Evolutionary tinkering produced complex proteins with diverse functions

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The atomic structure of nuclear receptor proteins reflects tinkering with an ancestral template. This cartoon rendering shows the superimposed atomic structures of five distantly related nuclear receptors that are activated by different chemical signals. The colored cylinders show the position of stable corkscrew-like helices in the receptor's atomic structure; the white strands show flexible loops. The chemical signals -- including hormones, fatty acids, retinoids and other molecules -- are shown as gray spheres. The ability of the proteins to be activated by different signals is due to subtle changes in the size and surface properties of the "pocket" where the signal binds, not a fundamental redesign of the receptor structure. Credit: Courtesy of Joseph Thornton

By reconstructing an ancient protein and tracing how it subtly changed over vast periods of time to produce scores of modern-day descendants, scientists have shown how evolution tinkers with early forms and leaves the impression that complexity evolved many times.

Human and other animal cells contain thousands of proteins with functions so diverse and complex that it is often difficult to see how they could have evolved from a few ancestral proteins, said biologist Joseph W. Thornton of the University of Oregon and the Howard Hughes Medical Institute, who led the research.

The team's findings are detailed in the October issue of the online open-access journal PLoS Biology.

Thornton's team, which included researchers from the University of Queensland (Australia) and Emory University in Atlanta, Ga., studied a large family of related proteins called nuclear receptors. These receptors regulate development, reproduction, metabolism and cancer by triggering the expression of specific genes in response to hormones, nutrients and other chemical signals.

A handful of nuclear receptors, however, do not have to be activated by a chemical signal: they are stable enough to trigger gene expression on their own. Scientists have long thought that the ancestral protein was of this simpler type, implying that the complex capacity to bind and be regulated by chemical signals evolved independently in many lineages.

Using a database of the molecular sequences, functions, and atomic structures of hundreds of modern-day receptor proteins, the researchers reconstructed the biochemical characteristics of the ancestral nuclear receptor, which existed before the last common ancestor of all animals on earth -- as much as a billion years ago.

They found that the ancestral receptor in fact required activation by a chemical signal – most likely a fatty acid, a class of substances commonly found in animal diets. They also found that the underlying atomic mechanisms that allowed the ancestral protein to be activated by chemical signals were conserved in virtually all present-day descendants.

The researchers then traced how evolution tinkered with the ancestral structure over time. They found that in various lineages, receptors evolved partnerships with new hormones or other signals, because a few mutations subtly changed the size and shape of the cavity where the signaling compound binds. Other members of the receptor family became independent of chemical signals; these proteins, like switches stuck in the "on" position, evolved when simple mutations increased the proteins' intrinsic stability, removing the need for it to interact with a chemical signal to activate gene expression.

"If you just compare the receptors in modern humans, the evolutionary events by which they could have evolved are not obvious. It may look as if the complex functions of each protein evolved independently," said Thornton, an HHMI early career scientist and professor in the UO's Center for Ecology and Evolutionary Biology. "But when we traced these proteins from their ancestor through time, we saw how evolution tinkered with the ancestral form, producing an incredible diversity of protein functions and the ability to interact with many different chemical signals.

Thornton's group was able to accurately reconstruct the ancestral receptor protein by gathering extensive new data about its descendants in species that diverged very early from other animals. They first scanned the genomes of sponges, sea anemones and a host of other animal species to collect the sequences of their nuclear receptors. Sponges, they found, had just two such proteins, while humans have 48. By reconstructing the evolutionary tree of the entire receptor family, they

found that the two sponge proteins branched off closest to the root, providing insights into the likely state of the ancestor.

The scientists then extracted the receptors from Amphimedon queenslandica, a sponge from the Great Barrier Reef, and showed that these receptors, like some of the other early-evolving receptors, bind fatty acids. They used computational methods to predict the three-dimensional atomic structure of the sponge proteins to show that they bound the fatty acid in a cavity very similar to that in some receptors in mammals.

"Nuclear receptors are a great case-study in protein evolution," he said. "It's likely that other protein families, when studied in similar detail, will turn out to have diversified by a similar kind of tinkering. What looks like novelty turns out to have evolved by making subtle changes to something very old."

Provided by University of Oregon

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