Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal 2022-2023

Title: The role of JAK-STAT signaling pathway in early arthritis

Synopsis:
Rheumatoid arthritis (RA) is a chronic, systemic immune-mediated inflammatory disease that can lead to joint destruction, functional disability and substantial comorbidity due to the involvement of multiple organs and systems. Despite the efficacy of synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs) in the treatment of RA, few patients reach sustained remission and refractory disease is a concern that needs critical evaluation and close monitoring. Janus kinase (JAK) inhibitors or JAKi are a new class of oral medications recently approved for the treatment of RA. JAK inhibitors suppress the activity of one or more of the JAK family of tyrosine kinases [JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)], thus interfering with the JAK-Signal Transducer and Activator of Transcription (STAT) signaling pathway. JAK-STAT signaling pathway is critical for immune cell proliferation, survival and differentiation and its inhibition leads to multi-cytokine blockade and abrogated inflammation. Tofacitinib is a JAK1 and JAK3 inhibitor, approved for the treatment of established refractory RA patients. However, preliminary clinical evidence indicate that patients treated in an earlier phase of the disease have a better response. Furthermore, our group has previously demonstrated that early treatment with tofacitinib in animal models of arthritis can abrogate disease and completely prevent bone and cartilage damage. Therefore, we hypothesize that JAK-STAT signaling pathway is key to chronic arthritis onset and its early inhibition might have a major effect on the immune cascade, allowing lasting disease control. The main goal of this study is to characterize the JAK-STAT signaling pathway activation in untreated early arthritis patients and to analyze the impact of conventional treatment on its activity. For that, blood samples will be collected from untreated early arthritis patients (<1 year of disease duration) followed up at the Rheumatology Department, Hospital de Santa Maria, Lisbon Academic Medical Centre, Portugal at baseline and after treatment with conventional DMARDs. At each time point, peripheral blood mononuclear cells (PBMC) will be isolated by density-gradient centrifugation, cell viability will be estimated with Trypan Blue dye exclusion and cells will be cryopreserved at -80ºC until use. After thawing frozen cells, the frequency, phenotype and JAK-STAT signaling pathway activation will be evaluated on peripheral blood leukocytes (B cells, T cells, monocytes and dendritic cells) by flow cytometry. In addition, a group of age and gender-matched healthy volunteers will be included as controls. All samples will be used for research purposes only. All the experimental work will be developed at Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Portugal.

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