Inhibitory effects of Berberine on the migratory and invasive abilities of cancer cells

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The Epithelial-to-Mesenchymal Transition (EMT) is the complex program that involve in oncogenic pathways regulating in migratory and invasion of cancer cells, angiogenesis, and metastasis. As such, targeting the critical EMT inducers or EMT pathways represents an important therapeutic strategy for preventing or treating cancer cells metastasis. Berberine, an isoquinoline alkaloid traditional herbal medicine with no organ toxicity. The increasing reports indicated that berberine played anti-angiogenesis, anti-invasion, and anti-metastasis roles in different human cancer cells. However, there is still unknown about the inhibitory effect of berberine on invasive behavior and EMT of prostate cancer cells. Our study shows for the first time to indicate important role played by berberine, in repressing the metastatic process and the invasive ability of prostate cancer cells. We showed that the migratory and invasive abilities of prostate cancer cells were inhibited by berberine through inhibition of TGF-β signaling. Among the TGF-β signaling molecules were inhibited by berberine, high BMP7 and NODAL gene expressions of metastatic prostate cancer tissues were associated with shorter survival of prostate cancer patients and provide potential therapeutic interventions.

Keywords: Epithelial-to-Mesenchymal Transition (EMT); Berberine; Cancer

downregulation of E-cadherin is linked to tumor progression and metastasis in a variety of human cancers. Moreover, the transforming growth factor (TGF)-β is the key player to induce EMT in cultures of epithelial cells which have been demonstrated in the most classical experimental models. The pathways were associated with EMT which was regulated by TGF-β, GSK3, and Wnt/β-catenin-mediated regulation. Eventually, these signal pathways will lead to activate any of the E-cadherin transcriptional repressors, including members of the Snail family (Snail1 and Slug) and ZEB (zinc finger E-box binding homeobox) family (ZEB1 and ZEB2) and Twist. Thus, inhibition the expression of these EMT inducers can reverse the characteristic of mesenchymal-like cancer cells.

Berberine a component of the Chinese herbal medicine Huanglian, is traditionally used as an antibiotic to combat digestive disorders, dysentery and diarrhea in China. In addition, berberine, a clinically important natural isoquinoline alkaloid, is characterized by a diversity of pharmacological effects. Accumulative evidences have found that berberine played an important role in inhibition of cancer cells growth or induction of cancer cells apoptosis in different human cancer cells such as lung, breast, prostate, and liver in both *in vitro* and *in vivo* studies. It is well-known that inhibitory effects of berberine on the growth inhibition of various types of cancer cells through inhibiting the activity of DNA topoisomerase I, inducing cell-cycle arrest and apoptosis mainly through intrinsic pathway of caspase-3 activation or extrinsic pathway of Fas/FasL activation. Taken together, these studies indicate that berberine could be a useful therapeutic agent in the treatment of cancers.

Recently, the use of berberine has attracted great attention as an alternative anti-migration, anti-invasion, anti-metastasis and anti-angiogenesis therapy of various lines of cancers such as gastric, oral, bladder, and liver cancers, considering its low toxicity and low cost (*Table 1*). For example, berberine could inhibit motility and invasion ability of the highly metastatic lung cancer cell line, A549 cells, via down-regulation of nuclear transcription factors of c-fos, c-jun and NF-κB or suppression of TGF-β-induced EMT. Other explorations for the anti-migration or anti-invasion effects of berberine were through suppression of matrix metalloproteinase-2 and 9 (MMP-2/9) in MDA-MB-231 human breast cancer, or suppression of MMP-1, -2, and -9 in human SNU-5 gastric cancer cells, and reduction the transcriptional activities of MMP-2 and urokinase-type plasminogen activator (uPA) in human cervical cancer cells (*Table 1*). Very recently, berberine was reported to suppress Inhibitor of differentiation (Id-1)
expression and inhibit the growth and development of lung metastases in hepatocellular carcinoma in vivo [23]. Collectivity, berberine may represent a promising therapy for against invasion and metastasis of cancer cells by its ability to suppress the cell from migrating and then invading the cellular matrix.

A recent study indicated that the growth inhibitory effect of berberine on human prostate cancer cell growth was through apoptotic cell death [24]. However, there is still unclear about the inhibitory effect of berberine on invasive behavior and EMT of prostate cancer cells. In addition to downregulate of nuclear transcription factors and matrix metalloproteinases, more investigations in the signaling pathway of berberine involved in anti-metastasis and anti-EMT are required to unravel. Thus, our study shows for the first time that berberine plays an important role in repressing the metastatic process and the invasive ability of prostate cancer cells [25]. We found that the migratory and invasive abilities of prostate cancer cells were inhibited by berberine through inhibition of TGF-β-related signaling molecules, such as TGF-β, bone morphogenetic protein 7 (BMP7), NODAL, and WNT11. This result is consistent with the findings of Qi et al. [22] to indicate berberine is an effective inhibitor of the metastatic potential of cancer cells through suppression of TGF-β-induced EMT. In addition, we also observed that expression of the well-known EMT inducers Snai1 was significant inhibited by berberine treatment. Among the EMT-related genes were inhibited by berberine, high BMP7, NODAL and Snai1 gene expressions of metastatic prostate cancer tissues were associated with shorter survival of prostate cancer patients and provide potential therapeutic interventions. Our another recent study reveal novel anti-migratory function of berberine in breast cancer cells through increased acetylation of α-tubulin to inhibit breast cancer cells migration [26]. In conclusion, berberine may represent a promising therapy for various cancers, potentially in the prevention the migration and invasion of cancer cells through inhibiting EMT-related genes.

Conflicting interests

The authors have declared that no competing interests exist.

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References


