Self-HIVEP : A NEW RAT MODEL TO STUDY THE CONTROL OF IMMUNE CENTRAL TOLERANCE BY THE HIVEP3 TRANSCRIPTION FACTOR

(M. GIRAUD)

The thymus plays a pivotal role in the establishment of immune tolerance by producing a diverse repertoire of non-autoreactive T cells. It is the intimate interactions formed by the developing thymocytes and the medullary thymic epithelial cells (mTECs) that sustain the maturation into mTEChi expressing high levels of MHC-II, the autoimmune regulator AIRE and a wide array of self-antigens whose presentation to developing thymocytes ensures the deletion of the autoreactive ones. Although NF-kB2 has been shown important to sustain the ability of mTECs to mature and express self-antigens, the identification of additional key regulators of mTEC maturation is lacking. Single-cell (sc)ATACseq experiments that we carried out in mouse mTECs identified the HIVEP transcription factors (TFs) as the highest active TFs in mTEChi, along with NF-kB2. We also found by comparison of mouse and rat mTEChi that HIVEP3 is the sole HIVEP member potentially active in rats. We will thus address the effect of HIVEP3 on the control of immune central tolerance by generating a Hivep3-deficient rat line using the CRISPR/Cas9 system at the Transgenesis Rat ImmunoPhenomic (TRIP) platform. We will establish the importance of Hivep3 deletion in characterizing the immune phenotype of the generated animals and evaluate immune tolerance defects by monitoring circulating autoantibodies and infiltration of inflammatory cells in peripheral tissues. We will determine the impact of Hivep3 KO on the maturation of mTEChi and more broadly on the mTEC compartment by scRNAseq. scATACseq will identify the impacted TF regulome and provide important clues into how HIVEP3 regulates mTEC maturation and controls an expected large repertoire of self-antigens that we will characterize. Hence, this project will provide key insights into our understanding of the mechanisms sustaining mTEC maturation and the expression of the “self” for the control of immune tolerance.