

# 学 位 論 文 の 要 約

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<p>主論文の題名</p> <p>Fibroblasts prolong serum prostate-specific antigen decline after androgen deprivation therapy in prostate cancer (前立腺線維芽細胞は前立腺癌アンドロゲン除去療法後の血中 PSA 低下を緩徐にする)</p> <p>Takeshi Sasaki, Kenichiro Ishii, Yoichi Iwamoto, Manabu Kato, Manabu Miki, Hideki Kanda, Kiminobu Arima, Taizo Shiraishi and Yoshiki Sugimura</p> <p>Laboratory Investigation (2016) 96, 338-349 doi:10.1038/labinvest.2015.136 published online 7 December 2015</p> <p>主論文の要約</p> <p>Introduction</p> <p>Prostate-specific antigen (PSA) is currently the most useful biomarker for the detection of prostate cancer (PCa). Measurement of serum PSA levels has facilitated changes in all aspects of PCa management. Serum PSA levels are generally proportional to tumor volume and the clinical stage of the disease. PSA is used to evaluate the effects of androgen deprivation therapy (ADT).</p> <p>Background</p> <p>Intuitively, most urologists expect that a more rapid PSA decline in response to ADT would be positively associated with extended survival. We have recently reported interesting and counterintuitive clinical evidence. Prolonged gradual serum PSA decline after ADT is strongly associated with favorable prognosis in PCa patients, however, the mechanism remains unknown. Tumor stroma surrounding cancer cells is enriched in fibroblasts secreting AR-stimulating factors. we hypothesized that the AR-independent and heterogeneous characteristics of fibroblasts in PCa tissue could regulate the AR dependence of</p>			

PCa cells, which is related to the decline in serum PSA after ADT.

### Objectives

We investigated the role of fibroblasts in serum PSA decline after ADT.

### Methods

We performed in vitro experiments using androgen-sensitive, androgen receptor (AR)-positive prostate epithelial cell lines (LNCaP, 22Rv1, and RWPE-1 cells), commercially available prostate stromal cells (PrSC), and primary cultures of prostate fibroblasts (pcPrFs).

### Results

In LNCaP and 22Rv1 cells, PSA production was increased by co-culture with fibroblasts under androgen-deprived conditions. In an in vivo model using LNCaP cells, serum PSA declined rapidly after ADT becoming undetectable within 14 days in mice inoculated with LNCaP cells alone. In contrast, when LNCaP cells were co-inoculated with fibroblasts, serum PSA levels were still high on 14 days post ADT and did not drop to undetectable levels until 21 days post ADT. Tumor volumes and Ki67 labeling indices were not altered between days 14 and 21 post ADT in mice inoculated with LNCaP cells; however, those in mice inoculated with LNCaP cells plus fibroblasts decreased gradually. PSA protein was detected in all tumors on 21 days post ADT by immunohistochemical staining. Microvessel densities were higher on 14 days post ADT for tumors from mice inoculated with LNCaP cells plus fibroblasts as compared with LNCaP cells alone.

### Conclusions

In summary, co-inoculation of fibroblasts with LNCaP cells prolonged serum PSA decline after ADT and enhanced the efficacy of ADT. Prolonged serum PSA decline may indicate the presence of protective fibroblasts that preserve the AR dependence of PCa cells, improving treatment efficacy.