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Thrombospondin-2 promotes metastasis by down-regulation of miR-376c through the MAPK signaling pathway in human prostate cancer cells

Thrombospondin-1 可通過 MAPK 路徑下調 miR-376c 促使人類前列腺癌細胞轉移

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Thrombospondin-2 (TSP-2) is a secreted matricellular glycoprotein that is found to mediate cell-to-extracellular matrix attachment and participates in many physiological and pathological processes. The expression profile of TSP-2 on tumors is controversial, it upregulation in some cancers, whereas, downregulated in others, suggesting that the functional role of TSP-2 on tumors are still uncertain. Based on the gene expression omnibus database and immunohistochemistry, we found that TSP-2 is increased with the progression of prostate cancer (PCa), especially in metastatic PCa and is correlated with matrix metalloproteinase-2 (MMP-2) expression. Additionally, through binding to CD36 and integrin $\alpha\beta3$, TSP-2 increased cell migration and MMP-2 expression. Inhibition of p38, ERK and JNK, the TSP-2-induced cell migration and MMP-2 expression were abolished, indicating that the TSP-2's effect on PCa is MAPK-dependent. Moreover, the microRNA-376c (miR-376c) was significantly decreased by TSP-2 treatment. Furthermore, the TSP-2-induced MMP-2 expression and the subsequent cell motility were suppressed upon miR-376c mimic stimulation. On the other hand, the animal studies revealed that the bone metastasis was abolished when TSP-2 was stably knockdown in PCa cells. Taken together, our results indicate that TSP-2 enhances the migration of PCa cells by increasing MMP-2 expression through down-regulation of miR-376c expression. Therefore, TSP-2 may represent a promising new target for treating PCa.

Keywords: Thrombospondin-2, metastasis, prostate cancer, microRNA