Interplay of human tissue kallikrein 4 (hK4) with the plasminogen activation system: hK4 regulates the structure and functions of the urokinase-type plasminogen activator receptor (uPAR).

The plasminogen activation system is involved in cancer progression and metastasis. Among other proteolytic factors, it includes the serine protease urokinase-type plasminogen activator (uPA) and its three-domain (D1D2D3) receptor uPAR (CD87), which focuses plasminogen activation to the cell surface. The function of uPAR is regulated in part through shedding of domain D1 by proteases, e.g., uPA itself or plasmin. Human tissue kallikrein 4 (hK4), which is highly expressed in prostate and ovarian tumor tissue, was previously shown to cleave and activate the pro-enzyme forms of prostate-specific antigen (PSA, tissue kallikrein hK3) and uPA. Here we demonstrate that uPAR is also a target for hK4, being cleaved in the D1-D2 linker sequence and, to a lesser extent, in its D3 juxtamembrane domain. hK4 may thus modulate the tumor-associated uPA/uPAR-system activity by either activating the pro-enzyme form of uPA or cleaving the cell surface-associated uPA receptor.