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Commentary

Changing Peptides Sequence in Globular Proteins

Robert Saine*

Department of Biochemistry, University of Cambridge, Cambridge, UK

DESCRIPTION

Binding of intrinsically disordered proteins to globular proteins may necessitate motif folding into helices. These interactions provide therapeutic opportunities, but modulating them with small molecules is difficult because they bury large surfaces. Linear peptides with key binding residues can be targeted to globular proteins when they form stable helices, which in most cases require chemical modification. They present rules for designing peptides that fold into single helices rather than polyglutamine helices by concatenating glutamine side chain to main chain hydrogen bonds recently discovered in polyglutamine helices.

The resulting peptides are uncharged, contain only natural amino acids, and can have their sequences optimized to interact with specific targets. Their findings provide design rules for obtaining single helices, which can be used in protein engineering and drug design. Proteins are essential components of biology because they perform a wide range of essential functions, from gene regulation to enzymatic catalysis, where their ability to specifically interact with other biomolecules is critical. In pharmacology, inhibiting their interactions with drug like small molecules is a common method for modulating biological functions that are relevant to disease.

When another protein is the binding partner, the binding interfaces are usually flat and extended, making it difficult to inhibit the interactions with small molecules, and it is generally preferable to target them with antibodies. Nonetheless, despite recent advances in intracellular antibody delivery, their clinical applications have been limited to targeting extracellular proteins, emphasizing the need for the development of new molecular tools to inhibit intracellular protein interactions.

Peptides have some of the benefits of small molecules, such as ease of synthesis, as well as some of the benefits of antibodies, such as their relatively large size. As a result, peptides have a high potential for pharmacological applications as modulators of protein-protein interactions. Protein-protein interactions with one partner in a helical conformation are especially common and amenable to inhibition by peptides: an excised linear peptide containing a suitable sequence can, in theory, inhibit the interaction if it can bind to its partner with high affinity.

Linear peptides, on the other hand, have a low proclivity to fold into stable helices, and the entropic cost of folding reduces both their affinity for their targets and their stability against proteolytic degradation, highlighting the need for new tools to stabilize their helical conformation. Protein aggregation is a major barrier to using proteins at concentrations far above those for which evolutionary selection has shaped them. Indeed, the global correlation between cellular abundance and protein solubility strongly suggests that proteins are operating at the limit of their solubility.

It follows that using a protein at higher than natural concentrations necessitates adaptation of its primary sequence, but it is unclear how much room for improvement natural sequences have and how many mutations are required for significant improvements. Furthermore, the fact that protein abundances are more conserved than mRNA levels may indicate a solubility deadlock for many protein sequences, limiting the scope for artificial protein improvement. Proteins are responsible for the majority of the complex biological processes required to sustain life. These functions frequently involve motions involving conformational dynamics, which are important in enzyme catalysis, allosteric regulation, and molecular recognition.

Despite the demonstrated importance of dynamics for protein function, the relationship between protein sequence and dynamics is poorly understood, and epistasis caused by the ruggedness of the protein energy landscape complicates efforts to study how sequence elements contribute to dynamics and thus function in natural proteins. Evolutionary studies have made progress toward this goal, with key findings demonstrating that novel protein functions can arise from new dynamic regimes that reorganize functional sites.

Correspondence to: Robert Saine, Department of Biochemistry, University of Cambridge, Cambridge, UK, E-mail: robertsaine@cam.uk

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