Tumor growth after subcutaneous injection of LL/2 cancer cells in C57/BL6 mice treated with PD123,319, an AT2R antagonist, was decreased when PD123,319 was given at an early stage, suggesting that AT2R is also involved in tumor promotion. In vitro proliferation of LL/2 cells was reduced by PD123,319 with a significant decrease in Ki67 expression and ERK1/2 phosphorylation. In addition, tumor vascular density, measured by CD31 labeling and angiogenesis using the aortic ring assay on Matrigel®, were reduced by PD123,319 and in AT2R-null mice. Therefore, we uncovered a novel mechanism by which AT2R promotes tumor development favoring both malignant cancer cell proliferation and tumor angiogenesis. Thus, blocking AT2R could be a new approach in tumor therapy.

D004 PHARMACOLOGICAL BLOCKADE OF ANGIOTENSIN II TYPE 2 RECEPTOR INHIBITS TUMOR GROWTH DECREASING CELL PROLIFERATION AND TUMOR VASCULARIZATION

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Angiotensin II type 2 receptor (AT2R) stimulation is thought to induce vasoconstriction and apoptosis. Nevertheless, its role remains controversial. In hypertension and aging, AT2R might promote vasoconstriction and cell growth. In cancer cells, AT2R is highly expressed but its role remains poorly understood. Thus, we investigated the role of AT2R in tumor growth, hypothesizing that AT2R affects cell proliferation and/or tumor vascularization.

Tumor induction by 3-methylcholanthrene was significantly delayed in AT2R knockout mice, suggesting a role for AT2R in tumor initiation.

D005 PROTEOLYSIS OF ANGIOGENIC FACTORS ASSOCIATED WITH INTRAPLQUE HEMORRHAGES IN HUMAN ATHEROTHROMBOTIC PLAQUES

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Increased permeability of, and bleeding from, microvessels within the atheromatous arterial wall participate in atherothrombosis progression. The VEGF family and angiopoietin system components govern microvesSEL development and maturation. Serine protease activities are proportional to atherothrombosis progression and linked to intraplaque hemorrhage. Here we investigated the relationship between angiogenic factors and proteases in human hemorrhagic and non-hemorrhagic atheromatous carotid plaques by immunohistochemistry, in situ hybridization and ELISA. Plaque activity of plasmin and leukocyte elastase and proteolysis of angiogenic factors by plaque extracts were determined. Smooth muscle cell migration induced by hemorrhagic and non-hemorrhagic plaques was assessed. The absence of α-actin-positive cells characterized microvessels in hemorrhagic areas in spite of similar expression of VEGF and angiopoietin system components in microvessels of hemorrhagic and non-hemorrhagic areas. However, VEGF, PI GF and angiopoietin-1 levels were significantly decreased in hemorrhagic compared to non-hemorrhagic plaques, whereas angiopoietin-2 did not change and soluble Tie-2 levels increased. Consequently, smooth muscle cell migration stimulatory activity of hemorrhagic plaques was reduced. Recombinant PI GF, VEGF and angiopoietin-1 added to plaque extracts were only degraded by hemorrhagic lesions. This proteolysis was prevented by inhibitors of plasmin and elastase, whose activity was increased in hemorrhagic plaques. No degradation was observed for angiopoietin-2. Decreased angiogenic factor levels caused by proteolysis may destabilize plaque microvessels via impairment of mural cell recruitment, thus leading to a vicious circle of intraplaque hemorrhages and lesion progression.