Errors in protein structure sparked evolution of biological complexity

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Over four billion years of evolution, plants and animals grew far more complex than their single-celled ancestors. But a new comparison of proteins shared across species finds that complex organisms, including humans, have accumulated structural weaknesses that may have actually launched the long journey from microbe to man.

The study, published in *Nature*, suggests that the random introduction of errors into proteins, rather than traditional natural selection, may have boosted the evolution of biological complexity. Flaws in the "packing" of proteins that make them more unstable in water could have promoted protein interactions and intracellular teamwork, expanding the possibilities of life.

"Everybody wants to say that evolution is equivalent to natural selection and that things that are sophisticated and complex have been absolutely selected for," said study co-author Ariel Fernández, PhD, a visiting scholar at the University of Chicago and senior researcher at the Mathematics Institute of Argentina (IAM) in Buenos Aires. "What we are claiming here is that inefficient selection creates a niche or an opportunity to evolve complexity."

"This is a novel bridge between protein chemistry and evolutionary biology," said co-author Michael Lynch, PhD, professor of biology at Indiana University. "I hope that it causes us to pause and think about how evolution operates in new ways that we haven't thought about before."

When mildly negative mutations arise in a species with a large population, such as the trillions of bacterial organisms that can fill a small area, they are quickly cleared out by selective forces. But when a new mutation appears in a species with a relatively small population, as in large mammals and humans, selection against the error is slower and less efficient, allowing the mutation to spread through the population.

To look at whether these mild defects accumulate in species with small populations, Fernández and Lynch compared over 100 proteins shared by 36 species of varying population size. Though these shared, "orthologous" proteins are identical in shape and function, genetic differences alter them in more subtle ways.

Fernández and Lynch focused on design flaws called "dehydrons," sites where the protein structure is vulnerable to chemical reactions with water. Proteins with more dehydrons are more "unwrapped" - unstable in an aqueous environment, and therefore prone to bind with another protein to protect their vulnerable regions.

A computational analysis of 106 orthologous proteins confirmed their hypothesis that proteins from species with smaller populations were more vulnerable in water. The result suggests that structural errors accumulate in large organisms such as humans due to random genetic drift.

"We hate to hear that our structures are actually lousier," Fernández said. "But that has a good side to it. Because they are lousier, they are more likely to participate in complexes, and we have a much better chance of achieving more sophisticated function through teamwork. Instead of being a loner, the protein is a team player."

On their own, these unstable proteins might be expected to perform their cellular duties more poorly, possibly causing harm to the organism. But

unstable proteins are also "stickier," more likely to form associations with other proteins that could introduce more flexibility and complexity into the cell. If these complexes create a survival advantage for the organism, forces of natural selection should take over and spread the new protein complex through the population.

"It's not an argument against selection, it's an argument for non-adaptive mechanisms opening up new evolutionary pathways that wouldn't have been there before," Lynch said. "It's those first little nicks getting into the protein armor that essentially open up a new selective environment."

To confirm that the accumulation of structural flaws in proteins preceded, rather than resulted from, the formation of complexes, Fernández and Lynch turned to a natural experiment. Some bacterial species have two types of populations: communities that live inside other organisms and larger populations living free in the environment. When orthologous proteins were compared between these two populations, the same pattern emerged – proteins from the smaller populations were more flawed than those from the free-living bacteria of the same species.

Despite these accidental benefits, the accumulation of too many structural flaws can be dangerous to an organism. When highly reactive proteins such as prions, amyloid-beta, or tau are too sticky, they can clump into aggregates that kill cells and cause diseases such as Alzheimer's and encephalopathy.

The implication that complexity initially arose by accident may be provocative within the field of evolutionary biology, the authors said. The discovery that flawed proteins are more likely to form complexes could also revolutionize the growing field of bioengineering, where the tools of evolution are used to create stronger, self-assembling, or self-reparing materials.

"Natural designs are often one notch more sophisticated than the best engineering," Fernández said. "This is another example: Nature doesn't change the molecular machinery, but somehow it tinkers with it in subtle ways through the wrapping."

More information: "Nonadaptive origins of interactome complexity," *Nature*, May 18 2011. doi: 10.1038/nature09992

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