Modulation of Cell Signaling with Synthetic Proteins

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Abstract

Affinity reagents that target and modulate proteins are of crucial importance for both basic research and therapeutic development. To date, antibodies derived by animal immunization have been the dominant source of affinity reagents, but in recent years, research in protein engineering has given rise to a new wave of technologies that promise to transform the field. "Synthetic antibodies" use man-made antigen-binding sites and thus circumvent the need for immune repertoires. We have developed simple synthetic antibodies that use a single human framework and limited chemical diversity in restricted regions of the antigen-binding site. Moreover, the use of synthetically designed libraries enables the use of alternative scaffolds for applications beyond the reach of the antibody framework. In particular, we have designed libraries of ubiquitin variants that can be used to inhibit or activiate virtually any of the hundreds of ligase and deubiquitinating enzymes in the ubiquitin system. These ubiquitin variants are adapted for intracelluar function, and thus, they can be introduced into cells to probe function in a living cellular context. In addition, we have developed small, optimized scaffolds that function like antibodies but are amenable to full chemical synthesis, thus enabling the incorporation of non-natural amino acids. The power of the technology has been demonstrated by the development of potent protein inhibitors composed entirely of D-amino acids. In sum, these advances in the design of synthetic binding proteins extend the applications for affinity reagents well beyond the range of natural antibodies and this should have a transformative effect on many areas of biological research.