

# Table of contents

Résumé .....	1
Summary .....	2
Acknowledgements .....	4
List of abbreviations.....	7
Chapter 1: Introduction.....	10
1.1. General introduction .....	10
1.2. Basic concepts in immunity .....	10
1.2.1. Innate immunity .....	10
1.2.2. Adaptive immunity .....	12
1.3. T cell development .....	14
1.4. CD4 T cell specialization .....	16
1.4.1. General concepts.....	16
1.4.2. Functional specialization .....	16
1.4.3. Regulatory T cells.....	22
1.5. Regulatory T cell specialization.....	30
1.5.1. Subset-specific regulatory T cells.....	30
1.5.2. Environmental specialization .....	34
1.6. Transcription factor c-Maf.....	41
1.6.1. General concepts.....	41
1.6.2. Role of c-Maf in effector T cells .....	42
Chapter 2: Research objectives .....	44
Chapter 3: Results and discussion.....	45
Part 1: Role of transcription factor c-Maf in Treg differentiation and function.....	45
3.1.1. c-Maf identifies a subset of effector Treg cells with an intestinal phenotype.....	45
3.1.2. c-Maf is dispensable for the maintenance of central tolerance by Treg cells .....	47
3.1.3. c-Maf-expressing Treg cells control homeostatic Th17 intestinal responses .....	50
3.1.4. c-Maf is not required for Treg cells to control acute intestinal inflammation.....	51
3.1.5. c-Maf controls the acquisition of ROR $\gamma$ t and IL-10 expression by intestinal Treg cells.....	52
3.1.6. c-Maf-expressing Treg cells promote the development of colorectal cancer during inflammation.....	53
Part 2: Molecular control over ROR $\gamma$ t expression in Treg cells .....	56
3.2.1. Multiple environmental signaling pathways control the differentiation of ROR $\gamma$ t-expressing regulatory T cells.....	56
3.2.2. Complementary results .....	58
3.2.2.1. IL-27 represses ROR $\gamma$ t expression in Treg cells in a STAT1-dependent manner .....	58
3.2.2.2. c-Maf deficiency hinders in vitro Treg differentiation in presence of IL-6 .....	59
3.2.2.3. Transient expression of c-Maf and ROR $\gamma$ t in Treg cells is inhibited by IL-2 and stabilized by IL-6 .....	59
Chapter 4: General discussion and perspectives.....	61

4.1.	c-Maf controls intestinal Treg specialization.....	61
4.2.	Multiple signaling pathways control intestinal Treg subsets.....	64
4.3.	c-Maf <sup>+</sup> Treg cells promote colon cancer development during inflammation.....	66
Chapter 5: Conclusion .....		69
Chapter 6: Materials and methods .....		70
6.1.	Mice .....	70
6.2.	Solutions and media .....	70
6.2.1.	General solutions and media.....	70
6.2.2.	Isolation of intestinal leukocytes .....	71
6.3.	Antibodies, intracellular staining, and flow cytometry.....	71
6.4.	Leukocyte purification.....	72
6.4.1.	Intestinal tissues .....	72
6.4.2.	Secondary lymphoid organs .....	72
6.4.3.	Liver and lung .....	73
6.5.	Acute DSS-induced colitis .....	73
6.6.	Anti-CD3-induced enteritis.....	73
6.7.	<i>Toxoplasma gondii</i> infection .....	73
6.8.	Antibiotics treatment .....	74
6.9.	T cell culture .....	74
6.10.	Retroviral infection .....	74
6.11.	Treg cell <i>in vitro</i> suppression assay .....	75
6.12.	RT-qPCR .....	75
6.13.	ChIP-seq data.....	75
6.14.	Ectopic tumor models .....	76
6.15.	AOM/DSS .....	76
6.16.	Histopathology .....	76
6.17.	Statistical analysis .....	77
Chapter 7: References .....		78
Chapter 8: Annexes.....		92
8.1.	Annex 1 – Literature review: “c-MAF, a Swiss Army Knife for Tolerance in Lymphocytes” .....	92
8.2.	Annex 2 – Research article: “The transcription factor c-Maf promotes the differentiation of follicular helper T cells” .....	93