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PRESS RELEASE

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Some proteins find their "soulmate" at birth

A study by UNIGE and the Weizmann Institute reveals how certain proteins assemble as soon as they are synthesized, ensuring their stability and efficiency.

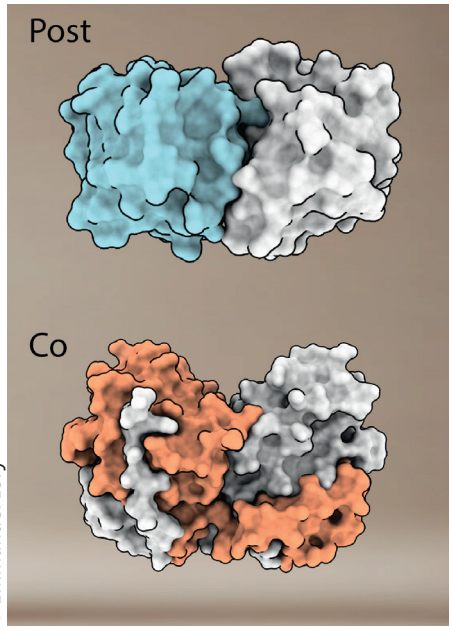

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Illustration of two protein complexes undergoing different assembly pathways: the upper complex undergoes post-translational assembly (blue and white subunits), while the lower complex undergoes co-translational assembly (orange and white subunits).

Pictures

Proteins, the pillars of cellular function, often assemble into "complexes" to fulfill their functions. A study by the University of Geneva (UNIGE) and the Weizmann Institute, in collaboration with the Technion, reveals why this assembly often begins during the very process of protein synthesis or "birth." These early interactions involve proteins whose stability depends on their association. They can be compared to a couple in which each partner supports the other. This model paves the way for new strategies to understand and correct assembly errors, which are often associated with pathologies, including neurodegenerative disorders and certain cancers. These findings are published in the journal *Cell*.

Proteins are large molecules composed of a chain of amino acids. They are produced by the ribosome, a cellular "machine" that reads the instructions contained in messenger RNAs. Once the protein is formed, interactions between the amino acids induce the chain to fold onto itself and adopt a specific structure. While some proteins function independently, many must assemble with specific partners into complexes to fulfill their roles.

The formation of these complexes is a delicate process. If proteins fail to find their partners or fold incorrectly, this can lead to cellular dysfunction and pathologies such as Alzheimer's disease or certain cancers. Until very recently, scientists believed that proteins only formed complexes after being fully synthesized (post-translational assembly). However, a recent study revealed that assembly between nascent proteins – co-translational assembly – is widespread. This study identified thousands of proteins involved but did not determine the specific pairs of proteins formed or the molecular signatures underlying this early recognition.

Thousands of Protein Structures Analyzed

The group led by Emmanuel Levy, a full professor in the Department of Molecular and Cellular Biology at the UNIGE Faculty of Science – previously a professor at the Weizmann Institute – in collaboration with the group of Ayala Shiber, a professor at the Technion, focuses on the fundamental principles governing protein self-organization. In other words, these scientists aim to identify the general rules of protein assembly. For this study, the team analyzed a list of proteins involved in co-translational assembly. By comparing their structures to those of proteins that assemble after translation, they were able to establish fundamental differences between these two mechanisms.

"Our bioinformatics analyses revealed that proteins interacting with their partners while still being synthesized tend to be unstable when isolated. These proteins depend on their partners and if they do not find it, they adopt a wrong shape and get degraded," explains Saurav Mallik, a researcher at the Weizmann Institute and co-first author of the study.

A Predictive Model

"Using this approach, we developed a model based on a large corpus of structural data, using both experimentally determined structures and those predicted by the artificial intelligence software AlphaFold. Our model leveraged structural properties of a complex to predict whether it associated co- or post-translationally," add Johannes Venezian and Arseniy Lobov, co-first authors of the study. The scientists notably discovered that binding sites are exposed early in these proteins, enabling them to interact with their partner shortly after emerging from the ribosome.

These predictions were validated using experimental data focused on several proteins. "These findings pave the way for a better understanding of protein assembly within cells and highlight the global impact of protein structure on the regulation of their synthesis," says Emmanuel Levy. Many diseases, including neurodegenerative disorders and certain cancers, are linked to misfolded proteins or defective complexes. By understanding the rules of co-translational assembly, scientists could develop strategies to prevent these errors and design new therapeutic approaches to correct them.

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