Internship Proposition
(one page max)
Master 2 GP Immunology & ImmunoIntervention (I^3)
2024-2025

Lab: Rudd

Team: Rudd

Name and position of the supervisor: Prof/Dr Christopher Rudd

Email of the supervisor: Christopher.e.rudd@umontreal.ca

Candidate (if internship filled):

Title of the internship: T-cell signaling in immunotherapy

Summary of the internship proposal:

Rasal1 is a GTPase-activating protein that we have shown associates with the T-cell receptor (TCR) and regulates the protein tyrosine kinase ZAP-70 and the p21ras-ERK pathways in T-cells (Thaker et al., 2019 Nat Commun. 10(1):4804). Our lab previously defined the CD4/CD8-p56lck complexes as initiators of the tyrosine activation cascade needed for T-cell activation (Rudd, 2021 Front Cell Dev Biol. 9:626095; Rudd, Nature Cancer, 2023 4(9):1214-1216). Rasal1 now represents a new component of the antigen receptor that binds to and inhibits the activity of ZAP-70 while concurrently inhibiting p21ras activity. In this context, previous studies have shown that the p21ras pathway plays a key role in regulating the induction of T-cell anergy or non-responsiveness. Anergy plays a central role in peripheral tolerance in response to pathogens, transplant rejection, and cancer. Our hypothesis is that the binding of Rasal1 to the antigen receptor is the missing link responsible for the induction of anergy in T-cells. To assess this, CRISPR-based endonuclease technology was used to generate mice with defective Rasal1 function (termed Rasal1-c-mut mice). We have shown that Rasal1c-mut T-cells are hyper-responsive to antigens and favor memory T-cell development, affecting the oxidative phosphorylation pathway of T-cell metabolism. The project for the student now aims to determine whether T-cells from wild-type versus Rasal1-c-mut mice differ in their ability to become anergic using *in vitro* and *in vivo* assays of anergy induction, as well as the potential application of this knowledge to the modulation of transplant rejection and tumor immunotherapy.

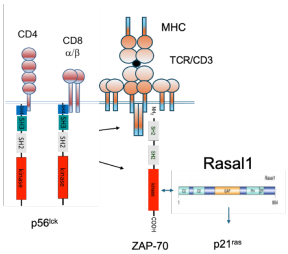

Figure 1: Model of the TCR receptor and associated intracellular signaling proteins in T-cells. CD4/CD8-$p56^{lck}$ complexes as initiators of tyrosine activation cascade are needed for the recruitment of ZAP-70. ZAP-70, in turn, associates with the GAP called Rasal1 which inhibits the $p21^{ras}$ pathway in T-cells.

Option(s) linked to the project:
X Experimental Biology Profile (Recherche Expérimentale)

Form to be sent by email to : gpi3@univ-nantes.fr