Contribution ID: **49** Type: **Oral contribution**

Exploring the role of protein folding intermediates: cryptic phosphosites as a new mechanisms of protein homeostasis regulation

Tuesday 8 July 2025 15:50 (30 minutes)

As the name suggests Post-Translational Modifications (PTMs) are commonly believed to happen after the production of the target protein is fully completed. However, by examining residues involved in the most widespread PTM, namely phosphorylation, one finds that some such residues cannot be accessed when the protein has reached its functional form. Indeed, one finds that a part of the experimentally validated phosphosites are buried inside the hydrophobic core of proteins in the native state.
We evaluated the extent of this phenomenon in the case of the entire human proteome by computing the relative solvent accessibility (rSA) of phosphorylation sites in the 3D structures predicted by AlphaFold2. To generate a more conservative dataset we then applied a filtering procedure based on the division of proteins into quasi-rigid domains. What we found is that roughly 5% of all phosphorylation sites are cryptic, which translates to about one out of three phosphoproteins having at least one cryptic phosphosite.
We hypothesize that these cryptic phosphosites may be exposed along the folding pathway and serve as a previously unappreciated mechanism for protein quality control.

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