Contents

Preface XIII

Mechanisms of Regulation

T Cell Tolerance

Vacchio, M.S.; Ashwell, J.D. (Bethesda, Md.) 1
Introduction 1
Tolerance Defined 2
How Is Tolerance Established? 3
Clonal Deletion 3
Deletion in the Thymus 3
Variability in TCR/Ligand Interactions that Affect Clonal Deletion 7
Types of Thymic APC Responsible for Clonal Deletion 9
Cellular Mechanisms of Clonal Deletion 11
Peripheral T Cell Deletion 11
Anergy 13
Thymocyte Anergy 13
Induction of Anergy in Peripheral T Cells 14
Mechanism of Anergy 17
Why Peripheral Anergy? 20
Other Mechanisms of Unresponsiveness 20
Receptor Down-Regulation 20
Discordance Between in vivo and in vitro T Cell Responsiveness 21
Conclusion 23
References 24

Pathways and Regulation of B-Cell Responsiveness and Tolerance
Scott, D.W. (Rochester, N.Y.); Warner, G.L. (Syracuse, N.Y.); Yao, X.;
Kent, S.C. (Rochester, N.Y.) 34

Historical Overview 34
The Need for B-Cell Tolerance 34
Models of B-Cell Tolerance 35
Anti-IgM as a Surrogate for Antigen 35
Mechanisms of Unresponsiveness 76
The Role of the Fc Receptor 76
Signaling through slg and the FcR 77
Effect of the Macrophage Product Prostaglandin E2 on Immune-Complex-Induced Unresponsiveness 78
Immune Complexes Inhibit Only Some Aspects of B Cell Responsiveness 79
Induction of Antibody Secretion by Immune Complexes 80
Immune Complexes and IFN-γ Promote Hapten-Specific IgG2a Secretion 81
PGE2 Potentiates IFN-γ, but not Immune Complex and IFN-γ Induction of Hapten-Specific IgG2a Production 82
cAMP-Dependent and cAMP-Independent Mechanisms Promoting Immune Complex-Induced FL-Specific IgG2a Production 83
Conclusion 86
Acknowledgements 87
References 87

T Cell Clonal Anergy
Gilbert, K.M. (La Jolla, Calif.) 92

Introduction 92
Inducing Tolerance of Th Cells in vitro 93
Inducing Th Cell Tolerance with Naturally Tolerogenic APC 96
Tolerance of Th1 and Th2 Cells in vivo 98
Examining the Mechanism for T Cell Tolerance 99
Role of Costimulator Signals in T Cell Anergy 100
Functional Consequences of T Cell Anergy 104
Molecular and Biochemical Consequences of T Cell Anergy 106
Concluding Remarks 109
References 109

Regulation of the Immune Response within Privileged Sites
Ksander, B.R.; Streilein, J.W. (Miami, Fla.) 117

Introduction 117
The Fetus as an Immune Privileged Site 119
Development of the Maternal-Fetal Junction 119
Expression of Class I and II Antigens on Trophoblasts 120
Resistance of Trophoblasts to Lysis by Cytotoxic Effector Cells 121
Identification of Unique NK-Like Cells within the Decidua 122
Role of the Local Microenvironment in Maintaining Immune Privilege 123
Anterior Chamber of the Eye 125
Induction of ACAID 126
Role of the Local Microenvironment in the Induction of ACAID 127
Role of the Local Microenvironment in the Efferent Phase of the Immune Response 128

Contents VIII

The Brain as an Immune Privileged Site 130
The Testis as an Immune Privileged Site 133
Tumors as Immune Privileged Sites 135
Conclusions 138
References 139

Suppressor Cells and Immunity

Historical Background 146
Demonstration of Suppressor Cells in in vivo Immune Responses 151
Role of Suppressor Cells in Infectious Disease 151
Role of Suppressor Cells in Autoimmune Disease 153
Role of Suppressor Cells in the Normal Immune Response 154
Role of Suppressor Cells in Cancer 156
Characterization of Suppressor Cells in vitro 157
Suppressor Cell Clones 157
Cytokines and Suppression 160
Antigen-Specific Suppressor Factors (TSF) 163
Use of TCR Immunoglobulin Genes by Antigen-Specific T Cells 165
Novel Approaches to Cloning the X Chain 167
Phenotypic Studies of Suppression 167
Antigen Recognition and Activation of Ts 171
Nonspecific Suppression 172
Veto Cells 175
Conclusions 176
References 177

Topics of Clinical Interest

T Cell Tolerance: Models for Clinical Application to Allergy and Autoimmunity
Schad, V.C. (Waltham, Mass.) 193

The Recognition Triad 193
Clonal Deletion 236
T Cell Clonal Deletion in the Thymus 236
B Cell Clonal Deletion 237
Clonal Anergy 237
T Cell Clonal Anergy 237
Anergy to Antigens Expressed Extrathymically in Transgenic Mice 239
B Cell Clonal Anergy 240
Suppression 241
Specific Suppression 241
Natural Suppressor (NS) Cells 242
Veto Cells 242
Strategies to Achieve Tolerance to Allografts 242
Bone Marrow Transplantation (BMT) 242
Intrathymic Injection 244
Chimerism Following Organ Transplantation 245

Contents X

Peripheral Tolerance Induction by Intravenous Injection of Donor Cells 245
APC Depletion and Modification 245
Monoclonal Antibodies 246
Conclusion 246
References 247

Oral Tolerance: A Biologically Relevant Pathway to Generate
Peripheral Tolerance against External and Self Antigens

Introduction and Historical Perspectives 259
The Intestinal Immune System 260
Ontogeny 260
Structure: Anatomy, Histology and Lymphocyte Populations 262
Function: Interpretation of Immunogenic and Tolerogenic Signals 264
Mechanisms for Oral Tolerance 268
General Considerations 268
Clonal Deletion 270
Anergy 270
Suppression 271
Clinical Application of Oral Tolerance 272
Autoimmune Disease and Allergies 272
Transplantation 277
The revolution in biology of the past two to three decades has led to a dramatic increase in our understanding of immune processes. It is now recognized that the immune response represents the activity of an enormous web of interacting cells and humoral factors. Furthermore, the
importance of intracellular signalling in these processes is now appreciated as is the role in immune responses of cells, such as keratinocytes and endothelial cells (amongst others), not usually thought of as immunologically relevant. These insights have led both to major advances in the basic molecular and cellular biology of the immune response and also have important implications for clinical immunology. The purpose of this volume is to present the current understanding of physiologic mechanisms of immune regulation along with the impact of this knowledge on selected clinical questions. Reviewed within this volume are such topics as T- and B-cell tolerance (including neonatal tolerance, clonal anergy and the role of immune complexes in tolerance), clonal deletion, suppressor cells, mechanisms of immune privileged sites, and experimental models of tumor immunity. The possible utility of manipulating the immune response for therapeutic benefits is explored in contributions discussing oral tolerance, ultraviolet radiation and photosensitized effects on immunity, T-cell vaccination and regulation of immunity with T-cell epitopes. Thus, our understanding of the regulation of the immune response has advanced dramatically in recent years. Of perhaps greater importance, this work has led to new approaches for the understanding and treatment of disease. Hopefully, the reader will find the fascinating articles in this issue of Chemical Immunology to be informative, useful and stimulating.