Ribosomal Crystallography Reveals Co-Translational Trafficking by Eubacterial Trigger Factor

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The correct folding of newly synthesized proteins is a vital process in all kingdoms of life. It is coordinated and concerted by a set of molecular chaperones that direct the folding of nascent proteins towards their final functional state. Nascent chains emerging out of the ribosomal tunnel are highly prone to aggregation and degradation. Consequently, chaperone activity is initiated during translation.

Trigger factor (TF), the first chaperone in bacteria to encounter the emerging nascent chain, binds to the large ribosomal subunit in the vicinity of the tunnel opening and forms a sheltered folding space. The 3.5Å crystal structure of the large ribosomal subunit of the eubacterium *Deinococcus radiodurans*, D50S, in complex with the TF binding domain (TFa) from *Deinococcus radiodurans*, reveals for the first time the molecular structure of **the entire** TFa bound to the bacterial ribosome. In comparison with structures of isolated TF/TFa molecules from different bacterial sources, the current structure displays a conformational change in the TFa domain that assures a degree of dynamic flexibility and may hint at mobility during early folding.

The signature part of TFa anchors on small exposed regions of ribosomal proteins L23 and L29 some 40Å away from the opening of the exit tunnel, in general agreement with the reported chimeric structure of the archaeal large ribosomal subunit (H50S) with the eubacterial TFa (Ferbitz et al., 2004). The chaperone TF does **not** exist in the archaeal kingdom, and therefore the similarity of its local interactions with both ribosomal systems highlights the high structural and sequence conservation of its contact region on the ribosome. Still, the archaeal ribosomal protein L23 lacks the sizable elongated loop, present in bacteria, which extends into the tunnel opening and can actively interact with the nascent protein passing through it. Our structure shows that TFa binds to two separate regions of L23 on both sides of the extended loop, thus linking the TF binding site with the ribosomal tunnel and enabling communication with the newly synthesized nascent chain.

Keywords: ribosome, chaperone, ribosomal tunnel