Master Position Life Science Zürich BioMed School

Principal Investigator: Müller, Bojana

Project title: Unraveling the Role of Nucleotide Metabolism in Rheumatoid Arthritis

Project Description:

Metabolic reprogramming has been increasingly recognized as a key regulator of immune responses in both health and disease. To identify metabolic disruptions associated with rheumatoid arthritis (RA), a prevalent autoimmune disease, we conducted transcriptomic, metabolomic, and proteomic analyses on peripheral blood monocytes from 10 RA patients and 10 healthy controls. Integrating these omics datasets revealed a metabolic signature indicative of impaired pyruvate dehydrogenase (PDH) activity, a shift towards anaerobic glycolysis (Warburg effect), and alterations in nucleotide metabolism, particularly with increased purine recycling. Nucleotide metabolism is known to play a role in RA, and nucleotide metabolism-targeting drugs are fundamental in RA treatment.
Importantly, this metabolic signature was observed early in disease progression, as shown in a cohort of first-degree relatives of RA patients (SCREEN-RA cohort), suggesting potential for early therapeutic intervention.

The general aim of this Master's project is to understand how nucleotide metabolism is regulated in monocytes from RA patients. The specific objectives are:

1. **To further analyze our omics data** regarding global nucleotide metabolism and related pathways. This analysis will include:
    - Transcriptomic, proteomic, and metabolomic data from peripheral blood monocytes.
    - Serum metabolomics and transcriptomics from a cohort of individuals at pre-clinical stages of RA.
    - Serum metabolomics from 100 patients with established RA.
    - Single-cell RNA sequencing from joint biopsies of RA patients and healthy controls.
2. **To characterize metabolic pathway usage in monocytes** from RA patients and healthy controls. This will involve:
    - Performing metabolic flux analysis.
    - Measuring PDH activity in vitro.
    - Investigating purine metabolism using pharmacologic inhibitors and CRISPR-based genetic editing.

We are seeking an MSc candidate with a strong interest in omics data analysis. The data have already been analyzed within the lab, so no prior bioinformatics skills are required. The

laboratory-based part of the project offers training in immune cell culture, CRISPR-based genetic editing, Western blotting, flow cytometry (FACS), and a range of immune-metabolism techniques, including metabolic flux analysis, mass spectrometry, and metabolomics.

Requirements:

We are looking for highly motivated candidates with a keen interest in immune metabolism and its translational applications. While knowledge in immunology, metabolism, and experimental techniques is of advantage, it is not essential. Candidates with backgrounds in pharmaceutical sciences, biochemistry, or organic chemistry are encouraged to apply. Strong teamwork skills are preferred.

Contact:

Bojana.Mueller-Durovic@uzh.ch