## Contents

Preface xiii  
Contributors xvii  

**PART I Transcription Factors: Partners of Immune Tolerance to Self**

1 Transcriptional regulation of T cell tolerance 3  
Brian T. Abe, Ayana Jordan, Vanessa M. Hubbard and Fernando Macian  
1.1 Introduction 3  
1.2 T cell anergy 4  
1.3 Ca$^{2+}$/calcineurin/NFAT signalling in T cell anergy 5  
1.4 Transcriptional programme of T cell anergy 7  
1.5 Transcriptional repression in T cell anergy: epigenetic modification of the \( \text{Il2} \) promoter 10  
1.6 Regulatory T cells 12  
1.7 Transcriptional control of Treg development and function 12  
References 15  

2 Epigenetic regulation of Foxp3 expression in regulatory T cells 21  
Julia K. Polansky, Stefan Floess, Jennifer Freyer, Alf Hamann and Jochen Huehn  
2.1 Introduction 21  
2.2 Naturally occurring CD25$^{+}$CD4$^{+}$ Tregs 22  
2.3 The transcription factor FOXP3: determining Treg function and identity 25  
2.4 Molecular regulation of FOXP3 26  
2.5 Tregs as a stable lineage: indications of epigenetic imprinting 28  
2.6 Induced Tregs: stable suppressors or transient immuno-modulators? 30  
2.7 Conclusions 32  
References 33  

3 The role of NF-κB in central tolerance 39  
Mingzhao Zhu, Matthew Ruddy and Yang-Xin Fu  
3.1 Introduction 39  
3.2 Canonical and alternative NF-κB pathways 40
3.3 Thymic stroma and central tolerance 43
3.4 NF-κB and regulatory T cell development 47
3.5 NF-κB and thymocyte positive and negative selection 48
3.6 Conclusions and perspectives 50
3.7 Acknowledgement 50
References 50

4 The role of Act1 in the control of autoimmunity 55
Trine N. Jørgensen, Natalia V. Giltiay, Angela Johnson and Xiaoxia Li
4.1 Introduction 55
4.2 Autoimmunity and autoimmune mouse models 56
4.3 Molecular mechanisms of autoimmunity 58
4.4 Act1: a modulator of autoimmunity 60
4.5 Conclusions 70
References 71

5 Regulation of T cell anergy and escape from regulatory
T cell suppression by Cbl-b 75
Stefanie Loeser and Josef M. Penninger
5.1 Introduction 75
5.2 Mechanisms of T cell tolerance induction 75
5.3 Molecular establishment of T cell anergy 78
5.4 Ubiquitin E3 ligases in T cell tolerance 79
5.5 Molecular function and regulation of Cbl-b 80
5.6 Physiological relevance of Cbl-b 83
5.7 The role of Cbl-b in T cell tolerance 84
5.8 Deregulation of Cbl-b in disease 86
5.9 Therapeutic potential of Cbl-b in tumour immunity 86
5.10 Implications for autoimmune disease 88
References 88

6 Indoleamine 2,3-dioxygenase: transcriptional regulation
and autoimmunity 95
Maria Laura Belladonna, Ciriana Orabona, Claudia Volpi, Ursula Grohmann,
Paolo Puccetti and Maria Cristina Fioretti
6.1 Introduction 95
6.2 L-Trp degradation along the kynurenine pathway and immune
functions of IDO 96
6.3 IDO immunobiology and therapeutic intervention 101
6.4 Transcriptional regulation of the IDO-encoding gene 101
6.5 Impaired IDO activity and loss of tolerance in autoimmune diseases 107
6.6 IDO-based therapies for autoimmune disease 109
6.7 Acknowledgement 110
References 111
## PART II Stress Responses that Break Immune Silence

### 7 Chromatin modifications, oxidative stress and nucleosome autoantibodies

*Annika Erbacher and Patrice Decker*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 Introduction</td>
<td>119</td>
</tr>
<tr>
<td>7.2 Nucleosome and SLE</td>
<td>120</td>
</tr>
<tr>
<td>7.3 Epigenetics and SLE</td>
<td>123</td>
</tr>
<tr>
<td>7.4 Oxidative stress in SLE: definition and mechanisms</td>
<td>124</td>
</tr>
<tr>
<td>7.5 Oxidative stress, epigenetic alterations and nucleosome immunogenicity</td>
<td>127</td>
</tr>
<tr>
<td>7.6 Conclusion</td>
<td>129</td>
</tr>
<tr>
<td>7.7 Acknowledgements</td>
<td>129</td>
</tr>
<tr>
<td>References</td>
<td>130</td>
</tr>
</tbody>
</table>

### 8 Stress, epigenetics and thyroid autoimmunity

*Agathocles Tsatsoulis*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 Introduction</td>
<td>135</td>
</tr>
<tr>
<td>8.2 The Th1/Th2 balance in immune-response regulation</td>
<td>136</td>
</tr>
<tr>
<td>8.3 Stress hormones and the Th1/Th2 balance</td>
<td>136</td>
</tr>
<tr>
<td>8.4 The Th1/Th2 balance in thyroid autoimmunity</td>
<td>138</td>
</tr>
<tr>
<td>8.5 Association of stress with thyroid autoimmunity</td>
<td>140</td>
</tr>
<tr>
<td>8.6 Stress in the clinical expression of thyroid autoimmunity: a unifying hypothesis</td>
<td>143</td>
</tr>
<tr>
<td>8.7 Epigenetic regulation of T cell differentiation and stress hormones</td>
<td>145</td>
</tr>
<tr>
<td>8.8 Conclusions</td>
<td>146</td>
</tr>
<tr>
<td>References</td>
<td>146</td>
</tr>
</tbody>
</table>

### 9 Reactive intermediates, inflammation and epigenetics in lupus

*Gary S. Gilkeson and Jim C. Oates*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Introduction</td>
<td>151</td>
</tr>
<tr>
<td>9.2 Biology of reactive intermediates</td>
<td>151</td>
</tr>
<tr>
<td>9.3 RNIs in murine models of lupus</td>
<td>155</td>
</tr>
<tr>
<td>9.4 Genetic associations of RNI/ROI and lupus</td>
<td>159</td>
</tr>
<tr>
<td>9.5 Conclusions</td>
<td>160</td>
</tr>
<tr>
<td>References</td>
<td>160</td>
</tr>
</tbody>
</table>

### 10 Post-translational modification of HMGB1 and its role in immune activation

*Anirudh J. Ullal and David S. Pisetsky*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 Introduction</td>
<td>165</td>
</tr>
<tr>
<td>10.2 Molecular biology of HMGB1</td>
<td>166</td>
</tr>
<tr>
<td>10.3 HMGB1 as an immune mediator</td>
<td>167</td>
</tr>
</tbody>
</table>
14 Long-range histone acetylation patterns in the development of autoimmunity

Thomas M. Aune, Shaojing Chang and Weisong Zhou

14.1 Introduction

14.2 The histone code hypothesis

14.3 Epigenetic defects as a mechanism of disease

14.4 Analysis of the histone code

14.5 Long-range histone acetylation patterns in Th cell differentiation

14.6 Long-range histone acetylation and autoimmunity

14.7 Perspectives

14.8 Acknowledgements

References

15 Roquin defects reveal a role for the microRNA machinery in regulating autoimmunity

Di Yu and Carola G. Vinuesa

15.1 Introduction

15.2 RNA silencing through the miRNA machinery

15.3 miRNAs regulate lymphoid cell development and immune responses

15.4 miRNAs as single drivers of immunodeficiency or inflammation

15.5 miRNAs regulate autoimmunity

15.6 Roquin regulates miRNA-mediated silencing of T cells and represses lupus

15.7 Concluding remarks

15.8 Acknowledgements

References

16 Autoimmune response to post-translationally modified (citrullinated) proteins: prime suspect in the pathophysiology of rheumatoid arthritis

Mireille Sebbag, Cyril Clavel, Leonor Nogueira, Jacques Arnoud and Guy Serre

16.1 Introduction

16.2 RA is associated with B cell autoreactivity to citrullinated proteins

16.3 Both ACPA and citrullinated antigenic targets are present in the RA synovium

16.4 Autoreactivity to citrullinated proteins probably plays a role in RA synovitis

16.5 The way ACPA could promote joint inflammation

16.6 Joint-expressed citrullinated autoantigen targets possibly involved in a pro-inflammatory effect of ACPA

16.7 Initial triggering of the autoimmune response to citrullinated proteins

16.8 Goals for future research

16.9 Acknowledgements

References
17  Hormones: epigenetic contributors to gender-biased autoimmunity  309
    Virginia Rider and Nabih I. Abdou

    17.1  Introduction  309
    17.2  Oestrogen receptors  309
    17.3  Oestrogen and autoimmunity  310
    17.4  Foxp3 and ERs  312
    17.5  ERs and histone modifications  313
    17.6  The histone code  313
    17.7  Co-activators  314
    17.8  Pioneer factors  314
    17.9  Co-repressors  315
    17.10  ERs and cell proliferation  315
    17.11  Epigenetic changes in disease  315
    17.12  ERs and SLE  316
    17.13  Co-activators and phosphorylation  317
    17.14  Endocrine disruptors  318
    17.15  Perspectives and future directions  318
    17.16  Acknowledgements  320
    References  321

18  Epigenetics and systemic sclerosis  327
    Serena Guiducci and Marco Matucci Cerinic

    18.1  Introduction  327
    18.2  Vascular alterations in SSc  328
    18.3  Tissue hypoxia, oxidative stress and SSc  329
    18.4  Respiratory burst and post-translational modifications in SSc  330
    18.5  The epigenome and its environmental reprogramming  331
    18.6  Epigenetics and SSc  332
    18.7  Conclusions  334
    References  335

19  Epigenetic regulation of B lymphocyte development and repertoire selection: relevance to autoimmunity  339
    Moncef Zouali

    19.1  Introduction  339
    19.2  Initiation of B cell fate choice  340
    19.3  Checkpoints of B cell tolerance to self  340
    19.4  Negative regulation of immunoglobulin gene joining  342
    19.5  B cell fate commitment and immunoglobulin gene accessibility  343
    19.6  Changes in chromatin structure during B cell development  344
    19.7  Epigenetic changes through association of different immunoglobulin loci  346
    19.8  Epigenetic factors that allow full utilization of the immunoglobulin repertoire  347
PART IV  Towards Novel Epigenetic-Based Immuno-Intervention Strategies in Autoimmune Disease

20  Protective effects of epigenetic modifications in experimental inflammatory bowel disease 359
Rainer Glauben, Elena Sonnenberg and Britta Siegmund

20.1  Introduction 359
20.2  Mechanisms of protein acetylation and deacetylation 360
20.3  Anti-inflammatory effect of epigenetic modifications in vitro 362
20.4  Impact of HDAC inhibition in models of experimental colitis 365
20.5  Perspectives 368
References 369

21  Epigenetic regulation of autoimmune diseases through deacetylase inhibition 373
Bin Li, Yuan Shen, Zhaocai Zhou, Xiaomin Song, Kathryn Bembas, Xiao Yun Zhao, Zheng Cai, Alan Berezov, Sandra J. Saouaf, Hongtao Zhang, Qiang Wang and Mark I. Greene

21.1  Introduction 373
21.2  Regulatory T cells 374
21.3  Epigenetic regulation of FOXP3 expression 375
21.4  FOXP3 acetylation and function 375
21.5  Protein lysine deacetylation 376
21.6  HDAC inhibitors in autoimmune disease 377
21.7  Dietary butyrate promotes lysine acetylation by inhibiting deacetylases 378
21.8  The HDAC inhibitor butyrate affects TGF-β signalling and increases Smad3 levels 378
21.9  HDAC inhibitors affect immune-cell proliferation and conversion of antigen triggered T cells into an unresponsive state 378
21.10 Conclusions 379
References 380

22  Histone deacetylases and autoimmunity 385
András Treszl, Gergő Mézsáros, Gergely Toldi and Barna Vásárhelyi

22.1  Introduction 385
22.2  Chromatin acetylation and deacetylation 385
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.3</td>
<td>Histone deacetylases and histone acetyltransferases</td>
<td>386</td>
</tr>
<tr>
<td>22.4</td>
<td>Histone acetylation, deacetylation and transcription factors</td>
<td>389</td>
</tr>
<tr>
<td>22.5</td>
<td>in autoimmunity</td>
<td>392</td>
</tr>
<tr>
<td>22.5</td>
<td>Acetylation state and lymphocyte functions</td>
<td>392</td>
</tr>
<tr>
<td>22.6</td>
<td>HDACs and their inhibition in autoimmune disease</td>
<td>393</td>
</tr>
<tr>
<td>22.7</td>
<td>Conclusions</td>
<td>398</td>
</tr>
<tr>
<td>22.8</td>
<td>Acknowledgements</td>
<td>398</td>
</tr>
<tr>
<td>References</td>
<td></td>
<td>398</td>
</tr>
<tr>
<td>23</td>
<td>Histone deacetylase inhibitors as a therapeutic modality</td>
<td>403</td>
</tr>
<tr>
<td></td>
<td>in multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steven G. Gray</td>
<td></td>
</tr>
<tr>
<td>23.1</td>
<td>Introduction</td>
<td>403</td>
</tr>
<tr>
<td>23.2</td>
<td>Linking the histone code with MS</td>
<td>404</td>
</tr>
<tr>
<td>23.3</td>
<td>Neuronal traits are modulated by HDAC transcription-factor complexes</td>
<td>405</td>
</tr>
<tr>
<td>23.4</td>
<td>Motor neurone genes modulated by HDACs</td>
<td>406</td>
</tr>
<tr>
<td>23.5</td>
<td>The transcription factor E2F1, HDACs and neuronal survival mechanisms</td>
<td>406</td>
</tr>
<tr>
<td>23.6</td>
<td>HDACs play important roles in stem cell neuronal differentiation</td>
<td>407</td>
</tr>
<tr>
<td>23.7</td>
<td>HDIs lead to acetylation of the Sp1 transcription factor</td>
<td>407</td>
</tr>
<tr>
<td>23.8</td>
<td>Immune-system effects of HDIs</td>
<td>408</td>
</tr>
<tr>
<td>23.9</td>
<td>HDACs and pro-inflammatory and stress-related pathways in immune settings</td>
<td>411</td>
</tr>
<tr>
<td>23.10</td>
<td>HATs, HDACs and the NF-κB pathway</td>
<td>411</td>
</tr>
<tr>
<td>23.11</td>
<td>HATs, HDACs and ER stress</td>
<td>414</td>
</tr>
<tr>
<td>23.12</td>
<td>Clinical trials and caveats of HDIs</td>
<td>415</td>
</tr>
<tr>
<td>23.13</td>
<td>Do HDIs target genes or help chaperone activity as their primary response?</td>
<td>417</td>
</tr>
<tr>
<td>23.14</td>
<td>Future directions</td>
<td>418</td>
</tr>
<tr>
<td>References</td>
<td></td>
<td>419</td>
</tr>
</tbody>
</table>

**Index** | 433