

Understanding Immunosenescence through a Systems Biology Approach

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1 USP

Abstract

The remodeling of the immune system that comes with age, known as immunosenescence, contributes to an increased susceptibility in elderly to infectious diseases, cancer, autoimmunity and decreased vaccines response. This remodeling is a complex and multifactorial process and, until now, there is little understanding of the molecular mechanisms involved. Several studies tried to understand and identify which genes and signaling pathways are involved in the ageing of our immune system. However, none has yet done a comprehensive analysis of a large amount of transcriptomic data of healthy subjects in a wide age spectrum. In this project we aim to create a predictive model for the biological age of the immune system using machine learning methods. For that we will perform a meta-analysis of microarray transcriptomic data available in the GEO public repository. We selected 29 studies containing 435 blood samples that had subject's age information. First, we will identify genes that are differently expressed between age groups, through the statistical method LIMMA. With such genes we can discover the gene signatures that are related with immunosenescence throughout a pathway enrichment analysis. In this step, we will also perform a coexpression analysis to build gene networks related to immunosenescence. This will be done using the CEMiTool, a tool developed in our laboratory that allow us to identify gene modules and sub-modules associated with a particular phenotype. The next step is to create a predictive model of the biological age of the immune system. We will use dimensionality reduction and feature selection algorithms, like PCA and the FSelector package, to select genes that optimize the predictive power of the model. Then, we will use various algorithms of machine learning, such as Support Vector Machine and Neural Networks, to create age group classification and age regression models. These models will then be validated with blood samples from children and elderly, which will be provided by the Liverpool School of Tropical Medicine. Once the model has been validated, genes used in machine learning algorithm as well as the regulation profile and co-expression of gene networks discovered in the meta-analysis will be used to understand the mechanisms of activation and deactivation of the genes they are related to immunosenescence.

Funding: FipFarma