lower respiratory tract. For instance, endogenous, viral and bacterial superallergens can activate primary effector cells of allergic reactions to release proinflammatory mediators and cytokines.

The rapid advances in this field make it difficult to produce a timely reference text. Despite this difficulty, I accepted the invitation of the Editors of the Chemical Immunology and Allergy series to produce a volume entitled Superantigens and Superallergens. This project was designed to highlight results obtained with the recent characterization of molecular and clinical aspects of T and B cell superantigens and of superallergens. Several issues remain to be solved. The evolution of pathogens and their hosts is inextricably intertwined and studies of superantigens/superallergens have revealed interesting dimensions in the complex ongoing battle between pathogens and their hosts. We should also remember that we are constantly exposed to superantigens and superallergens. This leads to the question: ‘why do bacteria and viruses produce superantigens?’ All these fascinating aspects are awaiting answers.

There are several important aspects still remaining to be fully addressed. First, novel bacterial and viral superantigens and superallergens should be identified. Secondly, we need to know more about the molecular events governing the immunological synapse induced by superantigens and certain superallergens. Similarly, there is still much to learn about the activation of different subsets of T and B cells, and of effector cells caused by superantigens and superallergens. The information that might arise from such studies may lead to the prevention and better management of superantigen/superallergen-associated diseases.

It has been a rewarding experience for me to interact with many friends and colleagues and I am pleased to acknowledge the excellence of their work. I would like to thank Karger publishers and their staff, as well as Jean Gilder for their assistance throughout the production of this volume.

This volume owes much to the stimulating intellectual environment provided by my colleagues at the Center for Research in Basic and Clinical Immunology (CISI) of the University of Naples Federico II.

Gianni Marone