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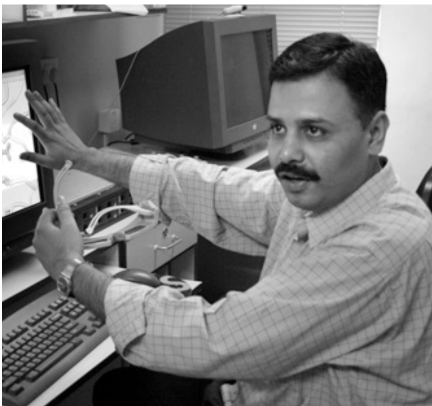
Mechanistic insights into proofreading during translation of the genetic code.



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Editing or proofreading domains of aminoacyl-tRNA synthetases (AaRSs) hydrolyze misaminoacylated-tRNAs thereby maintaining a high fidelity during translation. Archaeal threonyl-tRNA synthetases (ThrRSs) possess an editing domain that is unrelated to its eubacterial/eukaryotic counterparts. The domain bears a striking structural homology to D-aminoacyl-tRNA deacylases (DTDs), which remove D-amino acids charged on tRNA, that allowed us to propose a model for perpetuation of homochirality in proteins. Our studies showed that the ThrRS editing domain from *Pyrococcus abyssi* (Pab-NTD) does not use any specific side chains for catalysis but employs a RNA-assisted water mediated catalytic mechanism. Also, functional positioning of the substrate is the key for the catalysis in Pab-NTD rather than steric exclusion as proposed by the 'Double-sieve' model. The study presents a unique case of a proofreading enzyme where none of the side chains play any direct role either in catalysis or in substrate specificity in total contrast to the modern enzymes. I will also present some of our recent work in understanding the mechanistic basis of DTD, an absolute configuration specific enzyme, that removes D-amino acids erroneously coupled to transfer-RNAs. It reveals a chiral enforcement mechanism in proteins that might have played a crucial role in resisting D-amino acid invasion during the evolution of the translational machinery.