MASTER 2 BMC
PARCOURS GENOPATH
ANNEE 2024-2025

Titre : Natural Killer cell immunometabolism : competition, cooperation for nutrients to sustain functions

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Sujet de stage :
Natural Killer (NK) cells are innate lymphoid cells with anti-viral and anti-tumoral properties. In our team, we study the molecular mechanisms sustaining these functions using mouse models and human samples. We uncovered the role of a kinase, the mechanistic Target of Rapamycin (mTOR) as a checkpoint of NK cell development and effector potential[1,2]. Of note, mTOR is a major hub connecting a variety of immunological signals to cellular metabolism. Indeed, cellular metabolism is not only a housekeeping process sustaining cell survival, but also a highly adaptive guiding force for cellular fate decisions. Pursuing this path, we recently studied the nutrient requirements of human NK cells and described the pivotal role of exogenous pyruvate in regulating resting NK cell metabolism, functions and survival[3]. A number of questions arise from this study and will be the subject of this internship.

Regulation of Pyruvate bioavailability. Exogenous pyruvate is absolutely required for NK cell survival and functions. The source of this pyruvate *in vivo* remains elusive. Using the various cell types that can be sorted from the blood of healthy donors (monocytes, Dendritic Cells, lymphocytes…), we will test their ability to secrete pyruvate and provide a help to NK cells in a cooperative configuration. Conversely, whether certain cell types such as tumors consume pyruvate, therefore suppressing NK cell action, is unknown. We will test this hypothesis using a number of tumor cells available in the lab.

Role of the pathways fed by glucose-derived carbons. Using carbon tracing experiments, we have shown that glucose is not used as a bioenergetic substrate in human NK cells but rather feeds biosynthetic pathways such as the pentose phosphate pathway or the Serine-Glycine One carbon metabolism. The reason of this metabolic configuration is unknown. We hypothesize that these adjacent pathways are required to maintain NK cell redox equilibrium and cytotoxic granules loading. Using specific inhibitors of these pathways and conditioned media, we will test the actual role of these pathways in NK cell anti-tumor responses.
This Master's internship paves the way for a PhD project aimed at elucidating the metabolic reprogramming that governs the activation of human NK cells. This is a question of therapeutic interest given the increasing use of NK cells in clinical settings.

Modèle et techniques utilisées :
Human PBMCs including NK cells, monocytes, lymphocytes… Mouse models.
Flow cytometry, cell culture, biochemistry (capilary WB…), metabolic analysis (Seahorse, metabolomic), proteomic.

Publications d'intérêt :

1. Marçais, A., Cherfils-Vicini, J., Viant, C., Degouve, S., Viel, S., Fenis, A., Rabilloud, J., Mayol, K., Tavares, A., Bienvenu, J., et al. (2014). The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. Nat Immunol *15*, 749–757. 10.1038/ni.2936.

2. Marçais, A., Marotel, M., Degouve, S., Koenig, A., Fauteux-Daniel, S., Drouillard, A., Schlums, H., Viel, S., Besson, L., Allatif, O., et al. (2017). High mTOR activity is a hallmark of reactive natural killer cells and amplifies early signaling through activating receptors. eLife Sciences *6*, e26423. 10.7554/eLife.26423.

3. Kern, N., Picq, L., …, T Walzer* and A Marçais*. Exogenous pyruvate controls human NK cell bioenergetics to sustain their functions. In favorable revision Nature Metabolism * *co-last authors*.