Structure and Inhibition Mode of Protein I^c in Complex with Carboxypeptidase Y

Yasuo Hata[a], Minoru Hayashida[a], Tomomi Fujii[a], Joji Mima[b], Rikimaru Hayashi[b], Mitsuyoshi Ueda[b], [a]*Institute for Chemical Research,* [b]*Graduate School of Agriculture, Kyoto University, Kyoto, Japan*. E-mail: hata@scl.kyoto-u.ac.jp

Carboxypeptidase Y (CPY) inhibitor I^c from the yeast, consisting of 204 amino acid residues, belongs to the phosphatidylethanolamine-binding protein (PEBP) family. The 2.7 Å crystal structure of the I^c-CPY complex has been solved by molecular replacement [1, 2].

The structure of I^c consists of a major β-type domain and an N-terminal helical segment. I^c has two CPY-binding sites: the N-terminal inhibitory reactive site and the secondary CPY-binding site which interact with the S1 substrate-binding site of CPY and the hydrophobic surface flanked by the active site of the enzyme, respectively. I^c also has the ligand-binding site, the putative binding site of the polar head group of phospholipid, which is conserved among PEBPs and accommodates a sulfate ion in the crystal structure.

Along with the complex structure of I^c, its mutational analyses for inhibitory activity and binding to CPY demonstrate that the N-terminal inhibitory reactive site is essential for the complex formation with CPY as well as enzyme inhibition and that the I^c binding to CPY forms a novel mode of the proteinase-protein inhibitor interaction. The unique binding mode of Ic toward CPY gives insights into not only the inhibitory mechanism of PEBPs toward serine proteinases but also the biological functions of I^c belonging to the PEBP family.

[1] Mima J., Hayashida M., Fujii T., Hata Y., Hayashi R., Ueda M., *Acta Crystallog. Sect. D,* 2004, **60**, 1622. [2] Mima J., Hayashida M., Fujii T., Narita Y., Hayashi R., Ueda M., Hata Y., *J. Mol. Biol.*, 2005, **346**, 1323.

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