病態生化学分野　Division of Pathogenic Biochemistry

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◇研究目的　Aims of the research projects

本分野は，病態の生化学的研究を行うとともに，和漢薬を含む種々の薬物の病態に及ぼす効果を生化学的，免疫学的，あるいは遺伝学的に研究することを目的としている。

和漢薬を中心に，構造の明らかにされた成分あるいは化合物を用いて，種々の病態に有効な薬物の探索とその作用機序を分子レベルで解明する。「証」といわれる病態変化／徴候を遺伝子工学的，免疫学的手法等を駆使してその遺伝的背景を解析し，薬物の効果発現との関連性からその科学的基盤を解明する。現在，癌，免疫，アレルギー疾患などを中心にして検討を行っている。

研究概要　Research projects

Ⅰ）がん転移機構の解明とその制御

1）がん転移に対するケモカインの作用機序解明と治療への応用

2）がん転移病態モデルの作製とその形成に関与する標的分子の探索

3）伝統薬物を中心としたがん転移の抑制物質の探索

Ⅱ）シグナル伝達分子による病態制御機構の解析

1）TAK1 活性化の分子機構

2）NF-κB のリン酸化の解析

3）自然免疫シグナルに影響を及ぼす漢方薬の探索

Ⅲ）漢方方剤テーラーメード治療法の開発

1）漢方医学の証の解明を目指した血漿プロテオミック・パターン解析

◇原著

1）**Nakamura E.S., Koizumi K. Kobayashi M. and Saiki I.: Inhibition of lymphangiogenesis-related properties of murine lymphatic endothelial cells and lymph node metastasis of lung cancer by the matrix metalloproreinase inhibitor MMI270. Cancer Sci, 95: 25-31, 2004**

Abstract: Based on a previous report on the effect of a matrix metalloproteinase (MMP) inhibitory compound, MMI270, in regulating tumor-induced angiogenesis, as well as recent findings concerning functional correlations among tumor metastasis, angiogenesis and lymphangiogenesis, we investigated the anti-metastatic efficacy of MMI270 in a murine model of lymph node metastasis of lung cancer, and analyzed whether this inhibitor could also regulate lymphangiogenesis-related properties of murine lymphatic endothelial cells (LECs) and invasive properties of Lewis lung cancer (LLC) cells. The observation that MMI270 led to a significant decrease in the weight of tumor-metastasized lymph nodes of mice led us to test its anti-lymphangiogenic and anti-invasive effects in vitro. Murine LECs were characterized by an in vitro tube formation assay, by semi-quantitative RT-PCR assay to examine the expression of mRNAs for flt-4, Flk-1, Tie-1, Tie-2, CD54/ICAM1, vWF, MMPs and uPA, and by western blotting to confirm the protein expression of flt-4 and CD31/PECAM. This is the first report on the expression of MMP-2, MMP-9 and MT1-MMP in murine LECs, as well as on the inhibition of their enzymatic activity, and of the invasive ability and tube-forming property of LECs by an MMP inhibitor. Furthermore, MMI270 was shown to strongly inhibit the activity of MMP-2 and -9 produced by LLC cells and the invasion of these cells through Matrigel. In summary, the present results indicate that MMI270, apart from its anti-tumor angiogenic application, might be useful as an anti-metastatic drug, on the basis of its downregulatation of both the lymphangiogenesis-related properties of LECs and the invasive properties of LLC cells in vitro.

2）**Teerawatanasuk N., Nakamura E.S., Koizumi K., Wangmaneerat A., Komatsu K. and Saiki I.: Anti-invasive and ant-angiogenic activities of Curucuma sp. extracts. J. Trad. Med., 21: 27-33, 2004.**

Abstract: Extracts of a herbal plant, Curcuma sp. (Zingiberaceae), were investigated for their anticancer activities. The rhizome of this plant is used in Thai folk medicine to treat cancers and to promote wound healing. In the present study, we performed preliminary bioassays to assess the anti-invasive and anti-angiogenic activities of the methanol (MeOH) and ethyl acetate (EtOAc) extracts. We found that both extracts produced moderate cytotoxic effects against murine hepatocellular carcinoma CBO140C12 cells. Interestingly, the EtOAc extract exhibited remarkable inhibitory effects on the invasion and migration of tumor cells in vitro, and on the adhesion of tumor cells to various extracellular matrix proteins. Moreover, the EtOAc extract also inhibited the formation of tube-like structures by hepatic sinusoidal endothelial (HSE) cells cultured on Matrigel-coated substrate, suggesting its anti-angiogenic activity. Altogether, our preliminary results indicate that the EtOAc extract contains active constituents that could potentially be developed into anticancer agents.

3）**Majima T., Yamada T., Tega E., Sakurai H., Saiki I. and Tani T.: Pharmaceutical evaluation of licorice before and after roasting. J. Pharm. Pharmacol., 56: 589-595, 2004.**

Abstract: Liquorice has been used for allergic-inflammatory and liver disorders in both traditional Chinese and modern medicine. In traditional Chinese formulations, it is mainly roasted liquorice that has been used rather than un-roasted liquorice. We have compared the pharmaceutical characteristics of liquorice before and after roasting to clarify the pharmaceutical significance of the roasting. Although roasted liquorice contained less glycyrrhizin (an anti-allergic component) than un-roasted liquorice, the inhibitory potency of roasted liquorice extract (200 mg x kg (-1)) on immunoglobulin E (IgE)-mediated triphasic ear swelling in mice was much greater compared with un-roasted liquorice. To search for additional active ingredients, roasted liquorice extract was subjected to gel-chromatography to give an anti-allergic fraction (Fa) of molecular weight ranging from 15000 to 200000 or more,

in which glycyrrhizin was not detected. By testing the activity of the various fractions, it was proved that the anti-allergic effect of roasted liquorice was due to glycyrrhizin, its metabolite glycyrrhetic acid, and the Fa fraction. The inhibitory potency of the Fa fraction (15 and 75 mg x kg(-1)) prepared from roasted liquorice was stronger than that prepared from un-roasted liquorice. Therefore, a pharmaceutical implication of roasting the liquorice seems to be associated with an increase in the anti-allergic property of the Fa fraction. It is notable that oral administration of the high molecular mass fraction (Fa) significantly inhibited IgE-mediated ear swelling six days after challenge at doses as low as 3, 15 or 75 mg x kg(-1).

4）**Saiki I.: Review, Kampo formulations and allergic inflammatory diseases - Efficacy for murine IgE-mediated triphasic cutaneous reaction -. J. Trad. Med., 21: 51-66, 2004.**

Abstract: We found that passive sensitization with anti-DNP IgE antibody followed by the challenge with DNFB to the mouse ear can induce the triphasic cutaneous reactions (ear swelling) of immediate phase response (IPR), late phase response (LPR) and very late phase response (vLPR), peaking at 1 h, 24 h and 8 days after the challenge, respectively. IPR was absent in mast cell-deficient mice but LPR was sufficiently observed, and vLPR was partly attenuated. LPR is a T cell-independent response, while vLPR is almost completely absent in T cell-deficient nude mice. Thus, the third phase response (vLPR) with massive infiltration of eosinophil actually represents an important inflammatory reaction mediated by T cells and partially mast cells. In this model, some Kampo formulations and synthetic anti-allergic agents inhibited the IgE-mediated triphasic cutaneous reaction. The inhibitory effects of the Kampo formulations on the triphasic cutaneous reaction were divided into several groups according to the efficacies for IPR/LPR/vLPR. For instance, the group consisting of formulations such as Tokaku-joki-to (Tao-He-Cheng-Qi-Tang, 桃核承気湯), Ji-zuso-ippo (Zhi-Tou-Chuang-Yi-Fan, 治頭瘡一方), Sho-sei-ryu-to (Xiao-Qing-Long-Tang, (小青竜湯) and Sho-saiko-to (Xiao-Chai-Hu-Tang, 小柴胡湯) significantly inhibited IPR, LPR and vLPR (i.e. +/+/+ group that showed inhibitory effects against the triphasic response), similar to the effect of prednisolone as a positive control. Oral administration of Yokukan-san (Yi-Gan-San, 抑肝散), an anti-psychosis drug in Kampo medicine, attenuated the isolation stress-exacerbated triphasic skin reactions in a dose-dependent manner, while it had almost no effect on the cutaneous reactions in the unstressed group-housed mice. On the other hand, the i.p. administration of diazepam, a classic benzodiazepine receptor agonist, suppressed the enhanced IPR and LPR in socially isolated mice, but surprisingly stimulated vLPR in both stressed and unstressed mice, differing from the efficacy of Yokukan-san. This article focuses on the anti-allergic properties of Kampo formulations and describes the effect of some Kampo formulations on IgE-mediated triphasic skin reaction in group-housed or socially isolated mice. We also discuss the mechanism of the inhibitory action and the importance of the formulation and the constituent drugs in determining the efficacy.

5）**Suntornsuk L., Koizumi K., Saitoh Y., Nakamura E.S., Kammasud N., Vajaragupta O. and Saiki I.: Anti- angiogenic effect of curcumin, curcumin ethylenediamine derivative and curcumin ethylenediamine manganese complex. J. Trad. Med., 21: 94-99, 2004.**

Abstract: We investigated the anti-angiogenic effect of curcumin, curcumin ethylenediamine derivative (curcumin ED) and curcumin ethylenediamine manganese complex (curcumin EDMn) through the inhibition of the formation of tube-like structures by human umbilical vascular endothelial cells (HUVEC). Curcumin, curcumin ED, curcumin EDMn did not show cytotoxicity to HUVEC at concentrations equal and lower than 10 μM. At the concentration of 10 μM, curcumin, curcumin ED and curcumin EDMn inhibited the tube formation by approximately 94%, 40% and 65%, respectively. These results suggest that curcumin ED and curcumin EDMn might be useful as anti-angiogenic drugs in addition to their anti-lipid peroxidase and superoxide dismutase activities as described in our previous studies.

6) **Hirabayashi Y., Yamaguchi K., Shiraishi N., Adachi Y., Saiki I. and Kitano S.: Port-site metastasis after CO_2 pneumoperitoneum: Role of adhesion molecules and prevention with antiadhesion molecules. Surg. Endosc., 18: 1113-1117, 2004.**

Abstract: BACKGROUND: Port-site metastasis is a continuing problem in laparoscopic cancer surgery. To clarify the role of adhesion molecules in the development of port-site metastasis, particularly with regard to prevention, we performed experiments in which port-site metastasis was inhibited using antibodies against extracellular matrix proteins or the active Arg-Gly-Asp (RGD) peptide after CO_2 pneumoperitoneum in a murine model. METHODS: We examined the development of port-site metastasis under the following conditions: (1) CO_2 pneumoperitoneum with or without hyaluronic acid and anti-integrin or anti-CD44 antibody and (2) CO_2 pneumoperitoneum and a RGD peptide or pseudo-RGD sequence peptide (FC-336). BALB/c mice (n = 130) were injected with 5 x 10(5) human gastric cancer cells (MKN45) and either antibody or peptide, treated with CO_2 pneumoperitoneum, and injected intraperitoneally with antibody or peptide for 5 days. Three weeks after CO_2 pneumoperitoneum, the frequency and weight of port-site metastatic tumors were determined. RESULTS: Anti-integrin antibody significantly decreased the weight of port-site metastatic tumors without hyaluronic acid (control vs anti-integrin: 8.2 +/- 7.1 vs 3.6 +/- 4.5 mg; $p < 0.05$) but not the frequency of port-site metastases. With hyaluronic acid, the frequency of port-site metastasis and the weight of port-site metastatic tumors were significantly decreased both by anti-integrin and by anti-CD44 antibody (control vs anti-integrin and anti-CD44; 95% and 8.5 +/- 7.2 mg vs 50% and 3.1 +/- 4.3 mg and 55% and 3.3 +/- 5.1 mg, respectively; $p < 0.05$). RGD peptide and FC-336 also inhibited port-site metastasis in a dose-dependent manner. CONCLUSION: Cell adhesion molecules integrin and CD44 play an important role in the development of port-site metastasis after laparoscopic cancer surgery. Intraperitoneal injection of RGD peptide or pseudo-RGD sequence peptide (FC-336) can prevent port-site metastasis.

7) **Yoshioka Y., Tsutsumi Y., Mukai Y., Shibata H., Okamoto T., Kaneda Y., Tsunoda S., Kamada H., Koizumi K., Yamamoto Y., Mu Y., Kodaira H., Sato-Kamada K., Nakagawa S. and Mayumi T.: Effective accumulation of poly(vinylpyrrolidone-co-vinyl laurate) into the spleen. J Biomed. Mater. Res. 70A: 219-223, 2004.**

Abstract: To optimize polymer-conjugated drugs as a polymeric drug delivery system, it is essential to design polymeric carriers with tissue-specific targeting capacity. Previously, we showed that polyvinylpyrrolidone (PVP) was the most suitable polymeric carrier for prolonging the blood-residency of drugs, and was one of the best parent polymers to design the polymeric carriers with targeting capacity. In this study, we synthesized some hydrophobic PVP derivatives, poly(vinylpyrrolidone-co-styrene) [poly(VP-co-S)] and poly(vinylpyrrolidone-co-vinyl laurate) [poly(VP-co-VL)], and assessed their biopharmaceutical properties after intravenous administration in mice. The elimination of hydrophobic PVP derivatives from blood was the same as PVP, and the plasma half-lives of poly(VP-co-S) were almost similar to that of poly(VP-co-VL). Poly(VP-co-VL) efficiently accumulated in the spleen, whereas poly(VP-co-S) effectively accumulated in the liver. The level of poly(VP-co-VL) in the spleen was about 20 times higher than PVP and poly(VP-co-S). These hydrophobic PVP derivatives did not show any cytotoxicity against endothelial cells in vitro. Thus, poly(VP-co-VL) may be a useful polymeric carrier for drug delivery to the spleen. This study will provide useful information to design optimal polymeric carriers with targeting capacity to the spleen and liver.

8) **Nagakawa O., Akashi T., Hayakawa Y., Junicho A., Koizumi K., Fujiuchi Y., Furuya Y., Matsuda T., Fuse H. and Saiki I.: Differential expression of integrin subunits in DU-145/AR prostate cancer cells. Oncology Rep., 12: 837-841, 2004.**

Abstract: We have established a clonal DU-145 prostate cancer cell line (DU-145/AR) stably transfected with androgen receptor cDNA. We investigated the expression of integrin subunits, adhesion to extracellular matrices, the

invasion of DU-145/AR prostate cancer cells. The expression of various integrin subunits and adhesion to various extracellular matrices in DU-145, DU-145/Neo and DU-145/AR cells were examined. The haptoinvasion and the haptotactic migration of these cells were investigated using a Transwell cell culture chamber assay. DU-145/AR cells exhibited lower expression of alpha6 and beta4 integrin subunits and higher expression of alpha2 and alpha5 than DU-145 cells. DU-145/AR cells showed significantly lower adhesion to fibronectin, laminin-1 and laminin-5 than DU-145/ Neo cells, whereas DU-145/AR cells showed higher adhesion to type I and type IV collagen. Haptoinvasion of DU-145/AR cells into Matrigel/fibronectin-coated filter was significantly reduced as compared with DU-145/Neo or DU-145 cells, but there was no significant difference between DU-145/AR and control cells in the haptotactic migration to fibronectin. Dihydrotestosterone (DHT) inhibited the invasive ability of DU-145/AR cells. These results indicate that androgen receptor may play a role in the regulation of adhesion to the extracellular matrices and invasion of prostate cancer cells through influencing the expression of specific integrin subunits.

9) **Ishihara K., Kawaguchi T., Matsuya Y., Sakurai H., Saiki I. and Nemoto H.: Synthesis and Biological Evaluation of Macrosphelide Cores, Eur. J. Org. Chem., 19: 3973-3978, 2004.**

10) **Hu J., Nakano H., Sakurai H. and Colburn N.H.: Insufficient p65 phosphorylation at S536 specifically contributes to the lack of NF-κB activation and transformation in resistant JB6 cells. Carcinogenesis, 25: 1991-2003, 2004.**

Abstract: NF-κB activation is required for TNF-alpha-induced transformation of JB6 mouse epidermal cells. Deficient activation of p65 contributes to the lack of NF-κB activation in transformation-resistant (P-) cells. We hypothesized that the differential NF-κB activation involves differential p65 phosphorylation arising from enzyme activity differences. Here we show that TNF-α induces greater ERK-dependent p65 phosphorylation at S536 in transformation sensitive (P+) cells than in P- cells. Our results establish that limited ERK content contributes to a low IκB kinase (IKKβ) level, in turn resulting in insufficient p65 phosphorylation at S536 upon TNF-alpha stimulation in P- cells. Phosphorylation of p65 at S536 appears to play a role in TNF-α-induced p65 DNA binding and recruitment of p300 to the p65 complex as well as in release of p65 bound to HDAC1 and 3. Blocking p65 phosphorylation at S536, but not at S276 or S529, abolishes p65 transactivational activity. Over-expression of p65 but not p65 phosphorylation mutant (S536A) in transformation-resistant P- cells renders these cells sensitive to TNF-α-induced transformation. Over-expression of p65 phosphorylation mimics p65-S536D or p65-S536E in P- cells and also rescues the transformation response. These findings provide direct evidence that phosphorylation of p65 at S536 is required for TNF-α-induced NF-κB activation in the JB6 transformation model. The lack of NF-κB activation seen in P- cells can be attributed to an insufficient level of p65 phosphorylation on S536 that arises from insufficient IKKβ that in turn arises from insufficient ERK. Thus, p65 phosphorylation at S536 offers a potential molecular target for cancer prevention.

11) **Aozuka Y., Koizumi K., Saitoh Y., Ueda Y., Sakurai H. and Saiki I.: Anti-tumor angiogenesis effect of aminopeptidase inhibitor bestatin against B16-BL6 melanoma orthotopically implanted into syngeneic mice. Cancer Lett., 216: 35-42, 2004.**

Abstract: We investigated the effect of bestatin, an inhibitor of aminopeptidase N (APN)/CD13 and aminopeptidase B, on the angiogenesis induced by B16-BL6 melanoma cells. Oral administration of bestatin (100-200 mg/kg/day) was found to significantly inhibit the melanoma cell-induced angiogenesis in a mouse dorsal air sac assay. Additionally, anti-APN/CD13 mAb (WM15), which neutralizes the aminopeptidase activity in tumor cells, as well as bestatin inhibited the tube-like formation of human umbilical vein endothelial cells (HUVECs) in vitro. Furthermore, the intraperitoneal administration of bestatin (50-100 mg/kg/day) after the orthotopic implantation of B16-BL6 melanoma cells into mice reduced the number of vessels oriented towards the established primary tumor

mass on the dorsal side of mice. These findings suggest that bestatin is an active anti-angiogenic agent that may inhibit tumor angiogenesis in vivo and tube-like formation of endothelial cells in vitro through its inhibition of APN/CD13 activity.

12) **Ueda Y., Yamagishi T., Ikeya H., Hirayama N., Itokawa T., Aozuka Y., Samata K., Nakaike S., Tanaka M., Ono M. and Saiki I.: VGF1155, a novel binding antagonist of VEGF inhibits angiogenesis in vitro and in vivo. Anticancer Res., 24: 3009-3017, 2004.**

Abstract: The process of angiogenesis involves the formation of new blood vessels from established vasculature and is essential for progressive tumor growth and metastasis. Since vascular endothelial growth factor (VEGF) plays a pivotal role in tumor angiogenesis, it is reasonable to expect that antagonizing VEGF binding to its receptor may be effective in cancer therapy. Our previous study found that a novel low molecular weight compound, VGA1155, inhibited binding between radioisotope-labelled VEGF and cells overexpressing its two receptors, Flt-1 and KDR/Flk-1, that is, NIH3T3-Flt-1 and NIH3T3-KDR, respectively. In the present study, we investigated the anti-angiogenic effects of VGA1155 based on VEGF inhibition. VGA1155 inhibited VEGF-induced DNA synthesis of human umbilical vein endothelial cells (HUVEC) and human retinal endothelial cells (HREC) in a concentration-dependent manner. VGA1155 also inhibited VEGF-induced tube formation of HUVEC in vitro and tumor angiogenesis toward B16-BL6 melanoma after orthotopic implantation into the skin of the back. On the other hand, VGA 1155 did not affect the proliferation of human epidermoid carcinoma (KB) cells and mouse mammary carcinoma (MM2) cells. It also had no effect on the activity of several cytosolic kinases such as p55fyn and p56lck. These findings suggest that VGA1155 inhibits endothelial cell growth and angiogenesis by inhibiting VEGF function but not non-specific cytotoxicity. VGA1155 thus exhibits promise as an antiangiogenic or anti-tumor agent with fewer side-effects.

◇総　説

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◇研究費取得状況

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◇学位（修士，博士）取得者

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