Medical Biophysics
UNIVERSITY OF TORONTO

Special Guest Seminar

Dr. Xavier Roucou

Professeur titulaire
Dept de Biochimie
Université de Sherbrooke

Function of the alternative proteome in neurodegenerative diseases

A typical fully processed mRNA includes one reference-protein coding ORF (RefORF) or coding sequence. This overly simplistic view is however challenged by recent evidence of translation of alternative ORFs (AltORFs). AltORFs are defined as ORFs occurring either in untranslated regions, or overlapping the RefORF in the non-canonical +2 and +3 reading frames. The use of alternative translation initiation is well-described for viruses and provide small viral genomes with an increased coding capacity, but has been overlooked in eukaryotes. To address this issue, we generated a database of predicted AltORFs in the human transcriptome. We identified 83,886 AltORFs with a minimum size of 40 codons. This threshold was established to increase the chances of detecting the predicted alternative proteins by proteomic techniques, including tryptic digestion and mass spectrometry, and SDS-PAGE. For the majority of mRNAs (87.58 %) we found at least one predicted AltORF and, on average, 3.88 predicted AltORFs per mRNA. These predictions are in agreement with the number of detectable translation-initiation sites determined using the ribosome profiling data of 5,000 transcripts from mouse embryonic stem cells. Using this novel alternative-protein database and mass spectrometry, we directly detected more than a thousand alternative proteins in human cell lines, tissues and fluids. The functional importance of alternative proteins is strongly supported by significant evolutionary conservation in vertebrates, invertebrates, and yeast. We are currently focusing our research on two genes, *PRNP* and *ATXN1* involved in two neurodegenerative disorders, transmissible spongiform encephalopathie (TSE) and spinocerebellar ataxia type 1 (or SCA1). We recently discovered that these genes are dual-coding genes and produce two different proteins in cultured cells and in vivo. *PRNP* produces the well-known prion protein (PrP) and alternative prion protein (AltPrP), and *ATXN1* produces ataxin 1 (or ATXN1) and alternative ataxin 1 (AltATXN1). The role of AltPrP and AltATXN1 in TSE and SCA1 is under investigation.

Date & Time: Mon, Sept. 23rd, 2013 at 10:00 am
Location: MSB 2172

Hosted by: Emil F. Pai

Everyone Welcome!

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