Isoleucyl-tRNA synthetase: one process, two ends

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Aminoacyl-tRNA synthetases (aaRS) are essential enzymes that establish the correct reading of the genetic code. Their role is to charge a tRNA molecule, containing a particular anticodon sequence, with the appropriate amino acid. To maintain translational fidelity it is important that the different members of this class of enzymes recognize their substrates with high specificity.

While the active sites of all aaRS can be divided into two conserved classes, tRNA recognition can dramatically deviate between homologues. The recognition of tRNA by isoleucyl-tRNA synthetase (ileRS) is particular interesting as it must distinguish between its cognate $tRNA^{Ile}$ and $tRNA^{Met}$ by the wobble position base. Our current understanding of how IleRS does this is based on the structure the *Staphylococcus aureus* (SA) enzyme in complex with tRNA. However sequence alignment suggests that the proposed mechanism of tRNA recognition by IleRS-SA is not present in all life forms, and that the anticodon binding domain (ACBD) has diverged at least once during evolution.

Analysis of the sequence of the ileRS from the gram negative bacterium *Thermus thermophilus* (TT) shows that it contains the alternative ACBD. The structure of this particular enzyme has previously been solved but unfortunately the last 200 C-terminal residues, representing 50% of the ACBD and 20% of the full length protein, could not be traced. We have identified a new crystallization condition for this enzyme, which gave rise to a single crystal that yielded a 2 Å dataset. The calculated electron density map was of sufficient quality to solve the structure of the entire protein. The new structure shows, as expected, that the ACBD of IleRS-TT is distinct from that of IleRS-SA. The ACBD of IleRS-TT is composed of the canonical alpha-helix bundle, present in all class I AaRS family members, but is followed by three distinct domains. Despite low sequence conservation, these domains appear to be structurally preserved in representative ileRS homologues found in all kingdoms of life.