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Influence of sirtuins and sirtuin inhibitors on inflammatory and innate immune responses

Histone deacetylases (HDACs) comprise 11 “classical” HDACs (HDAC1-11) and 7 sirtuins (SIRT1-7), which target histones and non-histone proteins among which transcriptional regulators. Classical HDACs are a center of great interest due to their implication in cancer and the efficacy of HDAC inhibitors (HDACi) as powerful antitumor agents. Three HDACi have already entered the clinic. Interestingly, recent studies also highlighted the immune-modulatory and anti-inflammatory properties of HDACi used at low doses. In preclinical models, HDACi improved the outcome of rheumatoid arthritis, multiple sclerosis, colitis and sepsis to cite only a few. Sirtuins are less well characterized than HDACs. Sirtuins are NAD+-dependent deacetylases involved in metabolism, cell proliferation and development of age-related diseases. Although sirtuins share common targets with HDACs, among them some critical regulators of the immune response (e.g. NF-kB and AP-1 transcription factors), the role of sirtuins in immune responses is poorly understood and controversial.

Our laboratory is focused on the study of innate immunity and the pathogenesis of sepsis, one of the first causes of mortality worldwide. Tight regulation of the immune response is essential for pathogens elimination without arming the host. The aim of my thesis is to elucidate the role of sirtuins in innate immune responses with particular interest on their impact on the signaling pathways triggered by pattern-recognition receptors (PRRs), the receptors involved in microbial sensing by innate immune cells.

Cytokines from ImmunoTools will be useful for *ex vivo* experiments. Recombinant cytokines and growth factors will be used to differentiate bone marrow cells into macrophages (M-CSF), conventional dendritic cells (GM-CSF+IL-4) and plasmacytoid dentritic cells (Flt3L). Untreated cells, cells incubated with a panel of sirtuin inhibitors, and sirtuin-deficient cells will be stimulated with microbial products (LPS, Pam3CSK4, CpG, TSST-1, bacteria, fungi), pro-inflammatory cytokines (TNF, IL-6, IL-1b, IL-1a, IFNg, GM-CFS, M-CFS, IL-2 and IL-18), regulatory cytokines (TGFb, IL-10, IL-4, IL-13, IL-19, IL-20 and IL-22) and steroids. The expression of sirtuins, the activation of intracellular signaling pathways (MAPK phosphorylation, nuclear translocation and recruitment of transcription factors), the dynamic of histone acetylation, the production of cytokines, the expression of membrane receptors and

the rate of phagocytosis will be analyzed. Depending of the results, we will use mouse models of infection and septic shock to validate our *in vitro* observations.

These studies will contribute to better understand the role of sirtuins in innate immune responses and to evaluate the therapeutic potential of pharmacological inhibitors of sirtuins for diseases characterized by acute and chronic inflammatory responses.