学 位 論 文 の 要 約

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主論文の題名

Fibroblast-derived exosomal microRNA regulates NKX3-1 expression in androgen-sensitive, androgen receptor-dependent prostate cancer cells

（線維芽細胞由来エクソソーム microRNA はアンドロゲン感受性、アンドロゲン受容体依存性前立腺がん細胞における NKX3-1 の発現を制御する）

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主論文の要約

In prostate, the roles of androgen and androgen receptor (AR) signaling are important for normal development including epithelial proliferation and differentiation. Well-differentiated prostate cancer (PCa) cells are generally androgen- and AR-dependent. Regulated AR signaling is involved even in PCa progression, and thus therapies targeting androgen production and AR signaling (i.e., androgen-deprivation therapy: ADT) are the primary treatment for patients with advanced PCa. However, no clinically established molecular biomarkers have been identified to predict the effectiveness of ADT before starting ADT. The tumor microenvironment of PCa contains fibroblasts that regulate PCa progression by producing multiple soluble factors. We have previously reported that AR-activating factor-secreted fibroblasts increase the responsiveness of androgen-sensitive, AR-dependent PCa cells to ADT. Thus, we hypothesized that fibroblast-derived soluble factors may affect cancer cell

differentiation by regulating cancer-related gene expression in PCa cells and that the biochemical characteristics of fibroblasts may be used to predict the effectiveness of ADT. Here, we investigated the effects of normal fibroblasts (PrSC cells) and three PCa patient-derived fibroblast lines (pcPrF-M5, -M28, and -M31 cells) on the expression of cancer-related genes in androgen-sensitive, AR-dependent human PCa cells (LNCaP cells) and three sublines showing different androgen sensitivities and AR dependencies.

The mRNA expression of the tumor suppressor gene *NKX3-1* in LNCaP cells and E9 cells (which show low androgen sensitivity and AR dependency) was significantly increased by treatment with conditioned media from PrSC and pcPrF-M5 cells but not from pcPrF-M28 and pcPrF-M31 cells. Notably, no upregulation of *NKX3-1* was observed in F10 cells (AR-V7-expressing, AR-independent cells with low androgen sensitivity) and AIDL cells (androgen-insensitive, AR-independent cells). Among 81 common fibroblast-derived exosomal microRNAs that showed 0.5-fold lower expression in pcPrF-M28 and pcPrF-M31 cells than in PrSC and pcPrF-M5 cells, miR-449c-3p and miR-3121-3p were found to target *NKX3-1*. In only LNCaP cells, the *NKX3-1* mRNA expression was significantly increased by transfection of an miR-3121-3p mimic but not that of the miR-449c-3p mimic.

Thus, fibroblast-derived exosomal miR-3121-3p may be involved in preventing the oncogenic dedifferentiation of PCa cells by targeting *NKX3-1* in androgen-sensitive, AR-dependent PCa cells.