Heme oxygenase-1 inhibits breast cancer invasion via suppressing the expression of matrix metalloproteinase-9.

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Abstract

In the present study, we investigated the antitumor effects of the invasiveness and migration of heme oxygenase 1 (HO-1) in human breast carcinoma cells. 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced matrix metalloproteinase-9 (MMP-9) enzyme activity and gene expression at both protein and mRNA levels were examined in human breast carcinoma cells (MCF-7 and MDA-MB-231), and the addition of the MMP-9 inhibitor, SB3CT, significantly suppressed TPA-induced invasion and migration according to the in vitro Transwell assay. Elevation of HO-1 gene expression by ferric protoporphyrin IX inhibited TPA-induced invasion of MCF-7 cells, which was blocked by adding the heme oxygenase inhibitor, tin protoporphyrin IX, or transfection of cells with HO-1 short hairpin RNA. MCF-7 cells overexpressing HO-1 (MCF-7/HO-1) were established in the present study, and TPA-induced MMP-9 gene expression, tumor invasion, and colony formation were significantly reduced in MCF-7/HO-1 cells, compared with those in Neo-transfected cells. Activation of protein kinase Calpha/extracellular signal-regulated kinases/AP-1 with stimulation of reactive oxygen species production was involved in TPA-induced invasion of MCF-7 cells, which was attenuated by HO-1 protein induced by ferric protoporphyrin IX or transfection of HO-1 expression vectors. Additionally, the addition of carbon monoxide, but not ferric ions, biliverdin, or bilirubin, inhibited TPA-induced invasion through suppressing MMP-9, extracellular signal-regulated kinases, and AP-1 activation stimulated by TPA. The beneficial role of HO-1 in blocking tumor invasion was first identified in this study.