1α,25-dihydroxyvitamin D3 Inhibits Prostate Cancer Cell Invasion via Modulation of Selective Proteases

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摘要

Abstract

Inhibition of invasion and metastasis has become a new approach for treatment of advanced prostate cancer in which secondary hormone therapy has failed. Accumulating evidence indicates that la,25-dihydroxyvitamin D3 (1,25-VD) suppresses prostate cancer progression by inhibition of tumor growth and metastasis. However, the detailed mechanisms underlying these effects remain to be determined. Here, we used the in vitro cell invasion assay to demonstrate that 1,25-VD inhibits the invasive ability of human prostate cancer cell lines, LNCaP, PC-3 and DU 145. Three major groups of proteases, the matrix metallo-proteinases (MMPs), the plasminogen activators (PAs) and the cathepsins (CPs), that are involved in tumor invasion were then examined for changes in activity and expression after 1,25-VD treatment. We found that 1,25-VD decreased MMP-9 and CPs, but not PAs activities, while it increased the activity of their counterparts, tissue inhibitors of metalloproteinase-1 (TIMP-1) and cathepsin inhibitors. Mechanistic studies showed that 1,25-VD did not suppress MMP-9 expression at the transcriptional level, but reduced its mRNA stability. In addition, 1,25-VD increased AP-1 complexes binding to TIMP-1 promoter, which contributed to the enhancement of TIMP-1 activity, and thus resulted in inhibition of MMP activity and tumor invasion. These findings support the idea that vitamin D-based therapies might be beneficial in the management of advanced prostate cancer, especially among patients who have higher MMP-9 and CPs activities.