

SUPERANTIGENS

SUPERANTIGENS

Molecular Basis for Their Role in Human Diseases

Edited by

Malak Kotb

and John D. Fraser



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*This book is dedicated to the memory of Edwin H. Beachey,
a great scientist, mentor, and friend*

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PREFACE

Microbial superantigens are fascinating proteins that have structurally evolved to interact in a unique manner with host immune defense systems. These molecules are unusual in the sense that they can simultaneously activate cells involved in innate immunity as well as T cells, which normally mediate acquired immune responses. As a result of this unusual mode of interaction, superantigens have the capacity to stimulate large numbers of immune cells to release inflammatory mediators that, if uncontrolled, can inflict serious damage upon the host and may even cause death. Through our studies of the various superantigens, we have learned so much about immune system activation and regulation and about the various mechanisms by which different cells of the immune system interact and exchange biochemical signals that program their response and function.

Years prior to their designation as superantigens and the discovery of the mechanism by which they function, several laboratories had been studying these proteins and noticing the unconventional way by which they elicit immune activation. The massive proliferative response they elicit in resting leukocytes resembled that of polyclonal mitogens, yet the requirement for cells expressing HLA class II molecules to induce leukocyte activation resembled antigenic responses. Unlike conventional antigens, however, these molecules required no processing by antigen-presenting cells and their presentation to T cells was MHC unrestricted. These seemingly perplexing properties were resolved when it became evident that the superantigens interact in a unique manner with HLA class II as well as with specific elements within the variable region of the β chain of the $\alpha\beta$ T cell receptor (TCR). Furthermore, it was found that superantigens use these receptors as a means to bring different types of cells closer, forcing them to interact and exchange activation signals that trigger biochemical cascades, resulting in the elaboration of potent inflammatory cytokine responses and massive T cell proliferation.

Shortly after their discovery, it was believed that all superantigens were alike, that they interact in the same way with immune cells, and that they cause similar diseases, namely toxic shock, serious skin infections, and food poisoning. A common remark was “if you’ve studied one superantigen, you’ve studied them all.” We now know that nothing could have been further from the reality of these molecules. The fact that bacteria like *Streptococcus pyogenes* have over twelve different superantigens suggested that these microbial proteins are functionally nonredundant.

Thousands of articles have been published on superantigens, with a marked increase in the past two years, underscoring the fact that the field has been advancing considerably. This, we believe, is a result of the advent of sophisticated technologies and bioinformatics tools that unraveled new structure-function information and considerable differences in the way that distinct superantigens interact with HLA class II and/or TCR molecules. These new discoveries provided an impetus for more in-depth studies of molecular features underlying differences in the biological function of superantigens, their tissue specificity and capacity to cause or exacerbate different diseases.

Although several outstanding books on superantigens have been published, we wanted this book to highlight several new and exciting findings. We assembled an outstanding team of scientists with highly diverse expertise but a common interest in superantigen structure, function, and biology. These authors brilliantly captured some of the latest advances in the field, presenting information on newly discovered superantigens in bacteria and viruses, demonstrating how some superantigens interact with receptors other than, or in addition to, HLA class II and TCR molecules, and proposing novel mechanisms for the association of certain superantigens with various types of acute and chronic diseases, including autoimmune diseases. Exciting developments in therapeutic modalities for superantigen-mediated diseases are also highlighted in this book. This latter aspect has been given some priority in recent years, particularly since certain superantigens, in the aerosolized form, have potential for use as biological weapons and in bioterrorism.

More importantly, we wanted the readers of this book to develop a better appreciation for how newly discovered structural variations among superantigens affect the mode by which they interact with immune cells. We hope that the readers will have a better understanding of how these structure/function differences may explain why different superantigens contribute to the initiation and/or exacerbation of distinct diseases, why certain ones are effective in some tissues but not others, and how the host's genetic makeup can grossly alter the course of superantigen-mediated diseases. We also hope that the readers of this book will appreciate how this new information has informed the design and development of novel intervention strategies or suggested the use of existing modalities to ameliorate or modulate superantigen responses in severe acute infections or certain chronic illnesses.

On the flip side, however, the powerful immune-stimulating potential of certain superantigens may be exploited to modulate and direct the type of inflammatory responses in a way that increases the host's efficiency in overcoming certain chronic diseases and infections. These new insights may provide information on disease mechanism and thereby focus efforts to develop effective therapeutics and intervention measures for superantigen-mediated illnesses.

Malak Kotb
John D. Fraser

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