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] 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 [10].

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 [11], neural networks [12]). For instance, the student will derive signatures for stemness from transcriptomes of human induced pluripotent and embryonic stem cells [13] as “negative” markers of stem cell exhaustion [2,14], and analyse transcriptomes of cells undergoing senescence caused by different stimuli to derive their respective signatures [10,15]. (S)he will also run TelSeq [16] to estimate average telomere length from whole-genome sequencing of human samples with matching RNA-seq data [5], and then use 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 transcriptomes (with matching clinical information) from the Genotype-Tissue Expression project [4] to evaluate the relative prevalence of the aforementioned hallmarks in the ageing of each human tissue.

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.

Supervisor: Nuno Barbosa Morais (Disease Transcriptomics Lab, iMM)
nmorais@medicina.ulisboa.pt
https://imm.medicina.ulisboa.pt/en/investigacao/labs/morais-nuno-lab/
http://imm.medicina.ulisboa.pt/group/distrans/

Instituto de Medicina Molecular João Lobo Antunes

Bibliography:

[1] Partridge L et al. (2018) *Nature* 561:45–56
[2] López-Otín C et al. (2013) *Cell* 153:1194–217
[3] Yang J et al. (2015) *Sci Rep* 5:15145
[4] Mele M et al. (2015) *Science* 348:660–5
[5] Aguet F et al. (2017) *Nature* 550:204–13
[6] Wang K et al. (2018) *Sci Rep* 8:10929
[7] Barbosa-Morais NL et al. (2012) *Science* 338:1587–93
[18] Braunschweig U et al. (2014) *Genome Res* 24:1774–86
[19] Saraiva-Agostinho N & Barbosa-Morais NL. (2019) *Nucleic Acids Res* 47(2):e7
[10] Georgilis A et al. (2018) *Cancer Cell* 34:85–102.e9
[11] Friedman J et al. (2010) *J Stat Softw* 33:1–22
[12] Günther F & Fritsch S. (2010) *R J* 2:30–8
[13] Choi J et al. (2015) *Nat Biotechnol* 33:1173–81
[14] Oh J et al. (2014) *Nat Med* 20:870–80
[15] Hernandez-Segura A et al. (2017) *Curr Biol* 27:2652–2660.e4
[16] Ding Z et al. (2014) *Nucleic Acids Re*s 42:e75

Remunerated or volunteer training: Volunteer