DEGRADOME-WIDE SCREENING IDENTIFIED CALPAIN-2 AS A PRO-INVASIVE FACTOR IN PROSTATE CANCER

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Proteases play a pivotal role in the tumor microenvironment contributing, e.g., to tumor progression, invasion, and metastasis. Altered protease expression is a hallmark of cancer and dysregulated protease activity has also been implicated in prostate cancer. Of the almost 500 active proteases in human degradome, nearly half are expressed in the prostate.

We have performed a degradome-wide RNAi screen and identified over 30 proteases to affect cell growth and invasion of PC-3 prostate cancer cell spheroids in three-dimensional environment. The strongest hit of the screen was calpain-2.

In validation studies, siRNAs targeting calpain-1 and calpain-2, as well as calpain inhibitors all reduced formation of invasive PC-3 prostate cancer cell spheroids, whereas knock-down of endogenous calpain inhibitor, calpastatin, increased their size. Using a tumor explant culture on human benign leiomyoma tissue, we showed that calpain inhibitor reduces invasion from patient-derived tumor explants into myoma tissue. To further validate our findings in a system better recapitulating the tumor microenvironment, we have developed patient-derived extracellular matrix preparations from benign and cancerous prostate tissue and pelvic lymph nodes of prostate cancer patients.

Calpain-2 expression in prostate cancer tissues was studied using immunohistochemistry. In grade group 2-4 tumors, high calpain-2 expression was associated with metastatic progression after radical prostatectomy.

Our results support the role of proteases in prostate cancer progression and highlight the role of calpain-2 and in prostate cancer invasiveness, as previously reported.