

Crystal structure of human glutaminyl cyclase

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Introduction

N-terminal pyroglutamate (pGlu) formation from its glutaminyl (or glutamyl) precursor is required in the maturation of numerous bioactive neuropeptides, hormones, and cytokines during the maturation in their secretory pathway. The aberrant formation of pGlu may be related to several pathological processes, such as osteoporosis, rheumatoid arthritis 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 expressed human QC in *E. coli* cells and determined the crystal structure of the protein at 1.66-Å resolution.

Results and Discussion

The structure of the enzyme reveals a globular mixed α/β fold with a size of 63 x 58 x 41 Å³ (Fig. 1). It has an open-sandwich topology comprising a central six-stranded β -sheet surrounded by two and six α -helices on opposite sides and flanked by two α -helices at one edge of the β -sheet. This twisted β -sheet is formed by two antiparallel and four parallel strands, constituting the hydrophobic core of the molecule. The coil and loop regions of the structure represent 42% of the total residues; about half of them are major components of the active site.

The active site of the enzyme is mainly created by six loops. The catalytic pocket is near the C-terminal edge of the central parallel strands. It is relatively narrow but accessible to the bulk solvent by means of a solvent channel. The single zinc ion of human QC lies at the bottom of the active-site pocket and is tetrahedrally coordinated to three conserved residues and one water molecule. Interestingly, the active site of the enzyme displays alternate conformations due to the different indole orientations of Trp-207. These results provide a structural basis for the rational design of inhibitors against QC-associated disorders.

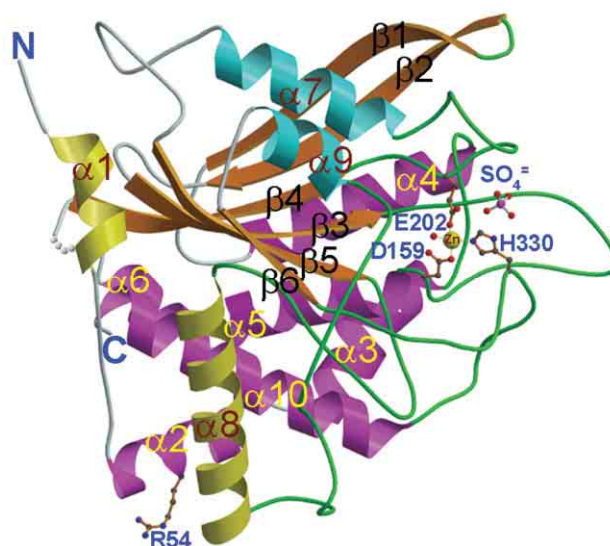


Fig. 1 A ribbon diagram of the human QC structure. The zinc-coordinated residues and Arg-54 (genetic mutation to Trp residue occurred frequently in adult women with osteoporosis) are depicted with a ball-and-stick model.

Reference

- [1] K.-F. Huang et al., *Protein Expr. Purif.* 43, 65 (2005).
- [2] K.-F. Huang et al., *Proc. Natl. Acad. Sci. USA.* 102, 13117 (2005).

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