

Ancient proteins studied in detail

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How did protein interactions arise and how have they developed? In a new study, researchers have looked at two proteins which began co-evolving between 400 and 600 million years ago. What did they look like? How did they work, and how have they changed over time? The findings, published in *eLife*, show how a combination of changes in the proteins' properties created better conditions for the regulation of a cellular process.

"We want to understand the process by which a new [protein-protein](#) interaction emerges and evolves," says Greta Hultqvist who co-led the study together with Per Jemth at the Department of Medical Biochemistry and Microbiology, Uppsala University.

Life depends on proteins; in particular, how proteins interact with each other. Most if not all basic cellular processes are dependent on protein interactions where a certain protein may enhance or reduce a specific cellular function. In many cases, the same protein interaction can be found across classes of [organisms](#) from mammals, to all animal phyla or even to all kingdoms of life.

When a protein interaction is specific for vertebrates, it means that the interaction emerged at a significant time point for the vertebrate ancestor. This protein interaction was then preserved in all evolutionary lines arising from the vertebrate ancestor and can be seen in all present day vertebrates. In fact, new and modified proteins appear continuously in organisms by way of gene modifications, but most of them disappear. However, some [protein-protein interactions](#) prove to be beneficial and as

a result are retained by the organism.

New or modified proteins could form novel interactions with existing proteins to elicit an advantageous protein-protein interaction. This has happened multiple times during evolution. It is easy to understand that protein interactions can be beneficial to an organism and as such it is retained. However, less is known about the molecular details of such historical protein evolution.

By analysing multiple amino acid sequences of two interacting proteins from different present-day organisms, the team reconstructed ancestral versions of the proteins present in species living between 400 million-600 million years ago. What the oldest of these ancestors looked like is not exactly known, but it can be speculated that it was a small animal with bilaterian symmetry. One evolutionary line led towards fishes and subsequently to the first tetrapod. The team resurrected proteins from these species and characterised their properties with experimental and computational methods.

"We found that the ancestral proteins interacted with each other more weakly compared to later generation variants. The ancestral proteins were probably also more flexible in terms of structure than the later generation ones when bound together. Another striking finding is that the strength of this protein-[protein interaction](#) has not changed over the last 450 million years," says Greta Hultqvist.

The proteins studied by the scientists belong to a class called '[intrinsically disordered proteins](#)'. This means that on their own they are highly flexible and could even exist as an extended chain, as opposed to the majority of proteins, which have a globular shape. However, when the disordered proteins bind to each other they often fold into a globular structure. Protein-protein interactions between intrinsically disordered proteins are very common and are often involved in cellular regulation.

"Our findings shed light on some fundamental principles of protein evolution and may be general for how new protein-protein interactions of intrinsically disordered proteins emerge and evolve. A weak and dynamic ancestral interaction could relatively quickly turn into an optimally strong one by random gene mutations followed by natural selection. The strength of the interaction is then maintained when the ancestral group of organisms diversifies into new species," says Per Jemth.

More information: Greta Hultqvist et al, Emergence and evolution of an interaction between intrinsically disordered proteins, *eLife* (2017). [DOI: 10.7554/eLife.16059](https://doi.org/10.7554/eLife.16059)

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