Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Gut Permeability in Children and Adults with Systemic Lupus Erythematosus

Synopsis:

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, whose etiopathogenesis is not completely understood. The burden of this illness is particularly high in children who have to physically and cognitively grow while facing the challenges of a chronic disease. Fatigue, depression, chronic pain, as well as multiple clinic visits and, often, the need to be admitted to the hospital, disrupt their youth and make them feel different from their peers. The high rates of school failure and unemployment in this group of patients urge us to do better and to find new ways to improve the care of lupus patients. In order to do so we need to better understand the pathogenesis of this disease.

Recently, it was found that monocytes from SLE patients not only had a transcriptome that exhibits quantitative changes as defined by the level of gene expression, but also qualitative differences with widely altered splicing preference and non-coding RNA transcription. Some novel transcripts expressed at higher abundance in SLE monocytes were inducible, *in vitro*, by lipopolysaccharides (LPS), known to activate type I interferons. Furthermore, it was recently shown that SLE patients have increased levels of circulating LPS.

In monocolonized and autoimmune prone mice, it was just found that microbial translocation induced autoantibodies and caused death, which was prevented by a vaccine against the microbe. Moreover, antibiotics against the microbe also eliminated autoantibodies and T cells and prevented death in this mouse model.

These data, collectively, suggest that a higher gut barrier permeability and microbial translocation may contribute to the chronic dysregulation of the immune system seen in SLE.

The goal of this project is to study the gut barrier integrity in SLE.

We will assess the gut barrier integrity in SLE patients and in healthy, sex and age-matched controls by performing lactulose tests, differential sugar absorption tests and by measuring Claudin-3 and fatty acid binding proteins in the urine and blood. We would also like to study these variables in the same patients during remissions and flares and correlate the gut permeability with disease activity, assessed using the SLEDAI (SLE Disease Activity Index).

The ultimate goal of this study is to develop new treatment strategies to control SLE activity and to stop its chronicity, including the use of antibiotics and vaccines to interfere with the gut pathobionts. These would be a disruption of the current paradigm of SLE treatment and it would open the door for new treatment strategies also in other autoimmune diseases.

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