

学位論文の要旨

三 重 大 学

所 属	甲 三枝学大学院医学系研究科 生命医科学専攻 腎泌尿器外科講座	氏 名	岩本 陽一
-----	------------------------------------	-----	-------

主論文の題名: **Oral naftopidil suppresses human renal cell carcinoma by inducing G1 cell cycle arrest in tumor and vascular endothelial cells**

主論文の要旨:

Renal cell carcinoma (RCC) is an angiogenesis-dependent and hypoxia-driven malignancy. As a result, several targeting agents are being investigated. However, the efficacy of current regimens is generally insufficient for their toxicity and poor overall response rates. We have recently reported that naftopidil exerts growth-inhibitory effects on human prostate cancer cells. In this study, we investigated the biochemical mechanisms by which naftopidil produces growth-inhibitory and antiangiogenic effects on RCC. We first tested the effects of naftopidil on the proliferation of ACHN and Caki-2 RCC cells. Next, we set up a model simulating the tumor microenvironment, in which ACHN cells were grafted onto the renal capsule of mice. We then tested the effects of naftopidil on human umbilical vein endothelial cells' cell proliferation and Matrigel plug vascularization. Finally, to establish the antitumor activity of naftopidil on RCC, we tested the antitumor effects of naftopidil on excised tumor specimens from 20 patients with RCC that were grafted beneath the renal capsule of mice. Naftopidil showed similar in vitro growth-inhibitory effects on all cell lines. Fluorescence-activated cell sorting analysis revealed an increase in G1 cell-cycle arrest in all naftopidil-treated cell lines. In vivo tumorigenic studies showed a significant reduction of ACHN tumor weight, Ki-67 index, and microvessel density (MVD) in naftopidil-treated mice. Naftopidil attenuated neovascularization in an in vivo Matrigel plug assay. Studies in mouse xenograft models also showed a significant MVD reduction in naftopidil-treated excised human RCC. The growth-inhibitory effects of naftopidil suggest it may be a novel anticancer agent and a potential preventive option for RCC.