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Structures and mechanism of human glutaminyl cyclase, an enzyme possibly involved in Alzheimer's disease and osteoporosis

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N-terminal pyroglutamate (pGlu) formation from its glutaminyl (or glutamyl) precursor is required in the maturation of numerous bioactive peptides. The aberrant formation of pGlu may be related to several pathological processes, such as osteoporosis and amyloidotic diseases. This N-terminal cyclization reaction, once thought to proceed spontaneously, is greatly facilitated by the enzyme glutaminyl cyclase (QC). To probe this important but poorly understood modification, we have solved the crystal structures of human QC in free form and bound to a substrate and three imidazole-derived inhibitors. The structure reveals an α/β scaffold akin to that of two-zinc exopeptidases but with several insertions and deletions, particularly in the active-site region. A single active-site zinc ion is ligated with three conserved residues and one water molecule, which is replaced by an imidazole nitrogen upon binding of the inhibitors. Together with structural and kinetic analyses of several active-site-mutant enzymes, a catalysis mechanism of the formation of protein N-terminal pGlu is proposed. Our results provide a structural basis for the rational design of inhibitors against QC-associated disorders.

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The antibiotic kasugamycin mimics mRNA nucleotides to destabilize tRNA binding and inhibit canonical translation initiation

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Kasugamycin (Ksg) specifically inhibits translation initiation of canonical, but not of leaderless mRNAs. The mechanism of Ksg inhibition is thought to occur via direct competition with initiator tRNA. The 3.3-Angstrom crystal structure of Ksg bound to the 30S ribosomal subunit presented here provides a structural description of two Ksg binding sites, as well as the basis to understand Ksg resistance. Surprisingly, neither binding position overlaps with peptidyl-tRNA, instead Ksg mimics codon nucleotides at the ribosomal P and E sites by binding within the path of mRNA. Coupled with biochemical experiments, our results suggest that Ksg indirectly inhibits peptidyl-tRNA binding through perturbation of the mRNA-tRNA codon-anticodon interaction during 30S canonical initiation. In contrast, for 70S-type initiation of leaderless mRNA, the overlap between the mRNA and Ksg is reduced and the binding of tRNA is further stabilized by the presence of the 50S subunit, minimizing Ksg efficacy.