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Targeted destruction

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Ubiquitination targets proteins for degradation by the sequential attachment of ubiquitin to lysine residues within the substrate molecule. Target specificity is determined by the E3 ubiquitin-protein ligases. One class of E3s consists of the heterotetrameric Skp1-Cullin-F box (SCF) complexes. The mammalian F-box protein β-TRCP directs the degradation of IκBα by binding to a phosphorylated decapeptide site within the IκBα molecule.

In the July 17 Proceedings of the National Academy of Sciences, Sakamoto *et al.* describe a method for artificially controlling protein degradation by exploiting characteristics of the SCFβ-TRCP ubiquitin ligase (*Proc Natl Acad Sci USA* 2001, **98:**8554-8559). To test the system they chose to target the methionine aminopeptidase (MetAP-2) protein which is bound by the angiogenesis inhibitor ovalicin (OVA). They synthesized an artificial compound called Protac-1 (proteolysis-targeting chimeric protein 1) which contained the IκBα phosphopeptide fused to ovalicin. They showed that Protac-1 can bind to MetAP-2 via the OVA moiety, and recruit it to the SCFβ-TRCP complex, leading to its ubiquitination and subsequent degradation by the proteosome. The authors suggest that synthetic Protacs will serve as useful research tools and therapeutic agents to target ubiquitin-dependent degradation of a chosen target protein.

References

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