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Crystal structure and cellular functions of uPAR dimer

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Receptor dimerization of urokinase-type plasminogen activator receptor (uPAR) was previously identified at protein level and on cell surface. Recently, a dimeric form of mouse uPAR isoform 2 was proposed to induce kidney disease. Here, we report the crystal structure of human uPAR dimer at 2.96 Å. The structure reveals enormous conformational changes of the dimer compared to the monomeric structure: D1 of uPAR opens up into a large expanded ring that captures a β-hairpin loop of a neighboring uPAR to form an expanded β-sheet, leading to an elongated, highly intertwined dimeric uPAR. Based on the structure, we identify E49P as a mutation promoting dimer formation. The mutation increases receptor binding to the amino terminal fragment of its primary ligand uPA, induces the receptor to distribute to the basal membrane, promotes cell proliferation, and alters cell morphology via β1 integrin signaling. These results reveal the structural basis for uPAR dimerization, its effect on cellular functions, and provide a basis to further study this multifunctional receptor.

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