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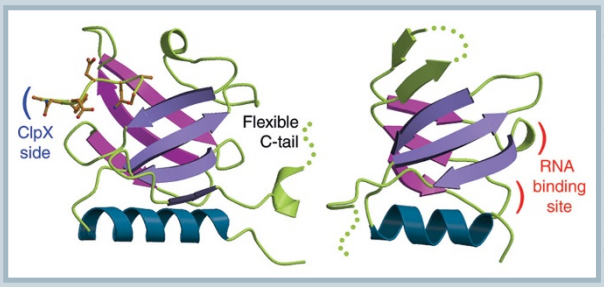
Tag, you're degraded

Protein degradation in the cytosol is a regulated process. The destruction of unwanted polypeptides, whether folded or unfolded, is mostly performed by large proteolytic machinery, but how does it know which proteins must be annihilated? It identifies these substrates by the tags they carry.

Eukaryotes most often attach a 76-residue ubiquitin to the free amino groups on a protein, a modification that potentially marks the protein for destruction by the proteosome. In contrast, eubacteria add an 11-residue peptide, the SsrA tag, to the C terminus of the protein that directs the protein to specific multisubunit protease complexes, ClpXP or ClpAP. The tag, which is encoded by an RNA molecule with properties of both transfer and messenger RNA, is coupled to the protein when the ribosome stalls. Protein factors modulate the recognition of the SsrA tag by the appropriate protease complex. For example, in *Escherichia coli*, stringent starvation protein B (SspB) binds to the SsrA tag and enhances its recognition by ClpXP. In an effort to understand how the SspB binds the SsrA, Hyun Kyu Song and Michael Eck (*Mol. Cell* **12**, 75–86; 2003) determined the crystal structures of the protein alone and in complex with the 11-amino acid tag.

The most surprising aspect of the SspB structure (left ribbon diagram) is the topology. Despite the lack of sequence similarity to RNA binding proteins, the overall fold resembles that of a small nuclear ribonucleoprotein, Sm D2, and more distantly to a portion of the ribosome-associated protein L1. The structurally related regions are visually apparent when comparing the purple and pink strands and the blue helix of SspB (left) and Sm D2 (right). The structural similarity to RNA-binding proteins and the observation that SspB copurifies with ribosomes, suggests the possibility that SspB might recognize an RNA component of the ribosome. Comparison of SspB and Sm D2 structures suggests that recognition of the ribosomal RNA might occur through the β-turns located on the opposite side of the structure from the ClpX recognition face. In effect, SspB could link the protein synthesis and degradation machinery, and in so doing, this protein would promote the binding of ClpX to SsrA-tagged polypeptides before they are released into the cytoplasm to cause damage. Alternatively, if the SsrA and ribosomal RNA binding sites overlap, the interactions with the tagged polypeptide could release SspB from the ribosome. Identification of the exact site of RNA binding in SspB will be essential to determining if and how this protein binds to the ribosomal RNA.



Modified with permission from *Molecular Cell*.

The structure of the complex (left) of SspB with the SsrA tag (ball and stick) explains why SspB is crucial for the specific recognition of SsrA-marked proteins by the protease complex. ClpX recognizes the C-terminal three residues in the SsrA tag, which does not provide sufficient specificity for or result in efficient degradation of the tagged protein. In contrast, SspB binds the eight N-terminal amino acids of the tag, six of which make specific interactions with the protein. Hence, it is SspB that makes the necessary interactions with the SsrA-marked proteins that results in their degradation.

These structural results open the way to additional studies of how SspB associates with ClpX, as well as of the mechanisms by which SspB feeds the SsrA tag into the protease and if SspB, through a possible association with the ribosome, maintains the balance between protein degradation and synthesis.

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