

Hypoxia-inducible factor 1alpha regulates lung adenocarcinoma cell invasion.

Shyu KG, Hsu FL, Wang MJ, Wang BW, Lin S.

Abstract

We studied the role of hypoxia-inducible factor-1alpha (HIF-1alpha) in human lung adenocarcinoma cell invasion using a metastatic cell model composed of low invasive CL1 and highly invasive CL1-5 cells. We showed that HIF-1alpha was expressed in CL1-5 but not in CL1 cells under normoxic condition, and that inhibition of HIF-1alpha expression by a small interfering RNA decreased invasiveness of CL1-5 cells. Complementary, overexpression of HIF-1alpha increased the invasiveness of CL1 and gastric cancer SC-M1 cells. Subsequently, we showed that urokinase-type plasminogen activator receptor (uPAR), and matrix metalloproteinases (MMPs) 1 and 2 were critical in HIF-1alpha-induced invasion. Mechanistic studies revealed that HIF-1alpha overexpression could increase the expression of uPAR and MMP1, but not MMP2. However, ELISA assays on the conditioned media generated from control CL1 and CL1 cells overexpressing HIF-1alpha showed that overexpression of HIF-1alpha increased the levels of endogenous free active MMP2 and total free MMP2, and the former was blocked by inhibition of MMP1 expression. We conclude that (i) HIF-1alpha overexpression enhances lung cancer cell invasion at least through up-regulating the expression and activities of uPAR, MMP1, and MMP2; and (ii) induction of MMP1 participates in cell invasion and also plays an important role in HIF-1alpha-induced activation of MMP2.