EMODIN INHIBITS VASCULAR ENDOTHELIAL GROWTH FACTOR-A-INDUCED ANGIGENESIS BY BLOCKING RECEPTOR-2 (KDR/FLK-1) PHOSPHORYLATION

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INTRODUCTION. Emodin is a tyrosine kinase inhibitor isolated an active constituent of Chinese herbs (1). The compound sensitizes HER-2/neu-overexpressing lung cancer cells, has antitumor effects on neuroectodermal, and represses transformation and metastasis-associated properties of HER-2/neu-overexpressing breast cancer cells (2,3). Given that numerous endogenous factors and pharmacological agents that regulate cancer progression and inflammation additionally affect angiogenesis, it seems likely that emodin would also affect angiogenesis. In the present study, we investigated whether emodin has anti-angiogenic activity especially on the VEGF-A-induced angiogenesis, and if so, the critical mechanism of action.

METHODS. To investigate the anti-angiogenic activity of emodin, we perform angiogenesis assay in vitro (endothelial cell proliferation, migration, invasion, and tube formation) and in vivo (Matrigel plug assay and chick corioallatoic membrane assay). We also perform immunohistochemistry, immunoprecipitation, and Western blot analysis to detect the expression and activation of signaling molecules.
RESULTS. In vitro, emodin dose-dependently inhibits proliferation, migration into the denuded area, invasion through a layer of Matrigel, and tube formation of human umbilical vein endothelial cells (HUVECs) stimulated with VEGF-A. Emodin also inhibits in vivo angiogenesis in Matrigel plug imbedded in mice (Fig. 1). emodin effectively inhibits VEGF-A-induced phosphorylation of VEGF-A receptor-2 (KDR/Flk-1) (Fig. 2) and downstream effector molecules in HUVECs, which might be the possible mechanism for anti-angiogenic activity of emodin against VEGF-A-induced angiogenesis.

Fig. 1. Emodin inhibits angogenesis in vivo. Fig. 2. Emodin inhibits KDR.Flk-1 Phosphorylation of VEGF-A

DISCUSSION. Emodin, a natural anthraquinone, preferentially inhibits VEGF-A-induced angiogenesis in vivo and in vitro, possibly through blocking the phosphorylation of KDR/Flk-1 and downstream effector molecules. We propose that emodin is a potential anti-angiogenic agent for the effective treatment of various diseases, including cancer.

REFERENCES.