腎母細胞瘤過度表達基因在攝護腺癌之移形及骨轉移中所扮演之角色

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Abstract:

Nephroblastoma overexpressed (NOV or CCN3) is a secreted, matrix-associated protein that belongs to the CCN gene family and is involved in many cellular functions, including growth, differentiation, and adhesion. The effect of CCN3 on human prostate cancer cells, however, is unknown. Here, we have shown that CCN3 increased cell migration and intercellular adhesion molecule-1 (ICAM-1) expression in prostate cancer cells. CCN3 activated a signal transduction pathway that included αvβ3 integrin, integrin-linked kinase (ILK), Akt, and NF-κB. Reagents that inhibit specific components of this pathway each diminished the ability of CCN3 to effect cell migration and ICAM-1 expression. Our results indicate that CCN3 enhances the migration of prostate cancer cells by increasing ICAM-1 expression through a signal transduction pathway that involves αvβ3 integrin, ILK, Akt, and NF-κB. CCN3 thus represents a promising new target for treating prostate cancer. Bone metastasis in patient with advanced-stage prostate cancer, the most commonly diagnosed malignancy in Western countries, increases the risk of intractable bone pain. We further investigated the role of CCN3 in prostate cancer bone metastasis. At first, CCN3 was found to be highly expressed in bone metastasis patients and positively correlated with malignancy in human prostate cancer cells. Prostate cancer conditioned medium (CM)-induced osteoclast differentiation was inhibited by neutralizing antibody against CCN3. Specifically, CCN3 was found to induce osteoclastogenesis through the receptor activator of NF-κB ligand (RANKL)-dependent pathway, and the focal adhesion kinase (FAK)/Akt/p38/NF-κB signal pathway was found to be involved in CCN3-mediated receptor activator of NF-κB (RANK) expression and RANKL-dependent osteoclastogenesis. In contrast, osteoblasts were observed to play an

important role in osteoclast differentiation by paracrine manner, with treatment of osteoblasts with CCN3 found to change the RANKL (osteoclastogenesis)/OPG (anti-osteoclastogensis) ratio. Compared with parental PC3 cells, highly invasive PC3 I3 cells markedly enhanced osteoclast activity and bone metastasis *in vivo*. These results all indicate that CCN3 can be used as a novel therapeutic target in the prevention of bone metastasis of prostate cancer.