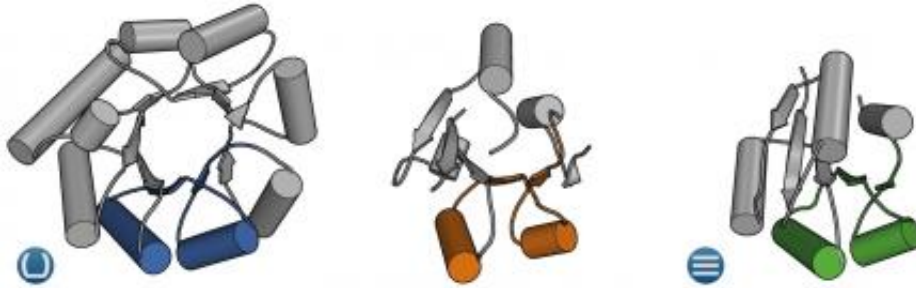


Protein evolution follows a modular principle

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At first glance, proteins that fold into a barrel-like shape (left) and proteins that fold into a sandwich-like shape (right) appear completely different. However, analyses of their amino acid sequences as well as a recently identified intermediate form (centre) have revealed similarities that suggest a common evolutionary origin. Credit: MPI for Developmental Biology /B. Höcker

Proteins impart shape and stability to cells, drive metabolic processes and transmit signals. To perform these manifold tasks, they fold into complex three-dimensional shapes. Scientists at the Max Planck Institute for Developmental Biology in Tübingen have now discovered that proteins can be constructed of similar amino acid chains even when their three-dimensional shapes differ significantly. This suggests that the proteins that exist today arose from common precursors. Presumably, in the course of evolution they were built up from smaller fragments according to a modular principle.

Proteins consist of long chains of 20 different amino acid building blocks that fold into a characteristic three-dimensional structure. It is

noteworthy that some modules, known as [protein](#) domains, occur more frequently than others. Scientists suspect that many of these domains share a common evolutionary origin.

To test this theory, the Max Planck researchers focussed on two large, evolutionarily ancient protein groups that differ significantly in their folding pattern. While "flavodoxin-like" protein domains fold into a kind of sandwich shape, so-called $(\beta\alpha)_8$ -barrel proteins stack two sandwich elements on top of each other to form a barrel-like structure. "In the folded state it's very difficult to recognize similarities between these two types," José Arcadio Farías Rico, first author of the study, explains. The Tübingen scientists therefore compared the amino acid chains of over a thousand representatives of both folding types in a computer analysis. They found that short, characteristic sequences of [amino acids](#) occur in both folding types.

In the next step, the team identified a third folding type whose [amino acid sequence](#) is an intermediate form between the other two types. To compare the amino acid sequences, the researchers used a highly sensitive method that enabled them to identify even the smallest shared features. "Analysis of the three-dimensional structure of the intermediate form by X-ray crystallography showed that the intermediate form has characteristics of both the barrel-like and the sandwich-like folding type," says Farias-Rico.

The similarity of the amino acid sequences and the existence of an intermediate form confirm a hypothesis proposed by Birte Höcker, head of the Protein Design Working Group at the Max Planck Institute for Developmental Biology, according to which the two folding types developed in the course of evolution from a common ancestor. "We assume that evolutionarily early proteins consisted of only short amino acid chains. Those fragments then joined together as in a construction kit to form new molecules with new functions," Höcker explains.

Höcker's team has thus provided fresh insights into the evolution of modern proteins and the origins of life on Earth. In addition, the Max Planck scientist is pursuing research in the field of synthetic biology and wants to apply this knowledge to construct variant proteins with new functions in the laboratory.

More information: José Arcadio Farías-Rico, Steffen Schmidt, Birte Höcker. "Evolutionary relationship of two ancient protein superfolds." *Nature Chemical Biology*, 14 July 2014, [DOI: 10.1038/NCHEMBIO.1579](https://doi.org/10.1038/NCHEMBIO.1579)

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