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ORIGINAL ARTICLE

Inhibitory effect of cathepsin K inhibitor (ODN-MK-0822) on invasion, migration and adhesion of human breast cancer cells in vitro

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Abstract

Approximately 90% of patients with advanced breast cancer develop bone metastases; an event that results in severe decrease of quality of life and a drastic deterioration in prognosis. Therefore, to increase the survival of breast cancer patients, the development of new therapeutic strategies to impair metastatic process and skeletal complications is critical. Previous studies on the role of cathepsin K (CTSK) in metastatic spreading led to several strategies for inhibition of this molecule such as MIV-711 (Medivir), balicatib and odanacatib (ODN) which were on trial in the past. The present study intended to assess the anti-metastatic efficacy of ODN in breast cancer cells. Human breast cancer cell lines MDA-MB-231 were treated with different concentrations of ODN and performed invasion, adhesion and migration assays and, RT-PCR and western blot to evaluate the effect of ODN on the metastatic potential of breast cancer cells. ODN markedly decreased wound healing cell migration, invasion and adhesion at a dose dependent manner. ODN inhibits cell invasion by decreasing the matrix metalloproteinase (MMP-9) with the upregulation of TIMP-1 expression. ODN effectively inhibited the phosphorylation of extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal Kinase (JNK), and blocked the expression of β-integrins and FAK proteins. ODN also significantly inhibited PI3K downstream targets Rac1, Cdc42, paxillin and Src which are critical for cell adhesion, migration and cytoskeletal reorganization. ODN exerts anti-metastatic action through inhibition of signaling pathway for MMP-9, PI3K and MAPK. This indicates potential therapeutic effects of ODN in the treatment of metastatic breast cancer.

Keywords Cathepsin K · Odanacatib · Breast cancer · Migration · Invasion · Adhesion

Introduction

Metastatic breast cancer tends to spread throughout the body but mainly spreads to bone, lungs, liver, brain and regional lymph nodes. Approximately 70% of breast cancer death is attributable to skeletal metastasis [1]. Although the advanced therapy is available in the treatment of breast cancer, the incidence and mortality rates continue to rise due to low efficacy, severe side effects and lack of treatment access [2, 3]. Therefore, the alternate therapies are needed to increase the current therapies.

Cathepsin K, a cysteine protease with strong collagenolytic and elastolytic activity produced by osteoclasts, appeared to be overexpressed in various types of cancers. Data accumulated over the past few years on CTSK expression in various cancers suggest both its critical role in tumour progression and its potential diagnostic and prognostic effects. Previous studies have shown that the CTSK expression level is associated with higher breast cancer stages and negative estrogen receptor status, two features associated with poor prognosis in patients [4, 5] and levels of CTSK in bone metastasis are higher than in primary tumour or non-osseous metastasis of the same patient [6, 7].

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