学位論文審査結果の要旨

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（学位論文審査結果の要旨）

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

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

Background: Androgen deprivation therapy (ADT) targeting androgen production and androgen receptor (AR) signaling is the primary hormonal therapy in the treatment of advanced prostate cancer (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.

Methods: 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.

Results: 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.
Conclusion: The 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.

本研究は、進行性前立腺癌におけるホルモン療法の有効性を予測するバイオマーカーを模索したもので、線維芽細胞が癌細胞分化を維持する作用機序の一部を明らかにした論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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