Unlocking mystery of protein function

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What makes the body of a person or any other organism work can for the most part be summed up in a word: proteins.

These big molecules carry out almost all processes in living organisms, including moving other molecules from one place to another, replicating DNA, conveying genetic information from genes to cells, controlling immune response, driving metabolism and building muscle. Not all protein molecules are created equal, though, and some are better understood than others.

Now, a team of scientists led by a Johns Hopkins University biologist has cracked a key part of the mystery surrounding proteins that emerged as a distinct type less than 30 years ago. The finding reported in the online journal *eLife* could eventually lead to treatments for diseases that range from cancer to neurological disorders.

Vincent Hilser, professor and chair of the Johns Hopkins Department of Biology, said it's not possible to say when this new research will translate into improved treatments, "but what is clear is understanding how these things work is a critical step toward that."

These so-called "intrinsically disordered proteins" do not look like the more familiar type, but they make up about 40 percent of all proteins. Perhaps more important, they constitute the majority of proteins involved in the process called "transcription." That's how the instructions in genetic code are conveyed to cells and ultimately body tissues.

It is not clear exactly how errors in transcription affect human health, but it is known that these errors are involved in most cancers, Hilser said.

"It's probably going to be the case that to understand many, if not most, cancers, you're going to have to understand disorder," he said, meaning disordered proteins.

Until the early 1990s, scientists only knew of "structured" proteins, existing as unique shapes that respond when a regulator molecule binds to them, changing their shape and controlling their function. These protein molecules have been compared to origami creations folded into a particular shape.

Anything showing up in experiments that did not fit that profile was often dismissed as some problem with the experiment, or an anomalous form that was not biologically significant.

These outliers have since been recognized as a legitimate form of protein, although given a somewhat disparaging name. They don't fold up, they don't assume any unique shape at all other than strands of "spaghetti," as Hilser puts it. Hence the "disorder" in the name, as opposed to "structured" proteins - and part of the mystery.

If the structure is the mark of the regulating molecule doing its work - determining protein activity and function - then what to make of proteins that do not do that? What controls the activities of these shapeless strands?

The scientists, nine from Johns Hopkins and one from the University of Houston, set out to answer the question. They chose for their study a disordered protein taken from human cells called glucocorticoid receptor, which regulates genes that control, among other functions, metabolism and immune system response.

By manipulating segments of the protein in the lab, they were able to show how one portion acts on another, and that the disordered protein creates versions of itself to act almost in place of regulator molecules that govern its activity. The disordered protein uses an activation-repression dynamic between sections within the disordered chain to regulate its own activities and those of other proteins.

"Our work uncovered the language of how these spaghetti pieces communicate," Hilser said. "We showed that those pieces of spaghetti interact with each other sort of like attracting and repulsing magnets, creating a kind of 'tug-of-war,' and that the body can make different versions of the protein to tune which part wins the tug of war."

Yet to be explained, he said, is how the interactions among these proteins and the sub-sections happen and how all this can ultimately be used to treat disorders that emerge when things go awry with these molecules central to almost all life function.

More information: Jing Li et al, Genetically tunable frustration controls allostery in an intrinsically disordered transcription factor, *eLife* (2017). DOI: 10.7554/eLife.30688

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