Abstract

Prostate cancer (PCa) is the 5th most common cancer overall in the world. Incidence of prostate cancer is increasing annually and is now the 6th most common cancer in Taiwan. More than 80% of patients died from prostate cancer developed bone metastases. Androgen ablation therapy is the primary treatment for metastatic prostate cancer. However, a majority of prostate cancer patients receiving the androgen ablation therapy will ultimately develop recurrent castration-resistant prostate cancer (CRPC) within 1-3 years after treatment with a median overall survival time of 1-2 years after relapse. Currently there is no effective standard therapy, thus new therapeutic targets are needed. Human histone lysine demethylases (KDMs) have only been discovered recently. Eight KDM families including 28 members have been identified. We are especially interested in KDM4C. KDM4C is an oncogene demethylates tri- and dimethylated lysine 9 on histone H3. It is an androgen receptor (AR) co-regulator. KDM4C expression is higher in castration-resistant prostate cancers (CRPC). Although role of KDM4C in prostate cancer is not fully understood, KDM4C has been shown to be an oncogene in other cancers such as breast cancers. In this study, we demonstrated that knockdown of KDM4C suppressed the proliferation, migration, invasion and motility of LNCaP and C4-2B human prostate cancer cells. Western blot indicated that knockdown of
KDM4C reduced the abundance of signaling proteins involved in epithelial-to-mesenchymal transition (EMT) and Wnt signaling pathway, including Slug, Snail, vimentin and β-catenin. Knockdown of KDM4C by siRNA repressed the cancer metastasis of C4-2B xenografts in nude mice. Our findings provide the rationale for targeting KDM4C as a treatment for advanced prostate cancer.
中文摘要

前列腺癌（Prostate cancer）在世界上最常見的癌症中排名第五。在台灣則是第六常見的癌症而且其發病率逐年增加。超過80%的前列腺癌患者死於骨轉移。賀爾蒙療法 (Androgen ablation therapy) 是治療轉移性前列腺癌的主要方法。然而，病患在接受賀爾蒙療法後1-3年會進展成去勢療法無效前列腺癌 (castration-resistant prostate cancer, CRPC)，復發後病患的中位存活期為1-2年且目前並無有效的治療方法。KDM4組蛋白去甲基酵素是調控外基因(epigenetics)的重要酵素。其中，KDM4C被發現是雄激素受體AR (androgen receptor)的共同調節受體(co-regulator)，在CRPC中也發現KDM4C的表現量較高。雖然KDM4C在前列腺癌中所扮演的角色尚不明確，但在乳癌的研究中，KDM4C被認為是一個致癌基因(oncogene)。因此，本實驗利用siRNA抑制前列腺癌細胞LNCaP和C4-2B的KDM4C，結果發現前列腺癌細胞的增生、移動和侵襲能力明顯下降。進一步透過西方墨點法發現，當KDM4C表現量下降時，與EMT (epithelial-to-mesenchymal transition) 和Wnt signaling pathway相關的蛋白質表現量亦下降，像是Slug, Snail, vimentin and β-catenin。在異種移植 (Xenograft) 原位模式 (Orthotopic model) 的動物實驗中也發現小鼠體內人類前列腺腫瘤的轉移能力受到抑制。我們的研究結果發現KDM4C能夠控制前列腺癌的發展與轉移，為KDM4C作為晚期前列腺癌治療標的提供了理論基礎。