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How is the human signal peptide recognized?

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Abstract

The crystal structure of human SRP54M from the signal recognition particle (SRP) reveals a homodimer interaction, which may be a model for the way signal sequences on nascent proteins recognize and activate the SRP.

Significance and context

The signal recognition particle (SRP) machinery performs three jobs in the cell: it captures an actively transcribing ribosome; links it to the endoplasmic reticulum (ER) membrane; and then threads the nascent protein chain into the ER for processing and transport. But the first capture step only happens when the nascent protein chain contains an amino-terminal signal sequence. No one knows exactly how signal sequences recognize and activate the SRP.In this paper, the authors describe the atomic-resolution structure of the M domain of human SRP54, a protein believed to bind the signal peptide directly. Clemons *et al*. use their new structure to propose detailed new models of signal peptide binding. They also compare and discuss models derived from a recent structure of the bacterial SRP54M homolog.

Key results

The structure of an SRP54M homodimer is solved. Representations of the Structure of the SRP54M homodimer and the Structure of the SRP54M monomer can be viewed online. The structure reveals that in this homodimer complex, the first β helix (called helix 1) of one monomer of SRP54M sticks like a finger into a deep binding pocket of the other monomer. The pocket binds helix 1 via hydrophobic and charge-charge interactions and by causing a (presumably favorable) kink in the helix. Clemons *et al*. propose that, *in vivo*, a nascent signal peptide would act as a similar finger, burrowing into the pocket of SRP54M in the same way. The authors also speculate that the helix 1 interaction could be used in autoregulation *in vivo*.

Conclusions

The authors compare their new structure with the previously published crystal structure of the *Thermus aquaticus* signal sequence binding subunit of the signal recognition particle, a bacterial SRP54M homolog. As Clemons *et al.* point out, there are major differences between the two. In the bacterial protein, helix 1 does not stick out like a finger into the next monomer. Instead, the dimer interaction is mediated by a loop, and the recognition pocket has a shallower shape. The bacterial structure, therefore, does not support the authors'model of signal peptide binding. This suggests three possibilities: first, the human or bacterial structure, or both, are artifacts and irrelevant to the biological situation; second, human and bacterial SRPs recognize signal peptides very differently; or third, human and bacterial SRPs recognize signal peptides by the same mechanism, but the two structures we have seen so far represent snapshots of different stages in the SRP functional cycle.

Reporter's comments

It is very tempting for Clemons *et al*. (and the rest of the field) to make models about signal-peptide binding from SRP54M homodimer structures. But at this stage no one has much external evidence to evaluate these models. For that, they will need atomic-resolution structures of SRP54M bound to a signal peptide, or they could make do with low-resolution spectroscopic experiments on SRP54M-signal peptide complexes in solution.

Table of links

Journal of Molecular Biology

Structure of the SRP54M homodimer

Structure of the SRP54M monomer

Thermus aquaticus signal sequence binding subunit of the signal recognition particle

References

1. Jr WM Clemons, Gowda K, Black SD, Ramakrishnan CZV: Crystal structure of the conserved subdomain of human protein SRP54M at 2.1Å resolution: evidence for the mechanism of signal peptide binding. J Mol Biol. 1999, 292: 697-705. 0022-2836