MOLECULAR AUTOIMMUNITY

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Edited by

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Preface

In 1977 I edited a book for Academic Press entitled *Autoimmunity: Genetic, Immunologic, Virologic, and Clinical Aspects*. There were 23 chapters written by outstanding scientists and physicians working in the field of autoimmune diseases. Four individuals who contributed to that book are also represented here although their topics are different. The study of autoimmunity has become more molecular over the last decade. This molecular approach as well as new therapeutic possibilities are emphasized in the current volume. I thank the contributors for their effort and timely preparation of manuscripts, and also express appreciation to the excellent staff at Academic Press.

NORMAN TALAL

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Overview and Introduction

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Considerable progress has been made since autoimmune diseases were recognized, several decades ago, as a distinct pathogenic entity highly deserving of intense investigation. Much of our insight in the pathogenesis of these diseases has depended upon a thorough analysis and detailed understanding of the basic mechanisms of immunity and self-tolerance. It has been clearly established that T cell tolerance to self proteins is the result of clonal deletion during thymic differentiation. However, the precise cellular interactions whereby the thymic repertoire is selected and potentially autoreactive T cell clones are deleted have not been identified as yet. Our understanding of this process is unfortunately still very fragmentary and intense investigations in many laboratories are directed to clarify our knowledge of self-tolerance.

This volume addresses many aspects of the complex phenomena which are the basis of autoimmunity with the help of the modern technologies of genetics, cellular immunology and virology and extends the application of this basic information to an analysis of autoimmune pathogenesis at the clinical level.

The ability to differentiate self and non-self, which is the basis of the prevention of autoimmunity, depends on the complex regulatory mechanisms which govern T cell immunity to protein antigens.

It is well-established that foreign protein antigens need to be processed by antigen presenting cells (APCs) to generate the immunogenic peptides capable of interacting with autologous molecules of the major histocompatibility complex (MHC) for these complexes to be recognized by the T cell receptor (Benacerraf, 1978; Babbitt *et al.*, 1985; Unanue and Allen, 1987). The APCs process exogenous autologous and foreign proteins in an identical manner. There is increasing evidence, however, that the proteins synthesized

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by an antigen presenting cell are handled differently than ingested proteins and that the peptides generated are associated preferentially with class I MHC molecules. The MHC molecules do not have the capacity to discriminate between the peptides generated from self and foreign proteins and are able to bind indifferently both types of peptides (Townsend *et al.*, 1986; Lorenz and Allen, 1988; Rothbard and Taylor, 1988). The development of autoimmunity is prevented by a mechanism whereby during thymic differentiation those T cell clones with receptors for autologous processed peptides presented in the context of self MHC molecules are deleted (Kappler *et al.*, 1988; Teh *et al.*, 1988) upon interaction with these complexes.

It is essential, therefore, that autologous proteins be processed identically in the course of tolerance induction in the thymus and later in the adult to avoid the generation of autoimmunity to autologous proteins.

Although the precise nature of antigen processing is not well-understood and is the subject of intense investigation in numerous laboratories, it is generally accepted that its mechanism involves primarily: (1) the unfolding of the protein, (2) the generation of peptides with hydrophobic and sometimes amphipathic sequences, and (3) often, but not always the digestion by proteolytic enzymes (Buus *et al.*, 1987; DeLisi and Berzofsky, 1985). Proteins can be similarly processed *in vitro*, denatured to expose hidden determinants, and digested to generate immunogenic fragments capable of binding to MHC molecules on fixed APCs and to stimulate T cells (Shimonkevitz *et al.*, 1984).

While writing the introduction to this volume I recalled an observation which we made many years ago in our laboratory (McCluskey *et al.*, 1962; Benacerraf, 1965) that may have identified an important molecular mechanism for the pathogenesis of autoimmunity, when considered in the context of our present understanding of the processing and presentation requirements for the generation of T cell immunity to protein antigens. We observed that whereas guinea-pigs did not respond to immunization with their own autologous gammaglobulins, they readily developed strong cellular immunity, manifested by skin reactivity, when immunized and tested with the same autologous protein which had been subjected to any of various forms of physical denaturation by heat, alkali or urea. In the light of our present knowledge of processing of and tolerance induction to self proteins in the thymus, these experiments indicate that the immune system is only tolerant to the determinants generated from autologous proteins processed in the standard manner by autologous APCs. Therefore, we are potentially vulnerable to the development of autoimmune responses to other determinants in autologous proteins, which can be generated either by some form of denaturation or alternative digestion by different proteolytic enzymes.

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Part I

Genetic and Immunologic Factors