Gordon Research Conference

Poster Abstract

Title: Bioinformatics Analysis of Human Ageing From Transcriptomics to Phenomics

Abstract

Almost all organisms on earth experience ageing, but at varying rates. Over the last two decades, conserved biological pathways involved in the ageing process, from yeast to human, have been identified. Model organisms such as *Caenorhabditis elegans* are indispensable in studying the biology of ageing. However, translating discoveries from model organisms to human is often challenging. The complexity of the ageing process has also motivated applying a systems-oriented approach through the creation and analysis of cellular networks. In this regard, recent human omics profiling efforts such as Genotype-Tissue Expression (GTEx), functional annotation of the mammalian genome (FANTOM), Human Protein Atlas and Human Metabolic Atlas projects, have generated large-scale human datasets, which would allow us to study human ageing process holistically. The challenge now is in extracting actionable insights from these datasets.

In this study, we focused on the relationship between ageing and metabolism. The close connection between ageing and metabolism has been well documented, most notably the longevity effects of caloric or dietary restriction. But, a genome-wide analysis of human metabolism during ageing has not yet been carried out. Here, we leveraged on transcriptomics data from the GTEx project and highly-curated genome scale metabolic network model, to identify age-related metabolic alterations in human
Briefly, we employed a linear mixed effects model to determine the set of "ageing genes", i.e. genes whose expression were altered with ageing across different human tissues. By projecting the age-related gene expression changes onto the human genome scale metabolic model, we were able to show specific age-related perturbations in metabolic pathways across different tissues. Our findings pointed to down-regulation of metabolic pathways related to cellular energy generation (e.g. tricarboxylic acid (TCA) cycle), amino acid homeostasis and xenobiotics. On the other hand, the predominant age-related upregulation was observed for pathways related to oxidative stress.

Expanding our study beyond metabolism, we developed an information theoretic based methodology for data analysis to elucidate the molecular pathways that are dysregulated during ageing. For this purpose, we manually curated a human trait – gene association database from Genome-Wide Association Studies (GWAS) and Mendelian mutations (Online Mendelian Inheritance in Man). Using Gene Ontology Semantic Similarity (GOSS) analysis, we could identify human traits that share similar biological processes with the ageing genes. A subsequent analysis of the genes associated with these human traits revealed significant enrichment of pathways in metabolism, immune system, cellular response to stress and apoptosis. Importantly, signal transduction events showed the most significant enrichment, especially pathways involved in the insulin receptor signaling cascade, insulin growth factor receptor and other nutritional sensing pathways (e.g. PI3K-AKT). The identification of cellular pathways that are dysregulated with ageing is an important step toward formulation an intervention strategy.