UNIVERSITÉ LIBRE DE BRUXELLES
FACULTÉ DES SCIENCES
DÉPARTEMENT DE BIOLOGIE MOLÉCULAIRE
LABORATOIRE D'IMMUNOBIOLOGIE

INTRINSIC AND EXTRINSIC CONTROL OF THE PROINFLAMMATORY CD70/CD27 PATHWAY

THÈSE PRÉSENTÉE PAR MAXIME DHAINAUT

EN VUE DE L'OBTENTION DU TITRE DE DOCTEUR EN SCIENCES

PROMOTRICE : MURIEL MOSER

ANNÉE ACADÉMIQUE 2014-2015

TABLE OF CONTENTS

SUMMARY

A key step in the development of an adaptive immune response is the activation of naive T cells by dendritic cells (DCs). DCs sample antigens in the periphery and migrate to the lymphoid organs were they provide different signals to T cells: they present antigenic peptides in the context of MHC molecules, express costimulatory or coinhibitory ligands and produce cytokines that influence T cell fate. The integration of these signals will either induce tolerance or lead to the activation and expansion of effector T cells which will mediate the immune response.

The costimulatory CD70/CD27 pathway plays important roles in the development of pro-inflammatory Th1 and CTL responses. CD70 expression on DCs has also been described as a molecular switch from tolerance to immunity. Accordingly, its activity is tightly regulated *in vivo*. The aim of this work was to investigate the mechanisms controlling the expression of CD70 on dendritic cells and CD27 on T lymphocytes.

First, we described a cell-extrinsic mechanism of inhibition exerted on DCs by regulatory T cells (Tregs). Indeed, Tregs controlled Th1 priming *in vivo* and *in vitro* by downregulating CD70 on DCs. This control involved a transfer of the CD27 receptor to DCs, possibly via the production of CD27-bearing microvesicles by T cells at the immunological synapse. Acquisition of CD27 by DCs induced the internalization of both CD27 and CD70 and probably their lysosomal degradation. As a consequence, DCs were impaired in their ability to efficiently prime Th1 cells. Second, we analyzed CD70 and CD27 expression in the periphery and provided evidence for a cell-intrinsic control of CD27 expression by ectodomain shedding in the gastrointestinal tract.

While they efficiently clear infections, inflammatory responses can also be deleterious to the organism. By restraining CD70 expression on DCs, Tregs would promote tolerance and limit inflammation. Interestingly, tolerance is particularly important in the intestines, which are in constant contact with dietary antigens and the commensal microbiota. Accordingly, we propose that a second layer of control of CD27-driven costimulation takes place in the gut : by shedding CD27, T cells would be desensitized for any potential CD70-dependent costimulation.

To further investigate the physiological significance of the mechanisms described above, the immune response will be monitored in animals specifically lacking CD27 expression in the Treg population or expressing a nonsheddable CD27 receptor.