Berberine, an isoquinoline alkaloid, inhibits melanoma cancer cell migration by reducing the expressions of cyclooxygenase-2, prostaglandin E₂ and prostaglandin E₂ receptors.


Source

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Abstract

Melanoma is the leading cause of death from skin disease due, in large part, to its propensity to metastasize. We have examined the effect of berberine, an isoquinoline alkaloid, on human melanoma cancer cell migration and the molecular mechanisms underlying these effects using melanoma cell lines, A375 and Hs294. Using an in vitro cell migration assay, we show that over expression of cyclooxygenase (COX)-2, its metabolite prostaglandin E₂ (PGE₂) and PGE₂ receptors promote the migration of cells. We found that treatment of A375 and Hs294 cells with berberine resulted in concentration-dependent inhibition of migration of these cells, which was associated with a reduction in the levels of COX-2, PGE₂ and PGE₂ receptors (EP2 and EP4). Treatment of cells with celecoxib, a COX-2 inhibitor, or transient transfection of cells with COX-2 small interfering RNA, also inhibited cell migration. Treatment of the cells with 12-O-tetradecanoylphorbol-13-acetate (TPA), an inducer of COX-2 or PGE₂, enhanced cell migration, whereas berberine inhibited TPA- or PGE₂-promoted cell
migration. Berberine reduced the basal levels as well as PGE$_2$-stimulated expression levels of EP2 and EP4. Treatment of the cells with the EP4 agonist stimulated cell migration and berberine blocked EP4 agonist-induced cell migration activity. Moreover, berberine inhibited the activation of nuclear factor-kappa B (NF-κB), an upstream regulator of COX-2, in A375 cells, and treatment of cells with caffeic acid phenethyl ester, an inhibitor of NF-κB, inhibited cell migration. Together, these results indicate for the first time that berberine inhibits melanoma cell migration, an essential step in invasion and metastasis, by inhibition of COX-2, PGE$_2$ and PGE$_2$ receptors.

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