The Epigenetics of Autoimmune Diseases

Editor Moncef Zouali
The Epigenetics of Autoimmune Diseases

Moncef Zouali

Inserm and University of Paris Diderot-Paris 7, France
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 \( \text{Ca}^{2+}/\text{calcineurin/NFAT} \) 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 \( Il2 \) 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-\( \kappa B \) in central tolerance 39
Mingzhao Zhu, Matthew Ruddy and Yang-Xin Fu

3.1 Introduction 39
3.2 Canonical and alternative NF-\( \kappa B \) pathways 40
## PART II  Stress Responses that Break Immune Silence

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Chromatin modifications, oxidative stress and nucleosome autoantibodies</td>
<td>Annika Erbacher and Patrice Decker</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td><strong>7.1 Introduction</strong></td>
<td></td>
<td>119</td>
</tr>
<tr>
<td></td>
<td><strong>7.2 Nucleosome and SLE</strong></td>
<td></td>
<td>120</td>
</tr>
<tr>
<td></td>
<td><strong>7.3 Epigenetics and SLE</strong></td>
<td></td>
<td>123</td>
</tr>
<tr>
<td></td>
<td><strong>7.4 Oxidative stress in SLE: definition and mechanisms</strong></td>
<td></td>
<td>124</td>
</tr>
<tr>
<td></td>
<td><strong>7.5 Oxidative stress, epigenetic alterations and nucleosome immunogenicity</strong></td>
<td></td>
<td>127</td>
</tr>
<tr>
<td></td>
<td><strong>7.6 Conclusion</strong></td>
<td></td>
<td>129</td>
</tr>
<tr>
<td></td>
<td><strong>7.7 Acknowledgements</strong></td>
<td></td>
<td>129</td>
</tr>
<tr>
<td></td>
<td><strong>References</strong></td>
<td></td>
<td>130</td>
</tr>
<tr>
<td>8</td>
<td>Stress, epigenetics and thyroid autoimmunity</td>
<td>Agathocles Tsatsoulis</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td><strong>8.1 Introduction</strong></td>
<td></td>
<td>135</td>
</tr>
<tr>
<td></td>
<td><strong>8.2 The Th1/Th2 balance in immune-response regulation</strong></td>
<td></td>
<td>136</td>
</tr>
<tr>
<td></td>
<td><strong>8.3 Stress hormones and the Th1/Th2 balance</strong></td>
<td></td>
<td>136</td>
</tr>
<tr>
<td></td>
<td><strong>8.4 The Th1/Th2 balance in thyroid autoimmunity</strong></td>
<td></td>
<td>138</td>
</tr>
<tr>
<td></td>
<td><strong>8.5 Association of stress with thyroid autoimmunity</strong></td>
<td></td>
<td>140</td>
</tr>
<tr>
<td></td>
<td><strong>8.6 Stress in the clinical expression of thyroid autoimmunity: a unifying hypothesis</strong></td>
<td></td>
<td>143</td>
</tr>
<tr>
<td></td>
<td><strong>8.7 Epigenetic regulation of T cell differentiation and stress hormones</strong></td>
<td></td>
<td>145</td>
</tr>
<tr>
<td></td>
<td><strong>8.8 Conclusions</strong></td>
<td></td>
<td>146</td>
</tr>
<tr>
<td></td>
<td><strong>References</strong></td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>9</td>
<td>Reactive intermediates, inflammation and epigenetics in lupus</td>
<td>Gary S. Gilkeson and Jim C. Oates</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td><strong>9.1 Introduction</strong></td>
<td></td>
<td>151</td>
</tr>
<tr>
<td></td>
<td><strong>9.2 Biology of reactive intermediates</strong></td>
<td></td>
<td>151</td>
</tr>
<tr>
<td></td>
<td><strong>9.3 RNIs in murine models of lupus</strong></td>
<td></td>
<td>155</td>
</tr>
<tr>
<td></td>
<td><strong>9.4 Genetic associations of RNI/ROI and lupus</strong></td>
<td></td>
<td>159</td>
</tr>
<tr>
<td></td>
<td><strong>9.5 Conclusions</strong></td>
<td></td>
<td>160</td>
</tr>
<tr>
<td></td>
<td><strong>References</strong></td>
<td></td>
<td>160</td>
</tr>
<tr>
<td>10</td>
<td>Post-translational modification of HMGB1 and its role in immune activation</td>
<td>Anirudh J. Ullal and David S. Pisetsky</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td><strong>10.1 Introduction</strong></td>
<td></td>
<td>165</td>
</tr>
<tr>
<td></td>
<td><strong>10.2 Molecular biology of HMGB1</strong></td>
<td></td>
<td>166</td>
</tr>
<tr>
<td></td>
<td><strong>10.3 HMGB1 as an immune mediator</strong></td>
<td></td>
<td>167</td>
</tr>
</tbody>
</table>
11 Idiosyncratic drug-induced liver injury: facts and perspectives
José V. Castell and Isabel Miñana

11.1 Introduction
11.2 Intrinsic drug toxicity to the liver
11.3 Idiosyncratic drug toxicity to the liver
11.4 Mechanisms of hypersensitivity reactions to drugs in the liver
11.5 Hypersensitivity versus tolerance
11.6 Hepatocyte injury as a consequence of allergic hepatitis
11.7 Drug-induced liver autoimmunity
11.8 Epigenetics of drug-induced liver injury
11.9 Acknowledgements

PART III  Epigenetic Modifiers of Autoimmunity

12 Epigenetic modifications associated with T cell tolerance
Andrè Andrew D. Wells and Rajan M. Thomas

12.1 Immunity versus tolerance
12.2 Epigenetic regulation of the physical structure of genomic DNA
12.3 Epigenetic control of pro-inflammatory cytokine gene transcription
12.4 Epigenetic silencing of cytokine genes in tolerant T cells
12.5 Targeting epigenetic modifications to cytokine genes in tolerant T cells
12.6 Common mechanisms of epigenetic silencing among distinct types of tolerant T cells?

13 DNA methylation alterations in systemic lupus erythematosus
Biola M. Javierre, Manel Esteller and Esteban Ballestar

13.1 Introduction
13.2 DNA methylation: an epigenetic determinant of lymphocyte function
13.3 DNA methylation changes in lupus
13.4 Epigenetic regulation as a therapeutic target
13.5 Future aims for epigenetic research into lupus
13.6 Acknowledgements

References
## 14 Long-range histone acetylation patterns in the development of autoimmunity

*Thomas M. Aune, Shaojing Chang and Weisong Zhou*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1 Introduction</td>
<td>247</td>
</tr>
<tr>
<td>14.2 The histone code hypothesis</td>
<td>247</td>
</tr>
<tr>
<td>14.3 Epigenetic defects as a mechanism of disease</td>
<td>249</td>
</tr>
<tr>
<td>14.4 Analysis of the histone code</td>
<td>250</td>
</tr>
<tr>
<td>14.5 Long-range histone acetylation patterns in Th cell differentiation</td>
<td>251</td>
</tr>
<tr>
<td>14.6 Long-range histone acetylation and autoimmunity</td>
<td>253</td>
</tr>
<tr>
<td>14.7 Perspectives</td>
<td>256</td>
</tr>
<tr>
<td>14.8 Acknowledgements</td>
<td>257</td>
</tr>
<tr>
<td>References</td>
<td>257</td>
</tr>
</tbody>
</table>

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

*Di Yu and Carola G. Vinuesa*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1 Introduction</td>
<td>261</td>
</tr>
<tr>
<td>15.2 RNA silencing through the miRNA machinery</td>
<td>262</td>
</tr>
<tr>
<td>15.3 miRNAs regulate lymphoid cell development and immune responses</td>
<td>263</td>
</tr>
<tr>
<td>15.4 miRNAs as single drivers of immunodeficiency or inflammation</td>
<td>264</td>
</tr>
<tr>
<td>15.5 miRNAs regulate autoimmunity</td>
<td>265</td>
</tr>
<tr>
<td>15.6 Roquin regulates miRNA-mediated silencing of T cells and represses lupus</td>
<td>266</td>
</tr>
<tr>
<td>15.7 Concluding remarks</td>
<td>272</td>
</tr>
<tr>
<td>15.8 Acknowledgements</td>
<td>273</td>
</tr>
<tr>
<td>References</td>
<td>274</td>
</tr>
</tbody>
</table>

## 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*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1 Introduction</td>
<td>279</td>
</tr>
<tr>
<td>16.2 RA is associated with B cell autoreactivity to citrullinated proteins</td>
<td>280</td>
</tr>
<tr>
<td>16.3 Both ACPA and citrullinated antigenic targets are present in the RA synovium</td>
<td>284</td>
</tr>
<tr>
<td>16.4 Autoreactivity to citrullinated proteins probably plays a role in RA synovitis</td>
<td>285</td>
</tr>
<tr>
<td>16.5 The way ACPA could promote joint inflammation</td>
<td>286</td>
</tr>
<tr>
<td>16.6 Joint-expressed citrullinated autoantigen targets possibly involved in a pro-inflammatory effect of ACPA</td>
<td>287</td>
</tr>
<tr>
<td>16.7 Initial triggering of the autoimmune response to citrullinated proteins</td>
<td>291</td>
</tr>
<tr>
<td>16.8 Goals for future research</td>
<td>297</td>
</tr>
<tr>
<td>16.9 Acknowledgements</td>
<td>298</td>
</tr>
<tr>
<td>References</td>
<td>298</td>
</tr>
</tbody>
</table>
PART IV Towards Novel Epigenetic-Based Immuno-Intervention Strategies in Autoimmune Disease

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

20.1 Introduction
20.2 Mechanisms of protein acetylation and deacetylation
20.3 Anti-inflammatory effect of epigenetic modifications in vitro
20.4 Impact of HDAC inhibition in models of experimental colitis
20.5 Perspectives

References

21 Epigenetic regulation of autoimmune diseases through deacetylase inhibition
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
21.2 Regulatory T cells
21.3 Epigenetic regulation of FOXP3 expression
21.4 FOXP3 acetylation and function
21.5 Protein lysine deacetylation
21.6 HDAC inhibitors in autoimmune disease
21.7 Dietary butyrate promotes lysine acetylation by inhibiting deacetylases
21.8 The HDAC inhibitor butyrate affects TGF-β signalling and increases Smad3 levels
21.9 HDAC inhibitors affect immune-cell proliferation and conversion of antigen triggered T cells into an unresponsive state
21.10 Conclusions

References

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

22.1 Introduction
22.2 Chromatin acetylation and deacetylation
CONTENTS

22.3  Histone deacetylases and histone acetyltransferases 386
22.4  Histone acetylation, deacetylation and transcription factors 389
      in autoimmunity
22.5  Acetylation state and lymphocyte functions 392
22.6  HDACs and their inhibition in autoimmune disease 393
22.7  Conclusions 398
22.8  Acknowledgements 398
References 398

23  Histone deacetylase inhibitors as a therapeutic modality 403
    in multiple sclerosis
Steven G. Gray

23.1  Introduction 403
23.2  Linking the histone code with MS 404
23.3  Neuronal traits are modulated by HDAC transcription-factor complexes 405
23.4  Motor neurone genes modulated by HDACs 406
23.5  The transcription factor E2F1, HDACs and neuronal survival mechanisms 406
23.6  HDACs play important roles in stem cell neuronal differentiation 407
23.7  HDIs lead to acetylation of the Sp1 transcription factor 407
23.8  Immune-system effects of HDIs 408
23.9  HDACs and pro-inflammatory and stress-related pathways in immune settings 411
23.10 HATs, HDACs and the NF-κB pathway 411
23.11 HATs, HDACs and ER stress 414
23.12 Clinical trials and caveats of HDIs 415
23.13 Do HDIs target genes or help chaperone activity as their primary response? 417
23.14 Future directions 418
References 419

Index 433
Investigation of the genome of several metazoan species revealed that the DNA sequences in all cells of a given individual are essentially the same, implying that genetic information, by itself, cannot fully account for the differential gene expression during cell differentiation and development. Parallel studies in the past decade also have unveiled the importance of an array of intricate epigenetic mechanisms that regulate transcription by affecting chromatin conformation—including DNA cytosine methylation, covalent modifications of histones, and certain aspects of RNA interference. Histones, for example, comprise a large number of residues that can be modified through several mechanisms, i.e. methylation, acetylation, phosphorylation, and ubiquitination. Such multiple, combinatorial modifications can give rise to highly complex patterns that can directly alter chromatin structure. Other modifications potentially serve as binding platforms to recruit additional effectors. The description of such a diversity of epigenetic factors led to several definitions of epigenetics. Recently, Adrian Bird proposed a revised definition that embodies contemporary usage of epigenetics: “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states”.

Epigenomic studies performed largely as a result of the availability of powerful high-throughput tools, i.e., high-density whole-genome microarrays, indicate that from the morphology of flowers to the eye color of insects, a variety of biological properties can be shaped by epigenetic influences. Investigation in different species also revealed that eukaryotic organisms can respond to environmental exposure by producing different phenotypes from the same DNA genome, implying that environmental stimuli could alter the state of the epigenome and affect gene expression by modifying DNA methylation and histone acetylation patterns. A striking example of this phenotypic plasticity has been reported in social insects by Ryszard Maleszka and co-workers. Thus, *Apis mellifera*, or honeybees, differentially feed genetically identical female larvae to create mainly workers and, when required, a limited number of queens. Despite their clonal identity at the DNA level, workers and queens differ markedly in morphological and physiological features, and exhibit contrasting reproductive capabilities, diverse life spans, and different behavioral repertoires. Remarkably, the honeybee has a full complement of all three functional DNA cytosine-5-methyltransferases with in vivo properties similar to those of the CpG methylation system in vertebrates. Its genome also encodes conserved methyl-binding proteins that include components of the nucleosome remodeling and histone deacetylase complex. This elaborate epigenetic
network that maintains the production of distinct adult morphologies, varied reproductive and behavioral systems, social organization and division of labor was demonstrated to be controlled by DNA methylation, a key epigenetic mark.

In rodents, such as the agouti mouse, a number of contrasting phenotypes, such as yellow and obese or brown and slim, can be controlled by varying the mother's diet before, during, and after pregnancy. Not only can gouti gene expression be silenced by DNA methylation, but its magnitude is variable in genetically identical individuals because of epigenetic modifications established during early development. In the rat, it appears that maternal reproductive tactics can alter the function of the neuroendocrine system associated with female sexual behavior and maternal behavior. Such maternal effects are mediated by epigenetic modifications at the promoter of estrogen receptor alpha and subsequent effects on gene expression, potentially underlying the coordinated variation in multiple forms of reproductive function and distinct reproductive strategies. Differential maternal behavior in the female rat also was found to alter the methylation status of the promoter of the glucocorticoid receptor of her pups. Even in psychopathology, there is evidence that interactions between genes and the environment can influence behavior. For example, experimental studies have shown that early life rearing experiences in rodents can alter gene expression, and that this epigenetic “reprogramming” involves specific genes as well as specific environments linked to later behavior.

In humans, it is remarkable that monozygotic twins do not always show the same disease susceptibility, suggesting that epigenetic differences can give rise to disease predisposition. The recognition of epigenetics as an important factor in health and disease has led to a surge in research aimed at uncovering epigenetic factors underlying pathogenesis. Epidemiological observations revealed that, in children, cardiovascular and diabetes mortality can be influenced by the nutritional status of their parents and grandparents. It has even been proposed that psychotropic drugs can rewrite the epigenetic code of the brain by switching on, or off, a number of genes through epigenetic modifications. The large amount of "epigenomic" data generated also is providing new insight into the mechanisms and functions of several regulatory pathways, and is broadening our understanding of aging and a variety of disorders, such as cancer development.

Until recently, epigenetic regulation of the immune system was considered of little importance. However, recent studies demonstrated that highly developed epigenetic mechanisms take part in several aspects of the development of immune cells and in the generation of innate and adaptive immune responses. Importantly, epigenetic changes represent suitable targets for the prevention and treatment of disease, implying that, potentially, they can be reversed by potent drugs. A detailed understanding of such mechanisms therefore can lead to novel therapeutic strategies based on manipulation of this previously unexploited facet of immune regulation.

Human autoimmune diseases represent a group of complex disorders that affect 5–10% of the world population. They can target virtually any organ and become life threatening. Their origin remains under scrutiny and the available treatments lack specificity and are associated with undesirable effects. Drawing on the research of
leading experts, *The Epigenetics of Autoimmune Disease* provides insights into a new area of autoimmunity. Firstly, it shows how highly developed epigenetic mechanisms take part in several aspects of normal immune regulation and in maintaining immune tolerance to self-determinants. Secondly, a number of chapters delve into specific epigenetic aspects of human autoimmune diseases—including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, autoimmune diabetes, thyroid autoimmunity, inflammatory bowel disease, and autoimmune hepatitis. In some of them, it is striking that the environment can prompt epigenetic changes that might influence autoimmunity development. Finally, this volume illustrates how understanding epigenetic mechanisms can lead to therapeutic strategies based on manipulation of this novel facet of immune regulation. Because epigenetic markers are easier to modify than the underlying sequences, they can be targeted for treatment. Discussed in this volume are therefore novel approaches that are being investigated to prevent or treat autoimmune diseases.

By providing a comprehensive review of epigenetic regulation of immune tolerance to self-antigens and its deregulation, I hope that this work will reveal new directions for future research in autoimmunity research. I also would like to thank the contributors to this volume for their patience and collegiality.

Moncef Zouali

*Paris, September 2008*
Contributors

Nabih I. Abdou, Center of Rheumatic Diseases, Allergy-Immunology, Kansas City, MO, USA

Jacques Arnaud, UMR 5165 CNRS-Université Paul Sabatier, Hôpital Purpan, Place du Dr Baylac, TSA40031, 31059 Toulouse Cedex 9, France

Brian T Abe, Albert Einstein College of Medicine, Department of Pathology, 1300 Morris Park Avenue, Bronx, NY 10461, USA

Thomas M. Aune, Division of Rheumatology, Department of Medicine and Department of Microbiology and Immunology. Vanderbilt University School of Medicine, MCN T3219, 1161 21st Ave. S., Nashville, TN 37232-2681, USA, e-mail: tom.aune@vanderbilt.edu

Esteban Ballestar, Cancer Epigenetics Group, Spanish National Cancer Research Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain, e-mail: eballestar@cnio.es

Maria Laura Belladonna, Department of Experimental Medicine, Section of Pharmacology, University of Perugia, via del Giochetto, Perugia 06126, Italy, e-mail: laurabell@tin.it

Kathryn Bembas, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Alan Berezov, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Zheng Cai, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

José V. Castell, Centro de Investigación. Hospital Universitario “La Fe”. Avda. de Campanar, 21. E-46009 Valencia, Spain, e-mail: jose.castell@uv.es

Shaojing Chang, Department of Medicine and Department of Microbiology and Immunology. Vanderbilt University School of Medicine, MCN T3219, 1161 21st Ave. S., Nashville, TN 37232-2681, USA

Cyril Clavel, UMR 5165 CNRS-Université Paul Sabatier, Hôpital Purpan, Place du Dr Baylac, TSA40031, 31059 Toulouse Cedex 9; and Laboratory of Cell Biology and Cytology, Institut Fédératif de Biologie, Hôpital Purpan, CHU de Toulouse, IFR30, 330 avenue de Grande-Bretagne, TSA40031, 31059 Toulouse Cedex 9, France
CONTRIBUTORS

Patrice Decker, Institute for Cell Biology, Department of Immunology, Auf der Morgenstelle 15, D-72076 Tübingen, Germany, e-mail: patrice.decker@uni-tuebingen.de

Annika Erbacher, Institute for Cell Biology, Department of Immunology, Auf der Morgenstelle 15, D-72076 Tübingen, Germany

Manel Esteller, Cancer Epigenetics Group, Spanish National Cancer Research Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain

Maria Cristina Fioretti, Department of Experimental Medicine, Section of Pharmacology, University of Perugia, via del Giochetto, Perugia 06126, Italy

Stefan Floess, Charité Universitätsmedizin Berlin, Campus Mitte, 10117 Berlin, Germany

Jennifer Freyer, Charité Universitätsmedizin Berlin, Campus Mitte, 10117 Berlin, Germany

Yang-Xin Fu, Department of Pathology, University of Chicago, 5841 S. Maryland Ave, MC 3083, Chicago, IL 60637, USA, e-mail: yfu@uchicago.edu

Gary S. Gilkeson, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite, 912, PO Box 250637, Charleston, SC 29425, USA, e-mail: gilkeson@musc.edu; oatesjc@musc.edu

Natalia V. Giltiay, Department of Immunology, Cleveland Clinic Foundation, Lerner Research Institute, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA

Rainer Glauben, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Medical Department I, Hindenburgdamm 30, 12200 Berlin, Germany

Steven G. Gray, Department of Clinical Medicine, Institute of Molecular Medicine, Trinity Centre for Health Sciences, St James’s Hospital, James’s Street, Dublin, Ireland, e-mail: SGRAY@STJAMES.IE

Mark I. Greene, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA, e-mail: greene@reo.med.upenn.edu

Ursula Grohmann, Department of Experimental Medicine, University of Perugia, via del Giochetto, Perugia 06126, Italy

Serena Guiducci, Department of BioMedicine, University of Florence, Viale Pieraccini 18, 50139 Florence, Italy

Alf Hamann, Charité Universitätsmedizin Berlin, Campus Mitte, 10117 Berlin, Germany

Vanessa M Hubbard, Albert Einstein College of Medicine, Department of Pathology, 1300 Morris Park Avenue, Bronx, NY 10461, USA

Jochen Huehn, Charité Universitätsmedizin Berlin, Campus Mitte, 10117 Berlin, Germany, e-mail: huehn@drfz.de

Biola M. Javierre, Cancer Epigenetics Group, Spanish National Cancer Research Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain
Angela Johnson, Department of Immunology, Cleveland Clinic Foundation, Lerner Research Institute, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA

Ayana Jordan, Albert Einstein College of Medicine, Department of Pathology, 1300 Morris Park Avenue, Bronx, NY 10461, USA

Trine N. Jørgensen, Department of Immunology, Cleveland Clinic Foundation, Lerner Research Institute, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA

Bin Li, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Xiaoxia Li, Department of Immunology, Cleveland Clinic Foundation, Lerner Research Institute, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA, e-mail: lix@ccf.org

Stefanie Loeser, IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Dr. Bohrgasse 3, A-1030 Vienna, Austria, e-mail: stefanie.loeser@gmail.com

Fernando Macian, Albert Einstein College of Medicine, Department of Pathology, 1300 Morris Park Avenue, Bronx, NY 10461, USA, e-mail: fmacianj@aecom.yu.edu

Marco Matucci Cerinic, Department of BioMedicine, Division of Rheumatology, University of Florence, Viale Pieraccini 18, 50139 Florence, Italy, e-mail: serena16@libero.it

Gergő Mézáros, Research Laboratory of Pediatrics and Nephrology, Hungarian Academy of Sciences, Semmelweis University, 1083 Budapest, Bókay u 54., Hungary

Isabel Miñana, SAIP, Hospital Clínicas Universitario, Consellería de Sanitat, Valencia Avda. de Blasco Ibáñez 17, 46010 Valencia, Spain

Leonor Nogueira, UMR 5165 CNRS-Université Paul Sabatier, Hôpital Purpan, Place du Dr Baylac, TSA40031, 31059 Toulouse Cedex 9; and Laboratory of Cell Biology and Cytology, Institut Fédératif de Biologie, Hôpital Purpan, CHU de Toulouse, IFR30, 330 avenue de Grande-Bretagne, TSA40031, 31059 Toulouse Cedex 9, France

Jim C. Oates, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite, 912, PO Box 250637, Charleston, SC 29425, USA

Ciriana Orabona, Department of Experimental Medicine, Section of Pharmacology, University of Perugia, via del Giochetto, Perugia 06126, Italy

Josef M. Penninger, IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Dr. Bohrgasse 3, A-1030 Vienna, Austria

David S. Pisetsky, Department of Medicine, Duke University, Durham, North Carolina, USA; and Medical Research Service, 151G Veterans Administration Medical Center; 508 Fulton Street, Durham, North Carolina 27705, USA, e-mail: piset001@mc.duke.edu

Julia K. Polansky, Charité Universitätsmedizin Berlin, Campus Mitte, 10117 Berlin, Germany
Paolo Puccetti, Department of Experimental Medicine, Section of Pharmacology, University of Perugia, via del Giochetto, Perugia 06126, Italy

Virginia Rider, Department of Biology, Pittsburg State University, Pittsburg, Kansas 66762, USA, e-mail: vrider@pittstate.edu

Matthew Ruddy, Department of Pathology, University of Chicago, 5841 S. Maryland Ave, MC 3083, Chicago, IL 60637, USA

Sandra J. Saouaf, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Mireille Sebbag, UMR 5165 CNRS-Université Paul Sabatier, Hôpital Purpan, Place du Dr Baylac, TSA40031, 31059 Toulouse Cedex 9, France, e-mail: sebbag@udear.cnrs.fr

Guy Serre, UMR 5165 CNRS-Université Paul Sabatier, Hôpital Purpan, Place du Dr Baylac, TSA40031, 31059 Toulouse Cedex 9; and Institut Fédératif de Biologie, Hôpital Purpan, CHU de Toulouse, IFR30, 330 avenue de Grande-Bretagne, TSA40031, 31059 Toulouse Cedex 9, France

Yuan Shen, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Britta Siegmund, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Medical Department I, Hindenburgdamm 30, 12200 Berlin, Germany, e-mail: britta.siegmund@charite.de

Xiaomin Song, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Elena Sonnenberg, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Medical Department I, Hindenburgdamm 30, 12200 Berlin, Germany

Rajan M. Thomas, Department of Pathology and Laboratory Medicine, 1Joseph Stokes, Jr. Research Institute, The Children’s Hospital of Philadelphia, USA

Gergely Toldi, Research Laboratory of Pediatrics and Nephrology, Hungarian Academy of Sciences, Semmelweis University, u 54., 1083 Budapest, Bókay Hungary

András Treszl, Research Laboratory of Pediatrics and Nephrology, Hungarian Academy of Sciences, Semmelweis University, Bókay u 54., 1083 Budapest, Hungary, e-mail: treszl@gyer1.sote.hu

Agathocles Tsatsoulis, Department of Endocrinology, University of Ioannina Medical School, 45110, Ioannina, Greece, e-mail: atsatsou@uoi.gr

Anirudh J. Ullal, Division of Rheumatology and Immunology, Department of Medicine, Duke University, Durham, North Carolina, USA

Barna Vásárhelyi, Research Laboratory of Pediatrics and Nephrology, Hungarian Academy of Sciences, Semmelweis University, Bókay u 54., 1083 Budapest, Hungary
Carola G Vinuesa, Division of Immunity and Infection, John Curtin School of Medical Research, Australian National University, Canberra, ACT 2601, Australia, e-mail: carola.vinuesa@anu.edu.au

Claudia Volpi, Department of Experimental Medicine, University of Perugia, via del Giochetto, Perugia 06126, Italy

Qiang Wang, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Andrew D. Wells, Department of Pathology and Laboratory Medicine, Joseph Stokes, Jr. Research Institute, The Children’s Hospital of Philadelphia, and University of Pennsylvania School of Medicine, 3615 Civic Center Boulevard, Philadelphia, PA, 19333, USA, e-mail: adwells@mail.med.upenn.edu

Di Yu, Immunology and Inflammation Research Program, Garvan Institute of Medical Research, Sydney, NSW 2010, Australia

Hongtao Zhang, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Xiao Yun Zhao, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Weisong Zhou, Division of Rheumatology, Department of Medicine and Department of Microbiology and Immunology. Vanderbilt University School of Medicine, MCN T3219, 1161 21st Ave. S., Nashville, TN 37232-2681, USA

Zhaocai Zhou, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, 19104-6082, USA

Mingzhao Zhu, Department of Pathology, University of Chicago, 5841 S. Maryland Ave, MC 3083, Chicago, IL 60637, USA, e-mail: zhumz@uchicago.edu

Moncef Zouali, Inserm U606; University Paris Diderot-Paris 7, Centre Viggo Petersen, Hôpital Lariboisière, 2, rue Ambroise Pare, 75475 Paris Cedex 10, France, e-mail: moncef.zouali@wanadoo.fr