

# Berberine inhibits HIF-1a expression via enhanced proteolysis

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摘要

## Abstract

We have studied the antiangiogenic property of berberine. We showed that berberine could directly inhibit in vitro human umbilical vein endothelial cell (HUVEC) tube formation and migration. In addition, to determine whether berberine could influence the cross-talk between the gastric adenocarcinoma cell line SC-M1 and vascular endothelial cells, we performed modified confrontation culture experiments and showed that berberine (7.5 microM, 16 h) could inhibit the capacity of hypoxic SC-M1 cells to stimulate HUVEC migration. These results demonstrated berberine's antiangiogenic property and its clinical potential as an inhibitor of tumor angiogenesis. Parallel Western blot analyses revealed that berberine prevented hypoxic SC-M1 cultures from expressing vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1alpha, two key factors in mediating tumor angiogenesis. However, overexpression of HIF-1alpha in SC-M1 cells dramatically reversed the inhibitory effect of berberine on SC-M1-induced in vitro HUVEC migration. These data indicated that HIF-1alpha repression is a critical step in the inhibitory effect of berberine on tumor-induced angiogenesis. Northern blot analyses plus pulse-chase assays revealed that berberine did not down-regulate HIF-1alpha mRNA but destabilized HIF-1alpha protein. We found that berberine-induced HIF-1alpha degradation was blocked by a 26S proteasome inhibitor. Moreover, immunoprecipitation and Western blot analyses showed that berberine increased the lysine-acetylated HIF-1alpha in hypoxic SC-M1 cultures. These data indicated that a proteasomal proteolytic pathway and lysine acetylation were involved in berberine-triggered HIF-1alpha degradation. In conclusion, our data provided molecular evidence to support berberine as a potent antiangiogenic agent in cancer therapy.