Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

Supervisor	Josep Vilardell
Email	josep.vilardell@ibmb.csic.es
Institution	institute of Molecular Biology of Barcelona
Website	www.ibmb.csic.es/vilardell
Group	Mechanisms of pre-mRNA splicing

Project

Computational genomics

Project Title:

Impact of the spliceosome on protein synthesis

Keywords:

splicing, spliceosome, ribosome, mRNA. differential expression

Summary:

The information content of genomes can be greatly expanded by pre-mRNA splicing. Virtually all human pre-mRNAs need to be spliced to become mRNAs. Furthermore, most pre-mRNAs can be spliced into different mRNAs by alternative splicing. Therefore, it is hardly surprising that perturbations in splicing are linked to disease. However, we know little on how the splicing of particular RNAs may be affected, and even less on how a number of splicing changes are coordinated during development or disease. To start addressing this question, we are analyzing WGS and RNASeq data from a number of cancer datasets. Although we are interested in all events of regulated splicing, we pay special attention to those related to the biosynthesis and function of the ribosome. A cycling cell depends on a suitable set of ribosomes to provide the necessary amount of structural and functional proteins before mitosis; paradoxically, making this machinery requires most of the cell's energy (as an illustrative example, a growing HeLa cell is making 1.6 x105 ribosomal proteins per minute). Thus, we expect that fast-growing cell, subjected to a strong selection (such as a tumor cell), will tweak this process to get any advantage. However, the analysis of the transcriptome of ribosomal proteins presents specific challenges because (a), it includes the mRNAs that are most abundant in the cell, but the amounts of each one are variable (while the ribosome has one copy of each protein); (b), the corresponding pre-mRNAs undergo little alternative splicing; and (c), the majority of human pseudogenes come from them, which introduces ambiguity when mapping reads to the genome. Our initial results suggest that processing of this set of transcripts is altered in cancer in unexpected ways, and we plan on strengthening our conclusions by expanding our analyses. In this context there are many opportunities for those with a strong motivation to document genomic strategies that control the tran-scriptome of specific gene families, like those related to the ribosome or the spliceo-some. The tasks involve quality analysis of raw RNASeq data, mapping using standard tools (for example, Hisat, STAR, and those related to direct sequencing of RNA), statistical analysis (Ballgown, Salmon, Vast-tools, DexSeq, or others), and modeling. Subject to progress, we would explore the use of transcriptomics data as a disease prognosis tool; namely, is a distinct distribution of transcripts indicative of a particular disease out-come?

References:

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/doi.org/10.1016/j.tibs.2018.02.007 * Guimaraes, JC. and Zavolan, M. (2016) “Patterns of ribosomal protein expression specify normal and malignant human cells” Genome Biol. 17:236-248 * Gupta, V. and J. R. Warner (2014). "Ribosome-omics of the human ribosome." RNA 20: 1004-1013. * Bitton, D. A., et al. (2014). "LaSSO, a strategy for genome-wide mapping of intronic lariats and branch points using RNA-seq." Genome Res 24(7): 1169-1179. * Acuna, L. I. and A. R. Kornblihtt (2014). "Long range chromatin organization: a new layer in splic-ing regulation?" Transcription 5. * Kawashima T et al (2014) Widespread use of non-productive alternative splice sites in Saccharo-myces cerevisiae. PLoS Genet. 2014 Apr 10;10(4):e1004249. * Zhang, J. and J. L. Manley (2013). "Misregulation of pre-mRNA alternative splicing in cancer." Cancer Discov 3(11): 1228-1237. * Fu, R. H., et al. (2013). "Aberrant alternative splicing events in Parkinson's disease." Cell Trans-plant 22(4): 653-661. * Plass, M., et al. (2012). "RNA secondary structure mediates alternative 3'ss selection in Saccha-romyces cerevisiae." RNA 18(6): 1103-1115

Expected skills::

knowledge of R is highly desirable

Possibility of funding::

No

Possible continuity with PhD: :

To be discussed

Comments:

We are a wet lab but with knowledge of Bioinformatics and several questions to be approached using Bioinformatics but for which we have many molecular data. This is therefore an excellent setting for any knowledgeable, independent, ambitious, and highly motivated Bioinformatics student.