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The alternative human proteome: functional proteomics and discovery of new proteins

Ten of thousands of ORFs are hidden within genomes. They have eluded annotations because they are either small or within unsuspected locations. These are named altORFs and have recently been highlighted by innovative proteogenomic approaches, such as our OpenProt (www.openprot.org), revealing their existence and implications in biological functions. (1) Genetic screens, ribosome profiling (Ribo-seq) and mass spectrometry (MS) studies have demonstrated the translation of thousands of altORFs into functional proteins (altProts) across several species. (2) AltORFs have been shown to be involved in human diseases, like apelin in diabetes or altFUS in ALS. (3) Due to the absence of altORFs from annotations, pathogenic mutations within these are being ignored. Since the apelin discovery, encoded within a RNA previously annotated as non-coding (ncRNA), missense variants have been identified and associated to cardiovascular diseases and obesity risks. (4) Our re-analysis of MS-based interactomics revealed altORFs within key biological complexes. A 5'UTR encoded altProt from the MIEF1 gene was shown to be a key component of the mitochondrial ribosome. (5) Several pseudogenes are up- or down-regulated and correlated to the prognosis of human diseases. Over-expression or knockdown of these pseudogenes have proven to rescue the phenotype. For example, BRAFP1 encodes a 244 amino acid long altProt (IP_556482) that cooperates with BRAF to promote MAPK signaling. These 5 lines of evidence ground our quest for the discovery of novel proteins, previously overlooked, involved in key biological complexes and pathologies, through the means of cutting-edge tools and our innovative OpenProt resource. The latter will promote a decisive shift in omics analyses by enabling biologists to access this wealth of novel genomic and proteomic information and facilitate future discoveries.

Expertise: biochemistry, bioinformatics, cell biology, molecular genetics, proteomics

For more information:

- Our proteogenomic resource: OpenProt
- An editorial in genetics and genomics in The scientist magazine
- A 5:28 min editorial video on the French Science & Vie TV channel
- An article in the French Science & Vie magazine