Inflammatory suppressive effect of prostate cancer cells with prolonged exposure to transforming growth factor β on macrophage-differentiated cells via downregulation of prostaglandin E₂

Transforming growth factor β1 (TGFβ1) regulates a variety of cellular functions, including cell growth, apoptosis and differentiation. The aim of the current study was to investigate the alterations of phenotypic events in the long-term exposure of prostate cancer (PCa) cells to TGFβ1 and its effect on macrophage-differentiated cells. The PCa cell line, PC-3, and the subclone, M1, were exposed to TGFβ1 for short- or long-term periods. TGFβ1 signaling was assessed by Smad3 phosphorylation, and non-canonical signaling was analyzed by quantitative polymerase chain reaction-based regulatory gene expression profiles. TGFβ1-exposed PCa cells were also co-cultured with phorbol 12-myristate 13-acetate (PMA)-treated THP-1 macrophages as a model of the tumor microenvironment. The phosphorylation of Smad3 in the PCa cells with long-term exposure was lower than that in the PCa cells with short-term exposure. Interleukin-6 mRNA expression in the PMA-treated THP-1 macrophages was significantly downregulated by co-culture with the PCa cells with long-term exposure. Cyclooxygenase-2 expression in the long-term TGFβ1-exposed PCa cells was lower than that in the control PCa cells, and the production of prostaglandin E₂ (PGE₂) in the long-term TGFβ1-exposed PCa cells was also significantly lower. The results of the current study demonstrated that the long-term TGFβ1 exposure of PCa cells induces phenotypic changes, including the downregulation of PGE₂ production. This indicates that prolonged TGFβ-exposed PCa cells may change the cytokine production of macrophages in
the tumor microenvironment.

TGFβ1を用いた前立腺癌細胞への長期刺激を検討した論文は初めてであり、今回の研究により長期間にわたるTGFβ1による刺激によって前立腺癌細胞にPGE2産生低下を伴う表現型の変化が引き起こされることを証明した。このことから長期にわたるTGFβ1による刺激を加えた前立腺癌細胞によって、がん微小環境におけるマクロファージのサイトカイン産生への影響を定量的に評価したものであり、学術上極めて有益であり、学位論文として価値のあるものと認めた。

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