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Efforts in the Crystallization and Structure Determination of a Ternary Complex of Human Urokinase and its Receptor. Qing Huai, Yongdong Li, Cai Yuan, Chuanbing Bian, Liqing Chen, Mingdong Huang., Div. of Haemostasis and Thrombosis, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 USA.

Urokinase plasminogen activator (uPA) and its cellular receptor (uPAR) have received extensive study as one of the two primary endogenous systems that mediate plasminogen activation. The uPA binds to uPAR at high affinity (K_d of 0.1–1nM), thus localizing the generation of plasmin from plasminogen onto pericellular regions of a variety of cells. uPA-uPAR binding is also involved in other general cellular functions and in subsequent diverse pathophysiological processes such as tissue remodeling, arteriosclerosis, tumorigenesis, and tumor metastasis. uPAR is heavily glycosylated and tends to oligomerize, posing difficulty for structural study. Here we report the crystal structure of soluble uPAR complexed with the urokinase amino terminal fragment and an anti-receptor antibody at 1.9Å (Huai, *et al.*, *Science* 2006; 311:659). suPAR is composed of three consecutive domains that form a concave shape with a diameter of about 52 Å and a height of 27 Å. At the center of teacup and surrounded by three suPAR domain is a cone shape cavity with wide opening (25 Å) and large depth (14 Å). All three domains of uPAR and two domains of uPA work in cooperation yielding high affinity uPA-uPAR binding. The structure provides insight into the flexibility of urokinase receptor that enables its interaction with a wide variety of ligands and a basis for design *de novo* uPA-uPAR antagonists that will be important for anti-tumor metastasis therapy.