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Extract from *Serenoa repens* Suppresses the Invasion Activity of Human Urological Cancer Cells by Inhibiting Urokinase-Type Plasminogen Activator.

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We used three human urological cancer cell lines, PC-3, LNCaP, and SKRC-1, to investigate the effects of the extract from *Serena repens* (Palmae) on tumor cell invasion. The invasion activity of PC-3 cells into Matrigel was effectively suppressed by the extract at the concentration range of 1 – 10 μg/mL, while that of LNCaP and SKRC-1 cells was unaffected by the extract. The extract did not affect the viability, adhesion ability, or motility of the cell lines. uPA is more strongly expressed on the membrane fraction of PC-3 cells than that of LNCaP or SKRC-1 cells. The purified uPA activity is inhibited by the extract from *S. repens* in a dose-dependent manner. These data suggest that the extract from *S. repens* specifically inhibits the uPA activity which is necessary for tumor cell invasion and may therefore be useful for the therapeutic treatment of prostate cancer.

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Decreases of Metallothionein and Aminopeptidase N in Renal Cancer Tissues.

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Sixteen kidney samples (clear cell RCC) were investigated to determine the differences in the protein components between renal cancer and surrounding tissues, using HPLC analysis. The metallothionein (MT) and zinc levels were consistently lower in renal cancer tissues compared with in surrounding tissues. An immunohistochemical study confirmed that the expression of MT in renal cancer tissues was lower that that in adjacent normal tissues. The Activities of aminopeptidases (APs) were significantly decreased in renal cancer tissues compared with in adjacent normal tissues. An immunohistochemical study and Western blot analysis confirmed that the expression of AP-N in renal cancer tissues was also lower than in adjacent normal tissues. These results suggest that the immunohistochemical detection of MT and AP-N could provide useful information as a pathological diagnostic tool for classifying renal cancer and surrounding tissues.

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Inhibition of Aminopeptidase N (AP-N) and Urokinase-Type Plasminogen Activator (uPA) by Zinc Suppresses the Invasion Activity in Human Urological Cancer Cells.

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The effects of zinc on the invasion activity of human prostate and renal cancer cell lines, PC-3, LNCaP, and SKRC-1, were investigate *in vitro* and were compared with specific protease inhibitors for MMPs, uPA, and AP-N, respectively. The invasion activity of PC-3 cells was effectively suppressed by zinc and by all protease inhibitors in a dose-dependent mannar. The invasion activity of LNCaP cells was almost unaffected by these inhibitors. In SKRC-1 cells, the invasion activity was strongly suppressed by MP03, although a moderate inhibition by zinc and bestatin was observed. The purified AP-N activity was strongly inhibited by zinc at a concentration similar to that suppressing the invasion activity of PC-3 cells and the purified uPA acivity was also inhibited by zinc. These results suggest that zinc probably participates in the regulation of cell invasion in human prostate cancer.

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Aminopeptidase N Regulated by Zinc in Human Prostate Participates in Tumor Cell Invasion.

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Aminopeptidase N (AP-N) degrades collagen type IV and is proposed to play a role in tumor invasion. However, the precise functions of AP-N in tumor cells and the relationship of AP-N to prostate cancer remains unclear. In our study, we examined a possible role for zinc in the regulation of AP-N enzymatic activity in relation to tumor cell invasion in human prostate. AP-N purified from human prostate was irreversibly inhibited by low concentration of zinc (ki=11.2μM) and bestatin. When the effects of zinc and bestatin on invasion of PC-3 cells were investigated *in vitro*, zinc and bestatin effectively suppressed cell invasion into Matrigel at the concentration range of 50 – 100 μM. These results strongly suggest that the suppression of PC-3 cell invasion by zinc is based on the inhibition of AP-N activity by zinc. AP-N was found to be located at the cytoplasmic membranes of prostate gland epithelial cells and to be expressed more in prostate cancer, suggesting that AP-N is potentially a good histological markers of prostate cancer.