'Selective promiscuity,' chaperones, and the secrets of cellular health

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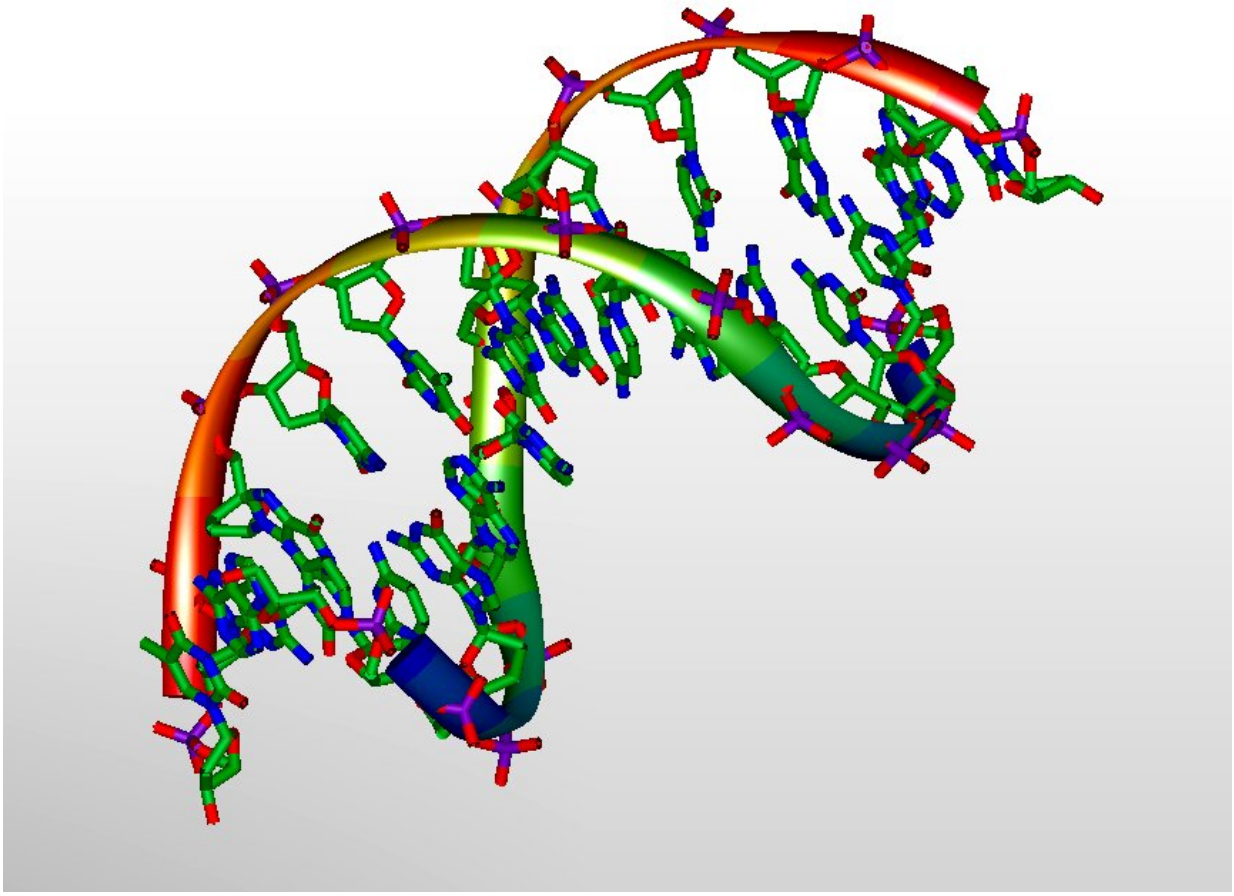

3D-model of DNA. Credit: Michael Ströck/Wikimedia/ GNU Free Documentation License

A team of researchers at the University of Massachusetts Amherst has announced a major new advance in understanding how our genetic information eventually translates into functional proteins—one of the building blocks of human life. The research, recently published in the *Proceedings of the National Academy of Sciences (PNAS)*, elucidates how chaperones display "selective promiscuity" for the specific proteins—their "clients"—they serve. This property enables them to play an essential role in maintaining healthy cells and is a step forward in understanding the origins of a host of human illnesses, from cancer to ALS.

There are four "letters" in the linear DNA code: A, C, G and T. Through the complex processes of transcription, followed by protein synthesis and finally protein folding, those four two-dimensional letters turn into a 20-letter three-dimensional recipe for proteins. Most of the time, this process works flawlessly, and our cells can build and reproduce themselves smoothly. But when something goes awry, the results can be catastrophic. Luckily, cells rely on a rigorous quality control to offset the devastating consequences.

The protein folding process, during which a chain of amino acids assumes its final shape as a protein, can be especially fraught. Researchers have long known that special molecules called chaperones help shepherd the protein into its final, correct shape. These "chaperones" can figure out which proteins are at risk of being deformed and can then lend that protein additional help. But how exactly they do their work has been poorly understood: "The chaperones do some kind of magic," says Alexandra Pozhidaeva, co-lead author of the paper who contributed to this study as a postdoctoral research associate at UMass Amherst and is currently a postdoctoral fellow at UConn Health. "What we've done is to reveal the mechanics behind the trick."

The trick is that though there are tens of thousands of different proteins

in our cells, each with a different shape and function, there are far fewer chaperones. "How is it," asks Lila Gierasch, Distinguished Professor of biochemistry and molecular biology at UMass Amherst and the paper's senior author, "that the same chaperones can help many different proteins?"

The answer lies in what the authors call the chaperones' "selective promiscuity."

The team relied on the cutting-edge, in-house resources of UMass Amherst's Institute for Applied Life Sciences for a novel combination of X-ray crystallography, which yields an incredibly detailed high-resolution but static snapshot of the chaperone's interaction with its protein client, and nuclear magnetic resonance, which can capture a fuller, more dynamic picture of this complex process. The team focused their efforts on a specific chaperone family known as the Hsp70s. Hsp70s, according to co-lead author Rachel Jensen, a UMass undergraduate at the time she conducted this research and now a graduate student at Berkeley, are among the most important of chaperones because "they carry out a wide range of critical roles within the cell and help execute many crucial cellular functions."

Whereas previous researchers used artificially shortened protein chains, the team used much longer chains to study how Hsp70's interaction with their clients. "We studied a much more complex system," says Eugenia Clerico, co-lead author and research professor of biochemistry and molecular biology at UMass. "We were able to study in the lab something that mimics what happens in our bodies."

What they discovered is that Hsp70s are both promiscuous—they can service many different proteins—but also selective: the range of proteins they can work with is limited. Additionally, Hsp70s "read" ambidextrously: They can identify which protein chains to help by

reading their sequences either from left to right, or right to left.

Not only is this breakthrough an advance in our understanding of how cells stay healthy, it has real-world applications. "Hsp70s," says Gierasch, "are involved in so many pathological diseases, from cancer to Alzheimer's, and host Hsp70s are exploited by parasites and viruses. Understanding how Hsp70s work can help us develop therapeutic strategies against these terrible diseases."

More information: Eugenia M. Clerico et al, Selective promiscuity in the binding of E. coli Hsp70 to an unfolded protein, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2016962118

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