Contents

List of contributors ix
Preface xi

1 Molecular Mechanisms of Glucocorticoid Receptor Action 1
Pankaj Bhavsar and Ian M. Adcock
1.1 Introduction 1
1.2 Glucocorticoid receptor 2
1.3 Gene induction by GR 2
1.4 GR transactivation and histone acetylation 3
1.5 Post-translational modifications of GR 5
1.6 Repression of NF-κB-induced inflammatory gene expression by GR–NF-κB 6
1.7 GR–NF-κB cross-talk 7
1.8 Role of HDAC2 in glucocorticoid function 8
1.9 Overexpression of HDAC2 restores glucocorticoid sensitivity in alveolar macrophages 9
1.10 Acetylation of hsp90 and regulation of GR function 10
1.11 Other mechanisms of GR action 10
1.12 Conclusions 12

2 Side Effects of Topical and Oral Glucocorticoids 19
Heike Schäcke, Khusru Asadullah and Wolf-Dietrich Döcke
2.1 Introduction 19
2.2 Glucocorticoid-induced side effects 21
2.3 Summary 33

3 Glucocorticoid Receptor Subtypes and Steroid Sensitivity 39
Robert H. Oakley and John A. Cidlowski
3.1 Introduction 39
3.2 Overview of classic GR function 40
3.3 GR subtypes arising from alternative splicing 43
3.4 GR subtypes arising from alternative translation initiation 47
3.5 Conclusions 49

4 Dissociated Glucocorticoids 55
Ian M. Adcock
4.1 Introduction 55
CONTENTS

4.2 Asthma and chronic obstructive pulmonary disease are chronic inflammatory diseases of the airways 55
4.3 Regulation of inflammatory gene expression 56
4.4 Effects on inflammation 57
4.5 Mechanisms of glucocorticoid action 58
4.6 Dissociated glucocorticoids 60
4.7 GR cross-talk with other nuclear receptors and coactivators 62
4.8 Overcoming steroid insensitivity 64
4.9 Glucocorticoid-sparing approaches to anti-inflammatory therapy 65
4.10 Conclusion 66

5 Generalized Glucocorticoid Insensitivity: Clinical Phenotype and Molecular Mechanisms 73
Evangelia Charmandari, Tomoshige Kino and George P. Chrousos
5.1 Introduction 73
5.2 Molecular mechanisms of glucocorticoid resistance 75
5.3 Conclusions 85

6 Corticosteroid Responsiveness in Asthma: Clinical Aspects 89
Kian Fan Chung
6.1 Introduction 89
6.2 Effects of corticosteroids in asthma 89
6.3 Definition of corticosteroid insensitivity 90
6.4 Oral CS responsiveness in asthma 91
6.5 ICS responsiveness in asthma 94
6.6 CS responsiveness in severe asthma 97
6.7 Surrogates for CS responsiveness in asthma 99
6.8 Pharmacokinetics of systemic CS in severe asthma 100
6.9 CS responsiveness in cigarette smokers and chronic obstructive pulmonary disease 101
6.10 Other diseases of CS insensitivity 102
6.11 Conclusions 102

7 Glucocorticoid-insensitive Asthma: Molecular Mechanisms 109
John W. Bloom
7.1 Introduction 109
7.2 GR abnormalities 110
7.3 GR nuclear translocation 112
7.4 Cross-talk with transcription factors 115
7.5 NF-κB, GR, histones and chromatin remodelling 116
7.6 Epigenetics and asthma 119
7.7 Conclusions 120

8 Cigarette Smoke, Oxidative Stress and Corticosteroid Responsiveness 125
Irfan Rahman and David Adenuga
8.1 Oxidative stress 125
8.2 Cigarette smoke/oxidative stress-induced NF-κB-mediated pro-inflammatory gene expression 127
CONTENTS

8.3 Histone acetylation and deacetylation 129
8.4 Corticosteroids 129
8.5 Histone deacetylases 133
8.6 Reversing Glucocorticoids / Corticosteroid resistance 138
8.7 Conclusion 141

9 Regulation of Glucocorticoid Sensitivity by Macrophage Migration Inhibitory Factor 145
Eric F. Morand
9.1 Introduction 145
9.2 MIF as a pro-inflammatory factor 145
9.3 Relationship between MIF and glucocorticoids 151
9.4 Conclusions 155

10 Steroid-sparing Strategies: Long-acting Inhaled β2-Agonists 163
Anna Miller-Larsson and Olof Selroos
10.1 Introduction 163
10.2 Why and when is a steroid-sparing effect of LABA important in asthma? 163
10.3 Effects of lower dose ICS/LABA versus a higher dose ICS on lung function, symptoms and use of reliever medication 164
10.4 Effects of lower dose ICS/LABA versus higher dose ICS on exacerbations 165
10.5 Protocols with tapering ICS doses with and without LABA while maintaining asthma control 166
10.6 Reducing ICS doses using an adjustable ICS/LABA dosing regimen 167
10.7 Reducing ICS doses using Symbicort® maintenance and reliever therapy 168
10.8 Does enhanced anti-inflammatory efficacy explain steroid-sparing effects in ICS/LABA therapy? 170
10.9 Possible Mechanisms of Steroid-sparing Effects by Addition of LABA to ICS 175

11 Steroid-sparing Strategies: Other Combinations 187
Gaetano Caramori, Kazuhiro Ito and Alberto Papi
11.1 Introduction 187
11.2 Theophylline as steroid-sparing treatment in asthma and COPD 187
11.3 Selective inhibitors of PDE4 190
11.4 Modulators of the synthesis or action of key inflammatory mediators 193
11.5 Anticholinergics 193
11.6 Leukotriene synthesis inhibitors and leukotriene receptor antagonists 195
11.7 Anti-IgE therapy 198
11.8 Macrolides/ketolides 199
11.9 TNFα inhibitors 200
11.10 Conclusions 202

12 Kinases as Anti-inflammatory Targets for Respiratory Disease 207
Iain Kilty
12.1 Introduction 207
12.2 Pharmacological targeting of kinases 208
12.3 Targeting NF-κB activation 210
12.4 Targeting the MAPKs 217
12.5 Targeting PI3K 225
12.6 Further potential kinase targets 229
12.7 Conclusions 232

13 Pharmacokinetic/Pharmacodynamic Factors and Steroid Sensitivity 243
Gönther Hochhaus
13.1 Introduction 243
13.2 What factors are important for pulmonary efficacy and safety? 243
13.3 Pharmacodynamic aspects 246
13.4 Pharmacokinetic drug properties 247
13.5 Conclusion 257

14 Improved Lung Deposition: New Inhaler Devices 263
Omar S. Usmani
14.1 Introduction 263
14.2 Historical review of inhaled drug therapy 263
14.3 Deposition of aerosols within the respiratory tract 265
14.4 Assessing drug deposition in the lungs 268
14.5 Aerosol generation devices for inhaled drug therapy 271

Index 283