Molecular basis of $tRNA^{His}$ guanylyltransferase

Eukaryotic $tRNA^{His}$ guanylyltransferase (Thg1) adds a guanylate (G_{-1}) to the 5' end of pre-$tRNA^{His}$. This additional G_{-1} provides the major identity element for histidyl-tRNA synthetase to recognize its cognate substrate $tRNA^{His}$ and differentiates $tRNA^{His}$ from the pool of tRNAs present in the cell. Interestingly, Thg1 is a structural homolog of canonical 5'-3' DNA polymerases in the catalytic core with no obvious conservation of the amino acid sequence, and its guanylylation is carried out as a reverse polymerization (3'-5'). In this study, we determined structure of Thg1-tRNA complex by X-ray crystallography. Thg1-tRNA complex consists of four Thg1 and two tRNA molecules. Each tRNA interacts with three Thg1 monomers and a domain of Thg1 (α5, α6, α7) in difference monomer plays dual recognition role for anticodon loop and acceptor stem of tRNA. Such interactions can be considered as the requirement for positioning tRNA, recognizing anticodon, and catalytic activation. Structural, biochemical, and phylogenetic data indicate that reverse polymerization appeared early in evolution and resembles a mirror image of the forward process.