

Critical Structural Determinants of Maspin in Suppression of Prostate Cancer

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Maspin is a 42 kDa non-inhibitory serine protease inhibitor (serpin), also known as SERPIN B5. Maspin inhibits prostate cancer (PCa) cell osteolysis, growth, and angiogenesis in the bone. Maspin specifically interacts with the pro-urokinase type plasminogen activator (pro-uPA) and its receptor (uPAR) complex on the surface of PCa cells, thereby inhibiting extracellular proteolysis, ECM degradation, and cellular detachment. Unique characteristics of maspin include: (i) maspin is an epithelial specific serpin; (ii) both the expression level and subcellular localization of maspin are differentially regulated in tumor progression; and (iii) the molecular partnerships of maspin deviate significantly from other members in the serpin family.

In order to determine what structural motifs/domains of maspin are important for the complex molecular interactions and biological activities, we used Adenoviral system to deliver wild type maspin (wt) and five rational maspin mutants to PCa DU145 cells expressing low endogenous maspin. Different maspin mutants had different pattern of interaction with pro-uPA/uPAR complex on the cell surface compared to the wt maspin and no maspin at all (empty Adenovirus). Based on the immunoprecipitation data different maspin mutants have different ability to interact with known maspin partners, Hsp90, HDAC1, and GST π . C-terminal truncation mutants interact readily with Hsp90, molecular chaperone, and form dimers. Here, we also show the first evidence that maspin point mutant in -KDEL motif (ER retention signal) was readily secreted. In conclusion, we learned that the C-terminus of maspin is necessary for proper folding, expression, and interaction of maspin with its cytoplasmic and periplasmic targets.