Berberine-induced AMPK activation inhibits the metastatic potential of melanoma cells via reduction of ERK activity and COX-2 protein expression.

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Source

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Abstract

Berberine is clinically important natural isoquinoline alkaloid that affects various biological functions, such as cell proliferation, migration and survival. The activation of AMP-activated protein kinase (AMPK) regulates tumor cell migration. However, the specific role of AMPK on the metastatic potential of cancer cells remains largely unknown. The present study investigated whether berberine induces AMPK activation and whether this induction directly affects mouse melanoma cell migration, adhesion and invasion. Berberine strongly increased AMPK phosphorylation via reactive oxygen species (ROS) production. 5-Aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR), a well-known AMPK activator, also inhibited tumor cell adhesion and invasion and reduced the expression of epithelial to mesenchymal transition (EMT)-related genes. Knockdown of AMPKα subunits using siRNAs significantly abated the berberine-induced inhibition of tumor cell invasion. Furthermore, berberine inhibited the metastatic potential of melanoma cells through a decrease in ERK activity and protein levels of cyclooxygenase-2 (COX-2) by a berberine-induced AMPK activation. These data were confirmed using specific MEK inhibitor, PD98059, and a COX-2 inhibitor, celecoxib. Berberine- and AICAR-treated groups demonstrated significantly decreased lung metastases in the pulmonary metastasis model in vivo. Treatment with berberine also decreased the metastatic potential of A375 human melanoma cells. Collectively, our results
suggest that berberine-induced AMPK activation inhibits the metastatic potential of tumor cells through a reduction in the activity of the ERK signaling pathway and COX-2 protein levels.

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