P-2408 The role of PAF and PAFR in malignant cancer cell migration and metastasis

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腫瘍の浸潤・転移における PAF-PAFRの役割についての検討

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et-activating factor (PAF) is a potent proinflammatory meditor produced membrane glycerophospholipids. PAF is secreted from a broad range l such as basophils, mast cells, monocytes, macrophages, neutrophils, ophils, vascular endothelial cells, and platelets. PAF triggers a variety of logical reactions through its G-protein coupled receptor, PAF receptor R). It was reported that the expression of PAFR is higher in high-grade r. So far, it was suggested that the proliferation, migration, and invasion were increased by the treatment of PAF; however, it was still unclear the mechanism of invasion, metastasis and so on. We found that migrating ability of cancer cells from apical part of endothelial cells into part of them was induced upon stimulation of PAF. We have analyzed pression of PAFR in tumor metastatic environment and will discuss how egulates in tumor in the session.

rds: PAF, migration

P-P5 Sep. 20 (Thu) 17:20 - 18:10

Tumor angiogenesis (2)
腫瘍血管新生 (2)

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P-2409 Role of secreted frizzled-related protein-1 in tumor angiogenesis

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管新生における secreted frizzled-related protein-1の役割

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creted frizzled related protein-1(sFRP-1) is soluble protein thought to re with the Wnt signaling. This protein expresses in the blood vessels mouse embryogenesis and modulates vascular cell proliferation. ver, aberrant activation of Wnt signaling is involved in several human ancies. In this study, we aimed to investigate the role of sFRP-1 in growth and angiogenesis. To better understand the role of the sFRP- pathway in tumor vascular formation, we examined tumor volume icroenvironment of Lewis lung carcinoma (LLC) cells implanted onto cks of sFRP-1-null mice. Unexpectedly, sFRP1 deficiency significantly ted LLC graft growth in vivo, which was accompanied by a higher density with a large amount of small vessels. From these results, we ed that sFRP-1negatively regulates tumor angiogenesis and this may therapeutic potential of sfrp1 protein in cancer.

rds: Angiogenesis, Wnt

P-2410 Critical Role of aquaporin-3 in vasculogenic mimicry of gastric adenocarcinoma

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ve:The objective of this study was to investigate the critical role of rin-3 in vasculogenic mimicry formation of GAC, and then reveal the lar mechanisms involved.
ds: The silencing of AQP3 (with lentiviral shRNA) in human GAC SGC7901 was performed to investigate the role of AQP3 in VM by ng the change of VM formation and the expression of VM related A Three-dimensional culture model was utilized for experiments in
The silence of AQP3 or inhibition of PI3K/AKT signal pathway in 01 led to a significant decrease in VM formation; Down-regulation of ated genes such as vascular endothelial (VE)-cadherin, membrane matrix metalloproteinase (MT1-MMP), and matrix metalloproteinase- 2) appeared correspondingly.
sions:The results of this study reveal AQP3 as an important regulator ic adenocarcinoma VM by mediating the expression of VE-cadherin, MP, and MMP-2 through PI3K/AKT signal pathway in SGC7901. rmore, AQP3 and related molecular pathways may represent a herapeutic target for the inhibition of GAC angiogenesis and tumor ment by cutting down the blood supply from VM.

Keywords: aquaporin, Angiogenesis

P-2411 CSC-3436 Induces Apoptosis of Human Umbilical Vein Endothelial Cells via p53-mediated Death Receptor Up-regulation

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CSC-3436 is a 2-phenyl-1,8-naphthyridin-4-one (2-PN) derivative, was synthesized and evaluated as an effective antitumor agent. However, its role in tumor angiogenesis is unclear. This study investigated the effects of CSC-3436 and the mechanisms by which exerts its antiangiogenic. We found that CSC-3436 significantly inhibited microvesselformation. CSC-3436 inhibited proliferation of human umbilical vein endothelial cells (HUVEC) by induction of apoptotic cell death in a concentration-dependent manner. CSC-3436 also suppressed HUVEC migration and capillary-like tube formation. We were able to correlate CSC-3436 induced apoptosis in HUVEC with the cleavage of procaspase-3 and -8, as well as with the cleavage of poly (ADP-ribose) polymerase by Western blotting assay. Such sensitization was achieved through up-regulation of death receptor(DR). CSC-3436 was also capable of increasing the expression level of p53. The results of this study indicated that CSC-3436 exhibited vascular targeting activity associated with the induction of DR-mediated endothelial cell apoptosis through p53 up-regulation, which suggests its potential as an antivascular and antitumor therapeutic agent.

Keywords: Angiogenesis, Death Receptor

P-2412 Direct renin inhibitor suppressed the hepatocarcinogenesis via angiogenesis suppression in rats

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ラットにおける直接的レニン阻害薬の血管新生抑制を介した肝発癌抑制効果

相原 洋祐、吉治 仁志、野口 隆一、波崎 正、鍛冶 孝祐、福井 博（奈良県立医科大学　第３内科）

We previously reported that the renin-angiotensin system(RAS) plays a pivotal role in hepatocarcinogenesis, and clinically used several RAS inhibitory agents suppressed it via angiogenesis inhibition. The aim of our current study was to elucidate the effect of a recently developed direct renin inhibitor (DRI),Aliskiren, in the rat hepatocarcinogenesis model. Hepatocarcinogenesis model was induced in male F344 rats by the choline-deficient L-aminoacid-defined diet for 12 weeks. The hepatocarcinogenesis was examined with clinically comparable low doses of DRI, especially in conjunction with neovascularization. The glutathione-S-transferase placental form-positive pre-neoplastic lesions were markedly attenuated by DRI along with the suppression of neovascularization and VEGF in adose-dependent manner. Our *in vitro* study showed that renin significantly augmented the *in-vitro*angiogenesis, whereas, interestingly, DRI did not inhibit the renin-induced EC proliferation even at high dose. Since DRI is widely used in the clinical practice without serious side effects, DRI could represent a potential new strategy against hepatocarcinogenesis in the future.

Keywords: Angiogenesis, Hepatocellular carcinoma

P-2413 Newly developed oral iron chelator inhibits murine hepatocarcinogenesis via multiple actions

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多様な機序による新規経口鉄キレート剤の肝発癌抑制効果

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Iron overload plays an important role in hepatocarcinogenesis via accumulation of reactive oxygen species (ROS) in the liver. Moreover, ROS is known as a key mediator promoting tumor angiogenesis. This study was designed to elucidate the effect of deferasirox (DSX), a newly developed oral iron chelator on hepatocarcinogenesis in conjunction with ROS and angiogenesis. To induce hepatocarcinogenesis, F344 rats were fed a choline-deficient L-amino acid-defined (CDAA) diet for 12 weeks. DSX at clinically comparable low dose suppressed CDAA-induced hepatocarcinogenesis in pallarel with the suppression of oxidative DNA damage and lipid peroxidation. Additionally, these inhibitory effects occurred almost concurrently with the attenuation of neovascularization and vascular endothelial growth factor (VEGF) expression in the liver. These results indicate that DSX inhibits hepatocarcinogenesis through antioxidative and antiangiogenic effects. Since DSX is widely used in clinical practice, this agent may represent a potential new strategy against hepatocarcinogenesis with multiple steps including anti-angiogenesis in the near future.

Keyword: Reactive oxygen species