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Crystal Structure of Human Urokinase Complexed with a Cyclic Peptidyl Inhibitor, Upain-1. Mingdong Huang, Gengxiang Zhao, Cai Yuan, Chuanbing Bian, Troels Wind, Peter Andreasen, Xiaoming Ye, Zixian Huang., State Key Lab on Structural Chemistry, Fujian Institute of Research on the Structure of Matter, 155 Yang Qiao Xi Lu, Fuzhou FUJIAN 350002, CHINA.

The urokinase-type plasminogen activator (uPA) is implicated in tumor cell migration, invasion and metastasis. The inhibition of uPA activity represents a promising mechanism for anti-tumor therapy. The structure analysis of protease-inhibitor complexes helps understanding the mechanism of inhibitor action and the design of inhibitors. A cyclic peptidyl inhibitor (CSWRGLENHRMC, upain-1) was identified (Hansen et al. *J Biol Chem* **280**, 38424-37) as an effective and highly specific uPA inhibtor with a *Ki* of 500 nM. We determined the crystal structure of uPA in complex with upain-1 at 2.14Å resolution. The structure reveals that the upain-1 binds with the S_1 and S_2 pockets of uPA, and with the 60-loop of uPA that renders it specific for uPA. The oxyanion hole of uPA was occupied by the Glu7 of upain-1, forcing upain-1 to behave as an inhibitor rather than a substrate of uPA. This study provides mechanistic information about the enzyme-inhibitor interaction, and a new pharmacophore for the design of specific uPA inhibitor.