Immune Response and the Eye
Chemical Immunology and Allergy

Vol. 92

Series Editors

Johnnes Ring, Munich
Luciano Adorini, Milan
Claudia Berek, Berlin
Kurt Blaser, Davos
Monique Capron, Lille
Judah A. Denburg, Hamilton
Stephen T. Holgate, Southampton
Gianni Marone, Napoli
Hirohisa Saito, Tokyo
20 Intraocular Immunosuppressive Microenvironment
21 Effect of Inflammation on Ocular Immune Privilege
22 References

Physiology of Immune Response and the Eye

27 The Induction of Anterior Chamber-Associated Immune Deviation
Niederkorn, J.Y. (Dallas, Tex.)

27 Abstract
28 The Induction of Anterior Chamber-Associated Immune Deviation
28 Ocular Phase of Anterior Chamber-Associated Immune Deviation
30 Thymic Phase of Anterior Chamber-Associated Immune Deviation
31 Splenic Phase of Anterior Chamber-Associated Immune Deviation
33 Role of the Sympathetic Nervous System in Anterior Chamber-Associated Immune Deviation
33 Conclusions
33 References

36 Anatomy and Immunology of the Ocular Surface
Knop, E. (Berlin); Knop, N. (Hannover)

36 Abstract
37 Anatomy of the Immune System at the Ocular Surface and Adnexa
37 Cornea
37 Conjunctiva
37 Morphology
38 Diffuse Leukocyte Subpopulations
39 Follicles
39 Lacrimal Gland
39 Lacrimal Drainage System
40 Tear Film and Integrated Proteins
40 Mucosal Immune Defense Mechanisms at the Ocular Surface
41 Innate Immunity at the Ocular Surface
41 Function of the Innate Immune System
41 Innate Effector Cells at the Ocular Surface
41 Toll-Like Receptors
43 Secreted Antimicrobial Peptides
43 Specific Adaptive Immunity at the Ocular Surface
43 Function of the Adaptive Immune System
44 Uptake of Antigen at the Ocular Surface
44 Immune Regulation in Follicular Lymphoid Tissue
44 Diffuse Lymphoid Tissue with Effector Cells
45 Defense Strategies: One Does Not Fit for All at the Ocular Surface
45 The Immune Privilege Approach
46 The Pro-Inflammatory Approach
47 Acknowledgments
47 References
50 Immune Privilege and Angiogenic Privilege of the Cornea
Cursiefen, C. (Erlangen/Boston, Mass.)

50 Abstract
51 Common Phenomenology of Corneal Immune and Angiogenic Privilege
52 Common Molecular Mechanisms of Corneal Immune and Angiogenic Privilege
53 Corneal Immune Privilege
53 Corneal Angiogenic and Lymphangiogenic Privilege
54 Immunomodulatory Effects of Anti-her- and Antilymphangiogenic Therapies in the Cornea
56 References

58 Corneal Antigen-Presenting Cells
Hamrah, P.; Dana, M.R. (Boston, Mass.)

58 Abstract
58 Introduction and Historical Overview
59 Resident Antigen-Presenting Cells in the Normal Uninflamed Cornea
59 Dendritic Cells, Langerhans Cells and Dendritic Cell Precursors
60 Epithelial Langerhans Cells
61 Corneal Stromal Dendritic Cells
62 Dendritic Cell Precursors
62 Macrophages
63 Antigen-Presenting Cells in Inflammation and Immunity
64 Antigen-Presenting Cell Trafficking and Their Role in Corneal Transplantation
64 Migration to Draining Lymph Nodes
65 The Role of Vascular Endothelial Growth Factor Receptor-3
66 Direct versus Indirect Pathway of Sensitization
66 Implications and Future Directions
67 References

71 Ocular Immunosuppressive Microenvironment
Taylor, A.W. (Boston, Mass.)

71 Abstract
72 Delayed-Type Hypersensitivity
73 Innate Immunity and T-Cell Activation in Delayed-Type Hypersensitivity
73 The Immunosuppressive Ocular Microenvironment
74 Regulation of T-Cell Activity by Aqueous Humor
78 The Immune Response within the Eye
80 Conclusions
81 References

86 Immunosuppressive Properties of the Pigmented Epithelial Cells and the Subretinal Space
Zamiri, P.; Sugita, S.; Streilein, J.W. (Boston, Mass.)

86 Abstract
87 Immunoregulatory Properties of Pigmented Epithelial Cells in the Eye
87 Transforming Growth Factor-β
119 Dendritic Cells and Antigen-Presenting Cells in the Anterior Chamber
121 Mechanisms of Anterior Chamber-Associated Immune Deviation in the Spleen
123 The Role of the F4/80 Protein in Anterior Chamber-Associated Immune Deviation
125 Role of the Ly49 Molecule
125 Similarity of Anterior Chamber-Associated Immune Deviation with Other Models of Tolerance
126 Summary and Conclusion
127 References

131 Regulatory T Cells and the Eye
Niederkorn, J.Y. (Dallas, Tex.)

131 Abstract
133 Ocular-Induced Regulatory T Cells
133 Regulatory T Cells Induced by Anterior Chamber-Associated Immune Deviation
135 Pigment Epithelium-Induced Regulatory T Cells
135 Regulatory T Cells Induced by Aqueous Humor
136 Regulatory T Cells Induced by Endogenous Retinal Antigens
136 Conclusions
137 References

140 The Role of Fas Ligand and TNF-Related Apoptosis-Inducing Ligand (TRAIL) in the Ocular Immune Response
Ferguson, T.A. (St. Louis, Mo.); Griffith, T.S. (Iowa City, Iowa)

140 Abstract
141 Death Receptors and the Eye
141 Fas Ligand
141 Overview
142 The Discovery
143 Localization
143 Corneal Transplantation
144 Immune Tolerance
145 Neovascularization
146 The Microenvironment
146 Inducible (Induced?) Immune Privilege
147 Pro-Inflammatory Properties
148 TNF-Related Apoptosis-Inducing Ligand/Apo-2L
148 Expression and Receptors
150 Immune Privilege
151 Conclusions
151 Acknowledgment
151 References
185 **Bacterial Infections of the Cornea** (*Pseudomonas aeruginosa*)
Hazlett, L.D. (Detroit, Mich.)

185 Abstract
185 Microbial Keratitis
186 MIP-2, IL-1, and PMN
186 CD4+ T Cells and Genetic Susceptibility to *P. aeruginosa*
187 MIP-1α Regulates CD4+ T Cell Chemotaxis
187 IL-12 and IFN-γ in C57BL/6 Mice
188 IL-18, IFN-γ and NK Cells in BALB/c Mice
188 Antigen Presentation: Langerhans Cells and Costimulation
190 Macrophages in Innate Response to *P. aeruginosa* Ocular Infection
191 Toll-Like Receptors in Bacterial Keratitis
191 Acknowledgment
192 References

195 **Cicatrizing and Autoimmune Diseases**
Rashid, S.; Dana, M.R. (Boston, Mass.)

195 Abstract
196 Mooren’s Ulcer
198 Peripheral Ulcerative Keratitis Associated with Systemic Immune-Mediated Diseases
199 Cicatrizing Conjunctivitis
199 Ocular Cicatricial Pemphigoid
200 Conclusion
201 References

203 **How Herpes Simplex Virus Type 1 Rescinds Corneal Privilege**
Lepisto, A.J.; Frank, G.M.; Hendricks, R.L. (Pittsburgh, Pa.)

203 Abstract
203 Role of T Cells
205 Antigen Presentation
206 Cytokines
207 Angiogenesis
208 Disease Models
209 Conclusion
210 Acknowledgment
210 References

213 **Intraocular Diseases – Anterior Uveitis**
Bora, N.S. (Little Rock, Ark.); Kaplan, H.J. (Louisville, Ky.)

213 Abstract
213 Uveitis
214 Epidemiology and Classification of Uveitis
215 Anterior Uveitis
215 Animal Models of Uveitis
216 Animal Models of Anterior Uveitis
216 Endotoxin Induced Uveitis
216 Collagen-Induced Anterior Uveitis – Experimental Autoimmune Anterior Uveitis
217 Experimental Melanin Induced Uveitis (EMIU)
217 Tolerance Induction for the Treatment of Anterior Uveitis
218 References

221 Glaucoma
   Tezel, G. (Louisville, Ky.); Wax, M.B. (Fort Worth, Tex./Dallas, Tex.)

221 Abstract
221 Aberrant T Cell Immunity
223 Humoral Immune Response
224 Tissue Stress in Glaucoma
225 Conclusion
225 References

228 Intermediate and Posterior Uveitis
   Forrester, J.V. (Aberdeen)

228 Abstract
229 The Clinical Problem
229 Infectious versus Non-Infectious Disease
231 Non-Infectious Uveitis: Is Posterior Uveitis One or Several Diseases?
232 Experimental Models
232 Historical Overview
233 Development of Spontaneous Models of Uveoretinitis
235 Site of Initiation of Disease
235 Mechanism of Tissue Destruction
236 Experimental Approaches to Modulating Disease in Experimental Autoimmune Uveoretinitis
238 Translational Studies
238 Current Therapies
238 Newer Approaches to the Management of Sight-Threatening Uveoretinitis
240 References

244 Acute Retinal Necrosis
   Kezuka, T. (Tokyo); Atherton, S.S. (Augusta, Ga.)

244 Abstract
245 Clinical Features of Acute Retinal Necrosis
247 Diagnosis and Virus Identification
248 Pathogenesis of Acute Retinal Necrosis
250 Puzzles and Questions
251 References
254 Onchocerca volvulus, Wolbachia and River Blindness
Pearlman, E.; Gillette-Ferguson, I. (Ohio)

254 Abstract
255 Infection and Disease – Host and Parasite Factors Determine the Balance between Pro- and Anti-Inflammatory Responses in Filariasis
256 The Pro-Inflammatory Response – Endosymbiotic Wolbachia Bacteria
256 Pathogenesis of Ocular Onchocerciasis
257 Role of Innate Immunity in O. volvulus Keratitis
259 Wolbachia and Toll-Like Receptors
262 Conclusion
263 Acknowledgments
263 References
265 Note Added in Proof

266 Role of Bacterial and Host Factors in Infectious Endophthalmitis
Gregory, M.; Gilmore, M.S. (Boston, Mass.); Callegan, M.C. (Oklahoma City, Okla.)

266 Abstract
266 Epidemiology and Etiology of Endophthalmitis
267 Bacterial Virulence Influences Outcome
267 Bacillus cereus Endophthalmitis
268 S. aureus Endophthalmitis
268 Enterococcus faecalis Endophthalmitis
269 Propionibacterium acnes Endophthalmitis
269 Gram-Negative Causes of Endophthalmitis
270 Host Response in Endophthalmitis
270 Chronic Inflammation
270 Acute Inflammation
270 Possible Role of Adaptive Immunity
271 Innate Immunity
273 Anti-Inflammatory Reagents
274 Conclusion
274 References

276 Influence of Immune Surveillance and Immune Privilege on Formation of Intraocular Tumors
Chen, P.W. (Dallas, Tex.); Ksander, B.R. (Boston, Mass.)

276 Abstract
277 Beginnings of the Immune Surveillance Theory
278 The Revival of Immune Surveillance
279 Involvement of Innate and Adaptive Immunity in Immune Surveillance
281 The Immuonooditing Hypothesis
283 Selective Pressure and Tumor Escape
283 Does Immune Surveillance Occur within the Immune-Privileged Eye?
284 Regulation of Immune Surveillance Effectors within the Eye

Contents XIII
284 NK Cells
285 DCs/Macrophages
285 NKT Cells
285 γδ T Cells
285 CD4+ and CD8+ T Cells
288 References

Treatment of Immune-Mediated Ocular Diseases

290 Immunogenicity and Immune Privilege of Corneal Allografts
Hori, J. (Tokyo); Niederkorn, J.Y. (Dallas, Tex.)

290 Abstract
291 The Immunogenicity of Corneal Allografts: Heterotopic Corneal Transplantation in Animal Models
292 Skin and Subcutaneous Space
292 Subcapsular Space of Kidney
292 Immunogenic Potential and Immune Privilege of Each Layer of the Corneal Allograft
294 Strategies to Eliminate the Immunogenicity of Orthotopic Corneal Allografts
294 Reconstitution of Immune Privilege and Promoting Corneal Allograft Acceptance in High-Risk Eyes
295 Immune Privilege of Corneal Allografts: Contributions of the Corneal Graft Bed and the Eye
295 Afferent Blockade of the Immune Response
296 Deviation of the Systemic Immune Response to Corneal Allografts
296 Efferent Blockade of Immune Response
297 Summary and Conclusions
297 References

300 Retinal Transplantation
Ng, T.F. (Boston, Mass.); Klassen, H.J. (Boston, Mass./Irvine, Calif.); Hori, J. (Tokyo); Young, M.J. (Boston, Mass.)

300 Abstract
301 Transplantation of Retinal Tissue and Retinal Pigment Epithelium to the Eye
302 Immune-Privileged Status of Potential Donor Tissues
304 Retinal Pigment Epithelium
305 Neuronal Retina
306 The Immunological Properties of CNS Stem Cells
307 Survival of Neural Stem Cells Placed beneath the Kidney Capsule
307 Donor-Specific Delayed Hypersensitivity
307 Presentation of Alloantigens to Primed T Cells
309 Survival of Neural Stem Cells before and after Sensitization in Mice
311 MHC and Fas Expression by Mammalian CNS Stem Cells
313 Changes in Immune Marker Expression in Response to IFN-γ
314 Conclusion
314 References
317 **Therapies Based on Principles of Ocular Immune Privilege**
Zhang-Hoover, J.; Stein-Streilein, J. (Boston, Mass.)

317 Abstract
319 F4/80+ Antigen-Presenting Cells: Messengers in the Camero-Splenic Axis during Anterior Chamber-Associated Immune Deviation
319 Mechanisms of Tolerance Induction by TGF-β2-Treated, Antigen-Pulsed Antigen-Presenting Cells
320 Therapeutic Application of Tolerance-Inducing Antigen-Presenting Cells in Disease Models
321 Experimental Autoimmune Encephalomyelitis
321 The Autoimmune Pulmonary Fibrosis Model
322 The Th2-Mediated Asthma Model
323 Conclusions, Future Perspectives, and Possibilities in Humans
324 References

328 **Author Index**

329 **Subject Index**
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>anterior chamber</td>
</tr>
<tr>
<td>ACAID</td>
<td>anterior chamber-associated immune deviation</td>
</tr>
<tr>
<td>ADT-HPIF</td>
<td>adoptively transferred-hapten immune pulmonary interstitial fibrosis</td>
</tr>
<tr>
<td>agr</td>
<td>accessory gene regulator</td>
</tr>
<tr>
<td>AH</td>
<td>aqueous humor</td>
</tr>
<tr>
<td>AIRE</td>
<td>autoimmune regulator</td>
</tr>
<tr>
<td>AKC</td>
<td>atopic keratoconjunctivitis</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>ARN</td>
<td>acute retinal necrosis</td>
</tr>
<tr>
<td>AU</td>
<td>anterior uveitis</td>
</tr>
<tr>
<td>BCR</td>
<td>B cell receptor</td>
</tr>
<tr>
<td>BM</td>
<td>bone marrow</td>
</tr>
<tr>
<td>BMZ</td>
<td>basement membrane zone</td>
</tr>
<tr>
<td>BRB</td>
<td>blood-retinal barrier</td>
</tr>
<tr>
<td>C3</td>
<td>complement 3</td>
</tr>
<tr>
<td>CB</td>
<td>ciliary body</td>
</tr>
<tr>
<td>CCC</td>
<td>chronic cicatrizing conjunctivitis</td>
</tr>
<tr>
<td>CFA</td>
<td>complete Freund’s adjuvant</td>
</tr>
<tr>
<td>CGRP</td>
<td>calcitonin gene-related peptide</td>
</tr>
<tr>
<td>CNV</td>
<td>choroidal neovascularization</td>
</tr>
<tr>
<td>CRP</td>
<td>complement-regulatory proteins</td>
</tr>
<tr>
<td>CTL</td>
<td>cytotoxic T lymphocytes</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>cytotoxic T lymphocyte antigen-4</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>DC</td>
<td>dendritic cell</td>
</tr>
<tr>
<td>DES</td>
<td>dry eye syndrome</td>
</tr>
<tr>
<td>DTH</td>
<td>delayed-type hypersensitivity</td>
</tr>
<tr>
<td>EAAU</td>
<td>experimental autoimmune anterior uveitis</td>
</tr>
<tr>
<td>EAU</td>
<td>experimental autoimmune uveoretinitis</td>
</tr>
<tr>
<td>EE</td>
<td>endogenous endophthalmitis</td>
</tr>
<tr>
<td>EIU</td>
<td>endotoxin-induced uveitis</td>
</tr>
<tr>
<td>EMIU</td>
<td>experimental melanin protein-induced uveitis</td>
</tr>
<tr>
<td>FasL</td>
<td>Fas ligand</td>
</tr>
<tr>
<td>GFP</td>
<td>green fluorescent protein</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GPC</td>
<td>giant papillary conjunctivitis</td>
</tr>
<tr>
<td>HEL</td>
<td>hen egg lysozyme</td>
</tr>
<tr>
<td>HSK</td>
<td>herpes stromal keratitis</td>
</tr>
<tr>
<td>HSV-1</td>
<td>herpes simplex virus type 1</td>
</tr>
<tr>
<td>I/CB</td>
<td>iris and ciliary body</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>intercellular adhesion molecule-1</td>
</tr>
<tr>
<td>ICE</td>
<td>interleukin-1β-converting enzyme</td>
</tr>
<tr>
<td>IEL</td>
<td>intraepithelial lymphocytes</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>iNKT</td>
<td>invariant natural killer T (cell)</td>
</tr>
<tr>
<td>IRBP</td>
<td>interphotoreceptor retinoid binding protein</td>
</tr>
<tr>
<td>iT&lt;sub&gt;reg&lt;/sub&gt;</td>
<td>induced CD4&lt;sup&gt;+&lt;/sup&gt; CD25&lt;sup&gt;+&lt;/sup&gt; regulatory T cell</td>
</tr>
<tr>
<td>KC</td>
<td>the murine homologue of Gro-α</td>
</tr>
<tr>
<td>KCS</td>
<td>keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>KO</td>
<td>knockout</td>
</tr>
<tr>
<td>LC</td>
<td>Langerhans cell</td>
</tr>
<tr>
<td>LFA-1</td>
<td>lymphocyte function-associated antigen-1</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>MAC</td>
<td>membrane attack complex</td>
</tr>
<tr>
<td>MCA</td>
<td>methylcholanthrene</td>
</tr>
<tr>
<td>MCSF</td>
<td>macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>MICA/B</td>
<td>MHC class I chain-related proteins A and B</td>
</tr>
<tr>
<td>MIP</td>
<td>macrophage inflammatory protein</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>MPO</td>
<td>myeloperoxidase</td>
</tr>
<tr>
<td>MSH</td>
<td>melanocyte stimulating hormone</td>
</tr>
<tr>
<td>MTU</td>
<td><em>Mycobacterium tuberculosis</em> adjuvant-induced uveitis</td>
</tr>
<tr>
<td>MyD889</td>
<td>myeloid differentiation factor 88</td>
</tr>
</tbody>
</table>
Abbreviations used in this book

MZ marginal zone
NK natural killer
NKT natural killer T (cells)
NNR neonatal neuronal retina
nT_reg naturally occurring CD4+ CD25+ regulatory T cell
OCP ocular cicatricial pemphigoid
OPG osteoprotegerin
OVA ovalbumin
PAC perennial allergic conjunctivitis
PAMP pathogen-associated molecular pattern
PDS pigment dispersion syndrome
PE pigmented epithelial
PEC peritoneal exudate cells
PMN polymorphonuclear neutrophils
POE postoperative endophthalmitis
POMC pro-opiomelanocortin
PTE posttraumatic endophthalmitis
PUK peripheral ulcerative keratitis
RA rheumatoid arthritis
RGCs retinal ganglion cells
RPE retinal pigment epithelial
SAC seasonal allergic conjunctivitis
sar staphylococcal accessory regulator
SC secretory component
SCF stem cell factor
SOM somatostatin
SRS subretinal space
TCR T cell receptor
TGF transforming growth factor
Th T helper (cells)
TLR Toll-like receptor
TNF tumor necrosis factor
TNFRII TNF receptor II
T_reg regulatory T cells
TSP thrombospondin
VEGF vascular endothelial growth factor
VIP vasoactive intestinal polypeptide
VKC vernal keratoconjunctivitis
VKH Vogt-Koyanagi-Harada disease
VZV varicella-zoster virus