Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: X chromosome inactivation in systemic lupus erythematosus

Synopsis:

Lupus is an autoimmune disease with high morbidity and mortality. There is a correlation between the number of X chromosomes and the prevalence of lupus. Women (XX) have more lupus than men (XY) (9:1), this disease being less prevalent in Turner syndrome (XO) and more prevalent in Triple X syndrome (XXX). Men with Klinefelter syndrome (XXY) have a higher risk of lupus than XY men.

The X-linked gene dosage is equalized between male and females by the inactivation of an X chromosome in all female cells. X-chromosome inactivation occurs randomly and allows only one X chromosome to be expressed in each cell, resulting in cellular mosaicism. Preferential inactivation of one X occurs in certain circumstances being linked to aging and disease. The master-regulator of XCI is the long non-coding RNA XIST, which is expressed only on the inactive X (Xi) in all cells. *XIST* will cover the X to be inactivated, promoting its heterochromatinization and consequent silencing of most of its genes. Interesting, a few X-linked can escape inactivation in the Xi.

The aim of this study is to assess whether disturbances in the XCI process in immune cells lead to an increased risk of lupus in women. Specifically, we ask: (1) is there preferential inactivation of one of X chromsomes in lupus?; (2) Is XIST dysregulated or displaced from the Xi in lupus? (3) Does a great number of genes escape XCI in lupus?

Samples from patients with lupus and healthy controls already stored in a Biobank will be used and the study is approved by the Ethics Committee and funded by an FCT grant.

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