

Contents

Disturbance of the T-cell receptor repertoire in HIV infection	14
1.1. The T-cell receptor (TCR) and TCR repertoire	14
1.2. Ligand recognition by $\alpha\beta$ and $\gamma\delta$ T-cells	14
1.3. How to analyze the TCR repertoire.....	15
1.4. Alterations of the $\alpha\beta$ TCR repertoire in HIV infection	16
1.5. Alterations of the $\gamma\delta$ TCR repertoire in HIV infection	18
1.6. Impact of HAART on the TCR repertoire.....	19
1.7. Conclusion	20
1.8. References.....	20
Cellular immune responses in HIV-1	25
2.1. Introduction	25
2.2. Role of HIV-1-specific CD8+ T-cells in the control of HIV-1 infection	25
2.3. Immune escape from CTL	26
2.4. Functionality of CD8+ T-cells in HIV-1 infection	27
2.5. Importance of HIV-1-specific CD4+ T-cells in control of HIV-1	27
2.6. Conclusions	29
2.7. References.....	29
Dynamics of lymphocyte turnover	35
3.1. Introduction	35
3.2. Lymphocyte proliferation following IL-2	35
3.3. Proliferation in peripheral blood and lymph nodes.....	36
3.4. Characterization of a novel CD4+/CD25+ phenotype in the naive CD4+ cell pool	39
3.5. IL-2 receptor expression in HIV patients.....	39
3.6. Changes in thymic output.....	39
3.7. Senescence of CD4 cells.....	40
3.8. Lymphocyte apoptosis following IL-2.....	41
3.9. References.....	42
Dermatological marker infections	45
4.1. Primary HIV infection	45
4.2. Herpes simplex virus (HSV)	45
4.3. Varicella zoster virus (VZV)	45
4.4. Epstein-Barr virus (EBV)	46
4.5. Cytomegalovirus (CMV)	46
4.6. Kaposi's sarcoma (KS)	46
4.7. Human papillomavirus (HPV)	47
4.8. Poxvirus	47
4.9. Bacillary angiomatosis (BA)	48
4.10. Mycobacteria	48
4.11. Syphilis.....	48

4.12.	Dermatophytes	48
4.13.	Yeast	49
4.14.	Cryptococcosis	49
4.15.	Penicillium marneffei	49
4.16.	Scabies	49
4.17.	References.....	50

HAART - present and future

51

5.1.	Introduction	51
5.2.	"Classic" triple combination therapy including a PI	51
5.3.	Triple combination therapies including a NNRTI.....	52
5.4.	Double PI therapy.....	53
5.5.	Class-sparing regimen	53
5.6.	Mega HAART	53
5.7.	Boosted PI regimen	53
5.8.	Boosted double PI regimen	54
5.9.	Regimen including a fusion inhibitor	54
5.10.	New drugs.....	55
5.11.	When to start therapy.....	55
5.12.	Drug interactions	55
5.13.	Individualization of therapy	56
5.14.	Where do we go from here?.....	56
5.15.	References.....	57

Immune reconstitution in HIV infection

60

6.1.	Introduction	60
6.2.	T-cell alterations in the pre-HAART era.....	60
6.3.	Dual dynamics of CD4 cell reconstitution	61
6.4.	Naive and memory CD4 T-cells are the two partners of CD4 cell reconstitution.....	62
6.5.	De-activation of the immune system is a major actor of immune reconstitution.....	63
6.6.	Reconstitution of immune defenses: successes and limits	63
6.7.	Conclusion	65
6.8.	Acknowledgments.....	65
6.9.	References.....	65

Interleukin-2: structure and function

70

7.1.	Introduction	70
7.2.	The Protein	70
7.3.	The Function	70
7.4.	Signals and receptors that control IL-2 gene transcription.....	70
7.5.	Cytotoxic T-cells and natural killer cells	71
7.6.	References.....	72

IL-2 in patients with low CD4 counts	74
8.1. Introduction	74
8.2. Fears for IL-2 use in patients with low CD4 counts.....	75
8.3. Clinical studies of IL-2 in patients below 300 CD4+ cells	75
8.3.1. Initial Studies.....	75
8.3.1.1. Low-dose IL-2	75
8.3.1.2. ACTG 328	76
8.3.1.3. ILSTIM (ANRS 082).....	76
8.3.2. Conclusions regarding initial studies.....	77
8.3.3. SILCAAT Study	77
8.4. Conclusions	78
8.5. References.....	78
Ongoing efficacy studies of IL-2 in HIV	79
9.1. Scientific rationale for use in HIV disease and impact on T-cell homeostasis	79
9.2. Efficacy in recent phase 2 clinical studies	80
9.2.1. Use of intermittent cycles of IL-2	80
9.2.2. Doses of IL-2	80
9.2.3. Clinical safety of IL-2.....	80
9.2.4. Maintenance therapy with IL-2.....	80
9.3. SILCAAT	82
9.3.1. Objectives	82
9.3.2. Study design	82
9.3.3. Eligibility criteria	82
9.3.4. Sample size, study power and statistical hypotheses.....	83
9.3.5. Interim and final analyses.....	83
9.3.6. Structure of the study	83
9.3.7. SILCAAT substudies	84
9.4. ESPRIT	84
9.4.1. Objectives	84
9.4.2. Study design	84
9.4.3. Eligibility criteria	84
9.4.4. Sample size, power of the study and statistical hypotheses	85
9.4.5. Monitoring of the study progress and results analyses	85
9.4.6. International structure.....	86
9.4.7. ESPRIT substudies	86
9.5. Challenges faced by phase 3 IL-2 clinical endpoint studies in HIV	86
9.5.1. Feasibility of long-term international studies	86
9.5.2. Retention of patients in the control group.....	87
9.5.3. Implementation and follow-up of a long-term open label study.....	87
9.5.4. Regulatory considerations	87
9.6. Conclusion	88
9.7. Acknowledgments.....	88
9.8. References.....	88

Toxicity of IL-2**91**

10.1.	Introduction	91
10.2.	IL-2 safety data reported in the literature	91
10.2.1.	Intermittent CIV IL-2 treatment regimens	91
10.2.2.	Intermittent SC IL-2 treatment regimens	92
10.2.3.	Daily low-dose SC IL-2 therapy	94
10.3.	Safety of IL-2 in hepatitis B or hepatitis C co-infected patients	95
10.4.	Overall summary of safety and guidelines for management of toxicities associated with IL-2 therapy.....	95
10.4.1.	Constitutional symptoms.....	95
10.4.2.	Capillary leak syndrome (CLS).....	95
10.4.3.	Injection site reactions.....	97
10.4.4.	Gastrointestinal/hepatobiliary events	97
10.4.5.	Cutaneous reactions.....	97
10.4.6.	Endocrine effects.....	97
10.4.7.	Neurological symptoms	98
10.4.8.	Renal/electrolyte and genitourinary effects.....	98
10.4.9.	Autoimmune/inflammatory effects	99
10.4.10.	Cardiovascular effects	99
10.4.11.	Hematological effects	99
10.4.12.	Infectious complications.....	99
10.4.13.	Respiratory system effects	99
10.4.14.	Hypersensitivity reactions	100
10.4.15.	Malignancy	100
10.5.	Conclusions	100
10.6.	References	101

Management of IL-2 toxicity**103**

11.1.	Pathophysiology of IL-2 toxicity	103
11.2.	Toxicity management.....	105
11.2.1.	Influenza-like symptoms	105
11.2.2.	Cardiovascular effects	105
11.2.3.	Nephrotoxicity.....	106
11.2.4.	Gastrointestinal symptoms	106
11.2.5.	Hematologic toxicity	106
11.2.6.	Central nervous system symptoms	107
11.2.7.	Bacterial infection.....	107
11.2.8.	Dermatological manifestations.....	107
11.2.9.	Autoimmune disorders.....	107
11.3.	Conclusions	107
11.4.	References	107

Interferon-alpha in HIV disease**110**

12.1.	Classification of interferons	110
12.2.	Interferon-alpha: antiviral modes of action	110
12.2.1.	PKR and 2'-5' OAS as "early effector" proteins.....	111
12.2.2.	The human MxA protein.....	111
12.3.	Immunomodulatory activity of IFN-alpha.....	113

12.4.	IFN-alpha and its putative interaction with B-memory cells.....	113
12.5.	The endogenous IFN-system in HIV.....	113
12.6.	Physiological function of MxA: a hypothesis	114
12.7.	Interferon-alpha: treatment potential in HIV	114
12.8.	Amelioration of IFN-alpha by pegylation	115
12.8.1.	Results of PegIFN-alpha2b in HIV: first clinical data	116
12.8.2.	PegIFN-alpha2b in acute HIV infection	117
12.8.3.	IFN-alpha2b in HAART-naive, HIV-positive patients	117
12.8.4.	PegIFN-alpha2b treatment during structured interruption of HAART.....	118
12.8.5.	PegIFN-alpha2b in salvage patients.....	118
12.8.6.	Combination treatment with PegIFN-alpha2b and ribavirin in patients with dual HCV-HIV co-infection.....	118
12.9.	References	119

Gene therapy of HIV-1 infection: Lentiviruses

123

13.1.	Introduction.....	123
13.1.1.	HIV-1 infectious cycle	123
13.1.2.	Antiviral strategies	123
13.1.3.	Murine retroviral vectors and lentiviral vectors	124
13.2.	Lentiviral vectors: structure and design	125
13.2.1.	Competitive structural interference of lentiviral vectors with HIV-1 and vector mobilization	126
13.3.	Delivery of antiviral genetic systems by lentiviral vectors.....	127
13.3.1.	Nucleic acid-based lentiviral systems for HIV-1 therapy.....	128
13.3.2.	Protein-based lentiviral systems for HIV-1 therapy.....	129
13.4.	Future directions	130
13.5.	Conclusions	131
13.6.	References	131

Therapeutic immunization with HIV vaccines targeting dendritic cells

135

14.1.	Introduction.....	135
14.2.	Therapeutic vaccination for HIV-1 infection.....	135
14.3.	Utilizing DCs to optimize therapeutic vaccination for induction of potent immunity	136
14.3.1.	Dendritic cells as professional antigen-presenting cells.....	136
14.3.2.	Maturation and migration of DCs to lymphoid organs	136
14.3.3.	Vaccine delivery.....	136
14.3.4.	DC-based therapeutic vaccines for the induction of virus-specific immunity.....	136
14.4.	The "autovaccination" hypothesis	138
14.5.	DermaVir: A topical DNA vaccine targeting dendritic cells.....	138
14.6.	Future perspectives.....	139
14.7.	Acknowledgements	140
14.8.	References	140

Index

143