Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Gut Permeability in a Mouse Model of Systemic Lupus Erythematosus

Synopsis:

In order to improve the care of patients with systemic lupus erythematosus (SLE), we need to know more about its pathogenesis and find new clinically relevant pathways. Recently, it was found that SLE patients have increased levels of circulating bacterial components (lipopolysaccharides). These data may suggest that a higher gut barrier permeability and chronic microbial translocation may contribute to the immunologic dysregulation and the type I interferon signature characteristic of SLE.

There is, indeed, mounting evidence pointing towards an involvement of gut barrier disruption and immune dysregulation at mucosal sites during the initiation and progression of autoimmune diseases. Interestingly, it was just found that pathobiont translocation in monocolonized and autoimmune prone mice induced autoantibodies and caused mortality, which could be prevented by an intramuscular vaccine targeting the pathobiont. Furthermore, antibiotic treatment also eliminated pathogenic autoantibodies and T cells and prevented death.

We hypothesize, therefore, that a defective gut barrier will contribute to higher permeability and chronic microbial translocation, which will potentiate the immune dysregulation seen in SLE. Moreover, we suggest that diet and the microbiome will have a role on the pathogenesis of this disease.

The goal of this master project is to study the gut integrity in a SLE mouse model.

We will compare control mice with (NZBxNZW)F1 mice, a lupus model, and with mice with a more severe phenotype, which can be induced in (NZBxNZW)F1 mice by infecting them with adenovirus expressing alpha interferon. In these three groups we will analyze the mucosal-blood flux using a tracer molecule (FITC-dextran) and we will study the transepithelial electrical resistance. We will also analyze the expression of tight junctions proteins and study the proliferation and apoptosis rates in the epithelial gut cells. Finally, we will perform an oral infection and determine the rate of bacterial dissemination.

The ultimate goal of this study is to establish strong foundations for the development of new strategies to stop the mechanisms responsible for chronicity in SLE, including the use of antibiotics and vaccines to interfere with the gut pathobionts. These would be a game changer in the way we think about autoimmunity and in the way we treat these patients.

Supervisor: *Patrícia Costa Reis, João Eurico Fonseca Lab, pcr.patricia@gmail.com*
Co-Supervisor: *Angelo Calado, João Eurico Fonseca Lab, acalado@medicina.ulisboa.pt*
Webpage of the group

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iMM : Instituto de Medicina Molecular João Lobo Antunes - Faculdade de Medicina da Universidade de Lisboa
Avenida Professor Egas Moniz - Edifício Egas Moniz - 1649-028 Lisboa - Portugal - P + (351) 217 999 411 – E imm@medicina.ulisboa.pt

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Remunerated or volunteer training: *Volunteer training*

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