The T-Cell Receptors

Edited by
Tak W. Mak

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Preface

The importance of thymus-dependent cells, or T cells, in the generation of a successful immune response was first realized in the early sixties. In the following two decades, a succession of elegant experiments established the antigen specificity of T cells and their ability to perform both as regulatory and effector cells. T cells were shown to be essential in most immune reactions, playing a crucial role in augmenting the activity of effector T and B cells against 'foreign' antigen, as well as in the suppression of effector activity against self antigens. The means by which T cells differentiate 'foreign' from 'self' antigens is based on their recognition of antigen almost exclusively in the context of self major histocompatibility complex products, unlike B cells, which recognize antigen alone. It is this recognition, mediated by the T-cell receptor, that sets into motion the diverse cell–cell interactions, which control the differentiation and regulation of the immune response.

Although its importance was well established, the molecular nature of the T-cell receptor remained elusive for two decades. Many hypotheses as to its structure and precise function were put forward, using immunoglobulin as a basis for conjecture, but "the Holy Grail of Immunology" remained ephemeral until three years ago. In the ensuing years, both immunologists and molecular biologists have contributed to an explosion of data unsurpassed by any previous period in the field.

This book is a collection of articles by major contributors to the field, summarizing our present knowledge of the receptor and the genes that encode it. The first part of the book describes the structure and function of the T-cell receptor, including its place in the immunoglobulin supergene family, the structure of the genes encoding the T-cell receptor heterodimer and the T3 proteins with which it is associated, the role of the major histocompatibility complex (MHC) products in T-cell recognition, and the biochemical events following receptor-mediated activation of T lymphocytes. The repertoire and potential diversity of the T-cell receptor in man and mouse and the rearrangement of the genes encoding the receptor during T-cell ontogeny in the thymus are also described. The latter half of the book deals with the use of T-cell receptor genes to investigate some interesting areas of immunology such as the repertoire of receptor genes in

mutant mice, the role of the T-cell receptor in MHC-related disease, and the involvement of the T-cell receptor loci in chromosomal abnormalities characteristic of T-cell malignancies. Other chapters describe the use of these genes in the definition of the clonality and lineage of malignant and proliferative T-cell diseases, and as probes for the identification and isolation of oncogenes involved in the generation of T-cell-related malignancies. The last chapter deals with the γδ heterodimer, another T-cell receptor, which is expressed on certain, T-cell subpopulations.

These chapters provide a synthesis of the large volume of data and the emerging concepts that lay a foundation for the resolution of some of the most fascinating puzzles facing immunologists today, including the relationship between the T-cell receptor genes and autoimmune disease, and the fundamental questions of how tolerance to self-antigens is acquired and how T cells learn to recognize antigens in the context of self MHC products.

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Tak W. Mak

Toronto

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Introduction

NICOLETTE CACCIA and TAK W. MAK

The regulation of the immune response is a complex process that involves a number of different cells and their products. Recent investigations of both autoimmune disorders and MHC-linked diseases have highlighted the important role that T cells play in these diseases and, thus their role in the maintenance of a well-balanced immune response crucial to the health of an organism.

T cells have a diverse, clonally distributed repertoire and recognize antigen in a specific manner, but this recognition is unique in that antigen can only be recognized on a cell surface and only in the context of major histocompatibility complex (MHC) products, a phenomenon known as MHC restriction. It is this restriction that enables T cells to distinguish 'self' antigens from 'foreign' molecules and thus to aid in the regulation of the response against foreign antigens, while preventing a response against self. The recognition of antigen is mediated by the T-cell receptor and in this book we have tried to summarize the present understanding of the receptor in the context of T-cell activation and function. We have divided the book into two parts: the first of which describes the structure and function of the T-cell receptor and the genes that encode it, while the second outlines the role that this receptor plays in a number of interesting immunological problems.

An understanding of the T-cell receptor remained an elusive goal for a number of years and with the recent cloning of the genes encoding it, an explosion of information was generated by the many interested investigators. The receptor itself is a cell surface heterodimer composed of an acidic α chain and a more basic β chain. Both chains contain variable and constant domains and the genes encoding these chains are composed of separate, noncontiguous gene seg-

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ments in the germline, which rearrange to produce a functional gene, allowing for the generation of a wide variety of receptors by the combinatorial use of these segments. Chapter 2 outlines the structure of the α and β chain genes, the rearrangement process involved in the generation of a diverse repertoire, and the role that these chains play in the recognition of antigen and MHC.

In the search for the receptor genes, a number of other T-cell specific molecules were isolated. One of the most interesting of these is the γ chain, a cell surface molecule that is homologous to the α and β chains and rearranges in T cells. The TcRα, TcRβ, and γ chains are all members of the immunoglobulin gene superfamily, which has taken shape over the past few years. Its members have diverse functions and expression patterns in various cell types and are, for the most part, unlinked in the genome, yet they share a number of characteristics, in addition to their structural similarities. The members of this superfamily are cell surface molecules with no known enzymatic activity, whose known functions include the binding to other molecules and the subsequent triggering of cellular events.

In Chapter 3, Barclay *et al.* describe the members of this superfamily, which includes molecules that may not be involved in the recognition of antigen, such as MRC OX-2, and those which are not apparently immune-system specific, such as Thy 1, as well as the more traditional proteins, which are involved in the binding of antigen (immunoglobulin and the T-cell receptor) or participate in immune interactions [MHC gene products, CD4 (Leu3/L3T4), CD2, CD1, CD5, and CD8 (Leu2a/Lyt2)]. All the members have regions of similarity that are about 100 amino acids long, have cysteine residues in similar positions, and seem to have similar β-strand folding patterns in the sequences between the cysteines, suggesting a common primordial ancestor with these features. These regions, or domains, can be classified as C-like or V-like based on the number of β-loops, with the V-like structures possessing an extra loop in the middle of the domain.

Barclay *et al.* propose a scheme for the evolution of this superfamily, based on homology between members, which suggests that their ancestral gene mediated recognition between cells that were not involved in immunity. They propose that immune recognition arose from a modification of a recognition system involved in programmed death of a given cell by another cell, in the course of cellular differentiation. It is interesting to note that this kind of programmed death is important in neural tissue development and that this hypothesis would explain the prevalence of molecules belonging to the immunoglobulin supergene family on the surface of brain cells. This scheme also proposes that the MHC genes were the first genes involved in immune recognition to arise, followed by T-cell receptor genes, and then by immunoglobulin genes, which is the order of appearance of these genes as one ascends the evolutionary ladder of organisms from coelenterates to mammals.

One of the more interesting phenomena that one sees when comparing im-

mune system genes from different species is the variation in the numbers of germline sequences from which an organism can draw to produce a sufficient repertoire of antigen-specific molecules to deal with the daily onslaught of foreign molecules. Examination of the number of V_β genes in different murine strains provides an interesting example of this variation. Certain laboratory mouse strains have lost a significant proportion of their germline V_β gene segments. In SJL mice, ten V_β from six subfamilies have been deleted from the genome, and have apparently not been replaced by new V_β sequences. These mice, however, seem to have an adequate immune response, implying that a large number of V_β genes may not be necessary.

In Chapter 4, Loh *et al.* discuss the T-cell receptor genes in mutant mice, including the differences in variable gene repertoire and the effects of changes in repertoire size on the immune response. They also explore possible interactions between the T-cell receptor and MHC genes, and the connection between T-cell receptor repertoire and MHC-linked disease.

Despite the fact that the thymus plays an important role in the selection and education of T cells, this organ remains very much a black box. T-cell precursors from the fetal liver, and in more mature animals, the bone marrow, migrate to the thymus where they proliferate and differentiate into functional T cells. One of the critical stages in the differentiation process involves the rearrangement of T-cell receptor genes to produce a functional cell surface molecule. Since it is this molecule that provides recognition of antigen and MHC, its expression enables the positive selection of cells bearing appropriate specificities and the negative selection of cells specific for 'self' antigens. The rearrangement and expression of TcR genes in different thymocyte subpopulations and the various differentiation pathways within the embryonic and adult thymus are presented in Chapter 5. The different maturation schemes proposed by different groups and the place that TcRα, TcRβ, and γ and δ gene rearrangement and expression take in the evolution of a coherent model of thymic development are also discussed.

In both the thymus and the periphery, the T-cell receptor heterodimer is closely associated with the T3 proteins on the cell surface, and it would seem that while the heterodimer provides the recognition function, it is T3 that plays a role in transmembrane signaling events. In Chapter 6, Terhorst *et al.* describe the component molecules of the T3 and their association with the T-cell receptor heterodimer.

Activation of T cells, upon the recognition of antigen and MHC gene products, gives rise to a number of events, including the production of lymphokines that regulate the immune response, the appearance of new cell-surface markers and the proliferation of T cells. The T-cell receptor complex mediates this activation by the recognition of antigen in the context of self MHC and the conversion of this specific recognition event into a transmembrane signal that initiates T-cell activation. The activation process would seem to be the same in all T

cells, but it has only been recently that the specific events that occur upon the binding of antigen by T cells have come to light. Manger *et al.* describe in Chapter 7 the role that the T-cell receptor complex plays in the initiation of activation and outline the investigation of the early events of this process.

Activation of a resting T cell is a two-signal event. In addition to the recognition of immobilized antigen in the context of self MHC, usually on the surface of an antigen presenting (APC), a second signal, which is usually provided by IL-1 secreted by the APC, is needed. The binding of antigen can be mimicked by T-cell receptor complex-specific antibodies and the effect of IL-1 by compounds such as PMA, allowing the dissection of activation events.

The binding of the receptor complex initiates polyphosphoinositide hydrolysis, leading to the generation of inositol triphosphate (IP_3) and diacylglycerol (DG). IP_3 induces the release of Ca^{2+} from intracellular stores, leading to an increase in the concentration of intracellular Ca^{2+}, while DG translocates protein kinase C (PKC) to the membrane from the cytoplasm, thereby activating it.

It is this PKC translocation that is effected by PMA, but unlike PMA, DG is rapidly metabolized within the cell leading to only a transient increase in PKC activity. If the moiety binding the T-cell receptor complex is immobilized, as is antigen on APC, the increase in PKC activity continues for a longer period of time, which is sufficient to restimulate activated T cells, perhaps by allowing for the phosphorylation of specific substrates necessary for further intracellular events of T-cell activation. However, activation of resting T cells requires a second signal, such as that delivered by the binding of IL-1.

The increase in Ca^{2+} concentration and activation of PKC are intracellular activation signals common to a variety of cell types. Manger *et al.* describe in detail the early events of T-cell activation and the means by which they were divined, providing a stepping stone for interesting avenues of investigation.

One of the more practical uses for the T-cell receptor genes is in the classification and management of patients with T-cell malignancies. Together with the immunoglobulin genes, the T-cell receptor genes can be used to diagnose a disease as one of B- or T-cell origin, and then can be used as probes to determine if the malignancy is clonal and to follow the course of the disease by monitoring changes in this clonality. These changes can be used to assess the effects of a chemotherapeutic program and to detect relapses earlier, as well as to identify the progression of the disease, in terms of the emergence of new clonal populations and other changes in tumor composition.

In Chapter 8, Slingerland *et al.* discuss the use of T-cell receptor probes in the diagnosis and management of T-cell disorders, as well as, in the study of chromosomal translocations characteristic of certain T-cell malignancies.

Over the past few decades, an increasing number of distinctive chromosomal abnormalities have become associated with certain neoplasias. The fact