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Uncovering new knowledge on protein post-translational modifications by large-scale reprocessing and analysis of public proteomics data

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SUMMARY

Proteins are essential for many biological processes. Their function depends mainly on their three dimensional structures, which varies based on their amino acid sequence. Proteins can also have post-translational modifications (PTMs), where a chemical group such as acetyl, phosphoryl, methyl or glycosyl is added to one or more amino acids of the protein. These PTMs affect a wide range of protein behaviour such as protein folding, structure, function, interactions and spatial localization of proteins, thus acting as an important regulatory mechanism for many cellular processes. The disruption of PTMs can result in diseases such as cancer and Alzheimer's. It is important to know where PTMs occur in proteins to understand the underlying structure-function relationships, so leading to a more effective understanding of protein regulation. Mass spectrometry (MS) based proteomics experiments, where proteins present in a cell are measured, is a powerful tool to identify these PTMs for proteins in their native environment.

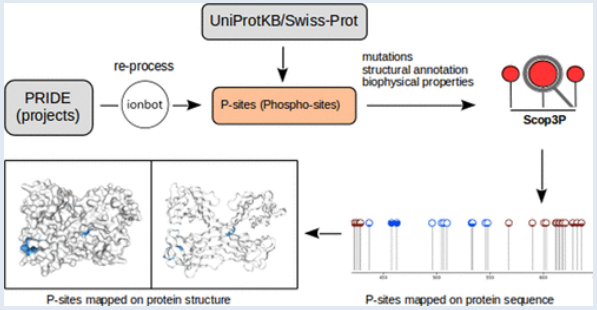

Image source: Ramasamy *et al.*, 2020

In this PhD research, I leverage the information available from public resources to effectively identify PTMs and establish a link to protein sequence, structure and biophysical properties. First, I built an interactive knowledge-base Scop3P (https://iomics.ugent.be/scop3p), that connects protein phosphorylation sites to available protein structures and their predicted biophysical properties.

Scop3P acts as a much-needed bridge between the fields of proteomics, structural bioinformatics (3D bioinfo) and IDPs, and also features in that capacity in an ELIXIR Inter-Community Implementation study between these three ELIXIR Communities. Moreover, Scop3P is also an emerging node service in ELIXIR-Belgium.

Scop3P was then extended to Scop3PTM, where all different PTM types were included by re-processing all available human proteomics projects using an open modification search. Scop3PTM contains 117 post-translational modification types identified in human proteins along with other non-biological modifications such as chemical derivatives and artefacts.

Combining the wealth of PTM information available in Scop3P and Scop3PTM, I tried to uncover the patterns of these post-translational modifications in different contexts. Firstly, I identified the patterns that could possibly differentiate the phosphorylation status of the protein and the behaviour of proteins in relation to phosphorylation. Secondly, an analysis of a tissue specific phosphorylation map of human proteome was performed. Lastly, the availability of AlphaFold2 predicted protein structures for the entire human proteome allowed a preliminary analysis on large-scale comparison on AlphaFold2 predicted structural regions to protein PTMs and biophysical properties. In conclusion, the unified reprocessing of public proteomics data sets provides extensive and unique information about the prevalence of PTMs and their reliability of identification across experiments. This is an initial step to further uncover the full-scale relation between the properties of proteins and PTMs in the context of the full proteome.

ABOUT THE AUTHOR

Pathmanaban Ramasamy did his bachelors in Bioinformatics at Tamil Nadu Agricultural University, Tamil Nadu, India. He moved to Germany for doing his masters in Bioinformatics at Saarland University, where he worked on detecting the similarity of proteins in fast evolving RNA viruses using graph mining approach.

In 2016, he joined as a joint PhD student between Ghent University (UGent) and University of Brussels (VUB) to work on the FoldMod project. In his PhD, he focus his research towards understanding the role of local amino acid interactions in protein folding, fold stability and the location of post-translational modifications. Applying his knowledge on structural bioinformatics and proteomics informatics he try to uncover the behaviour of proteins in relation to post-translational modifications.

An electronic version of this thesis can be obtained via UGent Biblio or on request (see contact information)

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