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THERAPEUTIC TARGETS OF THE TNF SUPERFAMILY
Edited by Iqbal Grewal

Therapeutic Targets of the TNF Superfamily

Edited by

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PREFACE

Tumor necrosis factor (TNF) superfamily is a rapidly growing family of cytokines that interacts with a corresponding superfamily of receptors. Ligand-receptor interactions of this superfamily are involved in numerous biological processes ranging from hematopoiesis to pleiotropic cellular responses, including activation, proliferation, differentiation, and apoptosis. The particular response depends on the receptor, the cell type, and the concurrent signals received by the cell. Worldwide interest in the TNF field surged dramatically early in 1984 with the cloning and defining of the profound cellular effects of the first member of this family, TNFα. Subsequently, the major influence of TNFα on the development and functioning of the immune system was established. Today, over 20 human TNF ligands and their more than 30 corresponding receptors have been identified. Few receptors still remain orphans. What has emerged over the years is that most TNF ligands bind to one distinct receptor and some of the TNF ligands are able to bind to multiple TNF receptors, explaining to some extent the apparent disparity in the number of TNF receptors and ligands. Yet, in spite of some redundancy in TNF ligand/receptor interactions, it is clear that in vivo spatial, temporal, and indeed cell- and tissue-specific expression of both ligands and their receptors are important factors in determining the precise nature of cellular, physiological and pathological processes they control.

TNF superfamily has been the most highly investigated area of basic medical research for over two decades. These investigations have benefited from the enormous growth in our understanding of the principal functions of the immune system and the explosion in the knowledge involved in regulation of normal and pathological immune response. In addition, much has been learned about the molecular mechanisms of programmed cell death and the escape of tumor cells from apoptotic demise and from discovery of the key role played by TNF ligands in this process. As the functioning of these superfamily members is very complex, understanding TNF ligands and their receptor biology requires a mélange of research activities in many different disciplines including organ development, molecular biology, experimental pathology, and immunology. As a consequence of intensive studies in multiple areas over many years, much has been learned. A key role of members of this superfamily

in normal functioning of the immune system, autoimmunity, and other fundamental cellular process by which tumor cells develop has been established. Many novel mechanisms involving TNF superfamily members in the disease development process have been defined, and a unified concept and new perspectives have also emerged. For example, abrasions in the innate immune system, not always considered critical in autoimmunity, have come under increasing attention. Additionaly, TNF-directed and not antigen- directed therapy has emerged as the most impressive therapeutic advance in managing autoimmunity in humans. These findings provide a foundation for novel drug design efforts that are poised to utilize newly acquired knowledge. Several of these strategies have already materialized into successful therapeutics such as use of TNF for cancers and anti-TNFα antibodies and TNFR-Fc for autoimmune diseases, and many have advanced to human clinical trials, while many more are still being tested in preclinical settings.

As in other rapidly evolving fields, these advances are not necessarily congruent and are often difficult to organize into a cogent whole. The aim of *Therapeutic Targets of the TNF Superfamily* is to make readily available the major research important in the exploitation of this family for developing therapeutic strategies for human diseases, in a single volume. Under the auspices of Landes Bioscience, I have undertaken the task to concisely consolidate current knowledge of key TNF superfamily members focusing on both basic aspects and their clinical application. In this volume, a number of leading scientists in the field cover many aspects of biology of TNF superfamily members, ranging from the cloning and characterization of TNF ligands and their receptors, through the use of animal models to study their functions in vivo and their exploitation for human therapeutic use. Each chapter also includes relevant background information and provides useful bibliography for a more detailed analysis, making the study of TNF ligands/receptors accessible at all levels of expertise.

I would like to express my sincere thanks to all of my contributors for their excellent effort and undertaking this project with such enthusiasm, to Cynthia Conomos and Ronald G. Landes for commissioning me to edit this volume, and Megan Klein and the staff of Landes Bioscience for help with publication coordination. This volume presents the state-of-the art account on the role of TNF superfamily members in the pathogenesis and their use in current intervention of cancers and autoimmune disease. This text will be highly valuable for investigators to understand the disease processes regulated by TNF superfamily members and to develop effective therapeutics. A view into the future, inspired by the comprehensive work presented in this volume, predicts that researchers studying TNF superfamily members will continue to make rapid progress in identifying relevant components to the disease process and new therapeutic strategies to target many human diseases including cancers, autoimmune disease, and others.

Iqbal S. Grewal, PhD

ABOUT THE EDITOR...

IQBAL S. GREWAL, PhD. is well-known in the field of T-cell co-stimulation and autoimmunity and has extensively investigated several members of the TNF superfamily and molecules important for lymphocyte co-stimulation. His research has focused on the basic molecular and cellular processes to determine the biological roles of these molecules in normal physiology and immunity and their potential utility as agents or targets for the treatment of autoimmune diseases and cancers. His experience in discovering and developing innovative protein-based biotherapeutics in many disease areas has translated some of his findings into key drug candidates for the treatment of autoimmune disease and cancers.

Dr Grewal currently holds the position of Vice President of Preclinical Therapeutics at Seattle Genetics, Inc. in Bothell, Washington. He is responsible for preclinical translational research functions in support of the development of monoclonal antibodies and antibody-drug conjugates as therapeutics in the areas of autoimmunity and oncology. Before joining Seattle Genetics, Inc. Dr Grewal performed drug discovery research and preclinical development at Genentech in South San Francisco, California, where he identified and validated several novel molecules as therapeutic candidates in oncology and autoimmune disease. Prior to Genentech, Dr Grewal worked at Yale University School of Medicine. Before that, he held various research positions at the University of California, Los Angeles (UCLA). Dr Grewal has presented his work at both national and international meetings, as well as published over 100 scientific publications, 75 abstracts, 60 patent applications. He is a fellow of the Royal College of Pathologists, London and member of several distinguished societies. Dr Grewal holds a PhD in Immunology from UCLA and completed his post-doctoral fellowship at Howard Hughes Medical Institute at Yale University School of Medicine.

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