Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title:

Development of combined gene expression and alternative splicing signatures for the ageing of human tissues

Synopsis:

The gain in human health span over the last two centuries did not match that in longevity, as age is the main risk factor for prevalent diseases in developed countries. Individual variation still often marks the responses to clinical interventions guided by biomarkers of physiological state [1].

To target the pathological phenotypes of ageing, we need to better understand its underlying molecular mechanisms. Nine interconnected hallmarks of ageing have been proposed: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [2]. Assessing their relative contribution to tissue ageing is challenging, given that they exhibit some compositional and functional redundancy and most lack specific experimental readouts.

Transcriptomes of *post mortem* human tissues have been used to infer gene expression predictors of age and find their association with disease markers [3–5]. Moreover, alternative splicing, a tightly regulated process by which one gene can originate multiple proteins, has recently been implicated in ageing of human tissues [6]. We are building on our forefront expertise in analysing splicing from RNA sequencing data [7–9] and in the definition of clinically relevant transcriptomic signatures [10] to develop novel methods for integrating splicing and gene expression analyses. These approaches already contributed to the findings of splicing-mediated regulation of the senescence-associated secretory phenotype [11] and we are currently analysing transcriptomes of cells undergoing senescence caused by different stimuli to derive their respective signatures [11,12]. Moreover, we are developing an interactive atlas of age-associated gene expression alterations in human tissues based on transcriptomes (with matching clinical information) from the Genotype-Tissue Expression (GTEx) project [4].

We thus propose a computational biology MSc project aimed at inferring combined gene expression and alternative splicing signatures for the hallmarks of ageing through the development and implementation of new machine learning approaches (e.g. elastic net [13], neural networks [14]). The student will, for instance, integrate the different signatures of cell senescence, derive signatures for stemness from transcriptomes of human induced pluripotent and embryonic stem cells [15] as “negative” markers of stem cell exhaustion [2,16], and run TelSeq [17] to estimate average telomere length from whole-genome sequencing of human samples with matching RNA-seq data [5], using machine learning on matching RNA-seq data to infer gene expression and alternative splicing profiles that are predictors of relative telomere length. The student will then profile the derived signatures on GTEx transcriptomes [4] to evaluate the relative prevalence of the aforementioned hallmarks in the ageing of each human tissue. That prevalence will be related with estimated cellular composition, facilitated by the increasing wealth of publicly available single-cell transcriptomes [18] and digital cytometry approaches [19].

This project will therefore help to define new robust markers, namely involving alternative splicing, for relevant cellular phenotypes such as senescence and contribute to unveil the transcriptional programs underlying human ageing. Moreover, it will contribute to the identification of not only candidate molecular causes of observed age-associated phenotypes, but also candidate small molecules to revert them, following approaches being developed in the lab [20].

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