Instituto de Medicina Molecular

Master Project Proposal

Title: Intron retention as a functional tune of transcriptional response to hypoxia

Synopsis:

The advent of next-generation sequencing impacted the ability to characterize genomes, epigenomes and transcriptomes. In particular, RNA-Seq allows the investigation of disease transcriptomes to be expanded from measuring the expression of protein-coding genes to the analysis of alternative splicing, non-coding RNAs, etc. The use of RNA-Seq to find disease-specific transcriptomic signatures beyond gene expression has though been very limited, despite the evidence for the involvement of splicing regulation in cellular programs altered in oncogenesis, for example. Ongoing studies in our lab are indeed finding, for some types of cancer, alternative splicing signatures with strong prognostic value beyond the known main molecular sub-classifications used in the clinic.

Hypoxia in solid tumours is very frequent and has been associated with poor patient outcome and both chemo- and radio-resistance. Alternative splicing switches between coding and noncoding isoforms, namely for components of the DNA damage response pathway, have been described to be induced by hypoxia in a colon cancer cell line and to occur in colon tumours *[Memon et al. 2016]*. Our analyses of unpublished RNA-Seq data from unrelated biological samples also suggest a widespread increase in intron retention in hypoxia. Our previous work shows that intron retention is an evolutionarily conserved mechanism of functionally tuning transcriptomes *[Braunschweig et al. 2014]*.

We propose a computational biology MSc thesis that aims at understanding the general molecular mechanisms by which hypoxia drives the aforementioned genome-wide alterations in alternative splicing programs and to characterize their functional and physiological implications. The student will work with RNA-Seq data from studies in which different cells are subjected to hypoxic conditions and the clinical relevance of the molecular targets resulting from their analyses will be assessed using data from The Cancer Genome Atlas, an effort involving the genome-wide molecular profiling of hundreds of samples of each of more than 20 types of cancer, comprising clinically annotated data for hundreds of tumours and matching normal tissues.

Supervisor:

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http://imm.medicina.ulisboa.pt/group/compbio/

Bibliography:

- Memon D, Dawson K, Smowton CSF, Xing W, Dive C, Miller CJ. *Hypoxia-driven splicing into noncoding isoforms regulates the DNA damage response.* (2016) npj Genomic Medicine 1:16020; doi:10.1038/npjgenmed.2016.20.
- Braunschweig U, Barbosa-Morais NL, Pan Q, Nachman EN, Alipanahi B, Gonatopoulos-Pournatzis T, Frey B, Irimia M, Blencowe BJ. Widespread intron retention in mammals functionally tunes transcriptomes. (2014) Genome Research 24(11):1774; doi:10.1101/gr.177790.114.

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