病態生化学部門

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◇研究目的

病態生化学部門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，構造の明かにされた成分あるいは化合物を用いて，種々の病態（癌，アレルギーなどの疾患）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。また，「証」といわれる病態変化を遺伝子工学的，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。

◇研究概要

Ⅰ．癌および癌転移の抑止に関する基礎的研究

1）癌および癌転移の抑制物質の探索（伝統薬物を中心に）
2）癌の悪性化・進展モデルの確立とその分子機序の解析
3）癌ワクチンを指向した免疫遺伝療法の開発と免疫力増強物質の検索
4）同所移植性転移モデルにおける転移の臓器特異（選択）性とその機序の解析
5）細胞接着の制御に基づく浸潤・転移の抑制
6）基底膜分解酵素の転写・産生・分解レベルでの阻害物質の探索

Ⅱ．免疫抑制に関する基礎的研究

1）アレルギー性／炎症性疾患モデルの確立と有効物質（抑制／増強）の探索
2）免疫応答調節機構解明と和漢薬への応用

Ⅲ．細胞の機能制御とシグナル伝達機構の解析

1）自己分泌型運動抑制因子の単離・精製とその構造解析
2）細胞運動と細胞内調節分子の関連性の解析
3）神経ペプチドによる細胞浸潤の制御と細胞内機能分子の関与

◇著　書

1）済木育夫，澤田成朗，塚田一博：漢方方剤を用いた免疫賦活効果と転移抑制，3. 免疫関連療法，「新しい癌免疫化学療法の指針，QOLを重視した癌薬物療法」，佐治重豊，峠哲哉／編集，医薬ジャーナル社，pp237-245，1999.

◇原　著

1）**Katagiri Y.U., Sleeman J., Fujii H., Herrlich P., Hotta H., Tanaka K., Chikuma S., Yagita H., Okumura K., Murakami M., Saiki I., Chambers A.F. and Uede T.: CD44 variants but not CD44s cooperate with β1-containing integrins to permit cells to bind to osteopontin independently of arginine-glycine-aspartic acid, thereby stimulating cell motility and chemotaxis. Cancer Res., 59 : 219-226, 1999.**

Abstract: The expression of osteopontin (OPN), CD44 variants, and intergins has been correlated with tumorigenesis and metastasis. Here we show that these proteins cooperate to enhance cell motility. First, we demonstrate that several different CD44 variants bind to OPN in an arginine-glycine-aspartic acid-independent manner, but that the standard form of CD44 does not. These CD44 variants bind to both the amino- and COOH-terminal portions of OPN independently of the arginine-glycine-aspartic acid sequence, suggesting that multiple domains on OPN can be bound by the CD44 variants. Antibodies directed against the integrin β1 subunit are able to inhibit this binding. The binding of CD44 variants to OPN is significantly augmented by both anti-CD44s and anti-CD44v antibodies. This augmentation by anti-CD44 antibodies is OPN specific and, again, can be blocked by anti-β1 antibodies. Finally, we show that OPN binding by CD44 variants/β1-containing integrins promotes cell spreading, motility, and chemotactic behavior.

2）**Watanabe C., Satoh T., Tahara E., Murakami K., Hayashi K., Hase K., Andoh T., Kuraishi Y., Kadota S., Nagai H. and Saiki I.: Inhibitory mechanisms of glycoprotein fraction derived from Miscanthus sinensis for immediately phase response of IgE-mediated cutaneous reaction. Biol. Pharm. Bull., 22 : 26-30, 1999.**

Abstract: We investigated the inhibitory effect of the glycoprotein fraction (fraction 2) extracted from *Miscanthus sinensis* Andersson (*M.sinensis*) on biphasic cutaneous reactions in mice passively sensitized with IgE. Biphasic skin reactions with peak responses at 1 (IPR, immediate phase reaction) and 24 h (LPR, late phase reaction) were caused by passive sensitization with an anti-dinitrophenol IgE monoclonal antibody (anti-DNP IgE mAb) followed by an epicutaneous challenge of 0.1% dinitrofluorobenzene (DNFB) in 100% ethanol. Intraperitoneal injection of fraction 2 before the DNFB challenge significantly inhibited the biphasic ear swelling response in passively sensitized mice in a dose-dependent manner (1-30 mg/kg). We also found that fraction 2 was effective at inhibiting the vascular permeability in mouse ear induced by an injection of compound 48/80, histamine or serotonin. In addition, fraction 2 inhibited scratching behavior as well as ear edema observed within 2 h after DNFB challenge. Marked inhibition was observed in both passively sensitized and non-sensitized

mice. The locomotor activity of mice was also reduced by the administration of fraction 2 as well as by diphenhydramine. These results suggest that the inhibitory effect of glycoprotein fraction 2 of *M. sinensis* on an IgE-mediated allergic inflammatory reaction is due to the protection of mediator-induced vascular permeability and that in addition to the inhibition of an inflammatory reaction, a sedative action is responsible for the inhibition of allergy-induced scratching responses.

3) **Doki Y., Murakami K., Yamaura T., Sugiyama T., Misaki T. and Saiki I.: Mediastinal lymph node metastasis model by orthotopic intrapulmonary implantation of Lewis lung carcinoma cells in mice. Br. J. Cancer, 79 : 1121–1126, 1999.**

Summary : This study is designed to establish a pulmonary tumor model to investigate the biology and therapy of lung cancer in mice. Current methods for forming a solitary intrapulmonary nodule and subsequent metastasis to mediastinal lymph nodes are not well defined. Lewis lung carcinoma cell (LLC) suspensions were orthotopically introduced into the lung parenchyma of C57/BL6 mice via a limited skin incision without thoracotomy followed by direct puncture through the intercostal space. The implantation process was performed within approximately 50 sec per mouse, and the operative mortality was less than 5 %. Single pulmonary nodules developed at the implanted site in 93 % of animals and subsequent mediastinal lymph nodes metastasis were observed in all mice that were succeded to form a lung nodule after intrapulmanary implantation. The size of tumor nodule and the weight of mediastinal lymph node increased in a time-dependent manner. The mean survival time of mice implanted successfully with LLC cells was 21 ± 2 days (range; 19-24 days). Histopathlogical analysis revealed that no metastatic tumor was detectable in the mediastinal lymph nodes on day 11, but metastatic foci mediastinal lymph nodes were clearly observed on days 17 and 21 after implantation. Other metastases in distant organs or lymph nodes were not observed at 21 days after the implantation. Comparative studies with intrapleural and intravenous injections of LLC cells suggest that the mediastinal lymph node metastasis by intrapulmonary impantation is due to the release of tumor cells from the primary nodule, and not due to extrapulmanary leakage of cells. An intravenous administration of CDDP on day 1 after tumor implantation tended to suppress the primary tumor nodule and significantly inhibited the lymph node metastasis. Thus, a solitary pulmonary tumor nodule model with lymph node metastasis approximates clinical lung cancer, and may provide a useful basis for lung cancer research.

4) **Murata J., Ayukawa K., Ogasawara M., Watanabe H. and Saiki I.: Induction of autocrine factor inhibiting cell motility from murine B16-BL6 melanoma cells by α-melanocyte stimulating hormone. Int. J. Cancer, 80 : 889–895, 1999.**

Abstract : We have previously reported that neuropeptide α-melanocyte stimulating hormone (α-MSH) successfully inhibited Matrigel invasion and haptotactic migration of B16-BL6 melanoma cells towards both fibronectin and laminin without affecting their growth. In

the present study, we investigated the inhibitory mechanism of tumor cell motility by α-MSH. α-MSH significantly blocked the autocrine motility factor (AMF)-enhanced cell motility. However, α-MSH did neither prevent the secretion of AMF from B16-BL6 cells nor alter the expression level of AMF receptor (gp78). On the other hand, α-MSH induced the secretion of the motility inhibitory factor(s) from B16-BL6 cells in a concentration- and time-dependent manner. The induction of the motility inhibitor(s) was proportional to increasing levels of intracellular cAMP induced by α-MSH as well as forskolin, and the activity was abolished by an adenylate cyclase inhibitor, 2',5'-dideoxyadenosine (DDA). The motility-inhibiting activity in conditioned medium (CM) from α-MSH-treated B16-BL6 cells was found to have a m.w. below 3 kDa after fractionation. This activity was abolished by boiling but insensitive to trypsin. The treatment of tumor cells with cycloheximide reduced the activity in α-MSH-stimulated CM. Our results suggest that α-MSH inhibited the motility of B16-BL6 cells through induction of autocrine factor(s).

5) **Stampoulis P., Tezuka Y., Banskota A.H., Tran K. Q., Saiki I. and Kadota S.: Staminol A, novel diterpene from *Orthosiphon stamineus*. Tetrahedr. Letts, 40 : 4239–4242, 1999.**

Abstract : From the aerial part of a Vietnamese medicinal plant, *Orthosiphon stamineus* BENTH.(Lamiaceae), staminol A (1), a diterpene with a novel carbon framework, was isolated together with four new isopimarane-type diterpenes, orthosiphols F-1 (2-5). Their structures were elucidated by the spectroscopic analyses.

6) **Saiki I., Yamaura T., Ohnishi Y., Hayakawa Y., Komatsu Y. and Nunome S..: HPLC analysis of Juzen-taiho-to and its variant formulations and their antimetastatic efficacies. Chem. Pharm. Bull., 47 : 1170–1174, 1999.**

Abstract : Our previous study demonstrated that the oral administration of Juzen-taiho-to resulted in a significant inhibition of the liver metastasis of colon 26-L5 cells as compared with the untreated control, without side effects. We attempted to investigate the relationship between the HPLC pattern (referred to as the fingerprint) of the formulation and its component crude drugs and the inhibition of tumor metastasis in order to obtain the optimal efficacy and constant quality of the formulation. Two Juzen-taiho-to formulations (batches #1 and # 2), which were individually prepared using the same 10 crude drugs and the same preparation procedure, showed similar anti-metastatic effects and absorbance patterns by HPLC analysis. Some variant formulations of Juzen-taiho-to, in which one crude drug was substituted with other crude drugs from different sources or places of origin, exhibited reduced efficacy as compared with the original formulation, as well as differences in the fingerprint pattern compared with the original formulation. Juzen (Naimo-Ogi→Kibana-Ogi), a variant formulation with the substitution of Astragali radix of a different origin and place of harvest, showed significant inhibition of the liver metastasis of tumor cells and a HPLC fingerprint pattern similar to that of the original formulation. Thus, HPLC fingerprint

analysis of Kampo medicines may provide a useful basis for obtaining their optimal efficacy as well as constant quality of the formulation, although it has some problems and limitations, such as detectability by and sensitivity to UV absorbance.

7) **Murakami K., Sakukawa R., Sano M., Hashimoto A., Shibata J., Yamada Y. and Saiki I.: Inhibition of angiogenesis and intrahepatic growth of colon cancer by TAC-101. Clin. Cancer Res., 5 : 2304–2310, 1999.**

Abstract : We demonstrated in this study that inhibition of intrahepatic growth of colon cancer by TAC-101 is mediated by inhibition of angiogenesis. *In vitro* experiments showed that TAC-101 inhibited the proliferation of murine hepatic sinusoidal endothelial (HSE) cells induced by coculture with murine colon 26-L5 (L5) cells. HSE cell proliferation was also enhanced by conditioned medium of L5 cells (CM-L5), and this enhancement of proliferation was abrogated by anti-VEGF antibody. CM-L5 also induced *in vitro* tube formation of HSE cells on Matrigel, and this activity of CM-L5 was abrogated by TAC-101 in a concentration-dependent manner. On the other hand, oral administration of TAC-101 inhibited tumor-induced angiogenesis *in vivo* and decreased the weights of L5 tumors in the mouse liver. RT-PCR analysis using *in vivo* tumor tissue suggested that repression of VEGF expression by TAC-101 was associated with the antiangiogenic activity. TAC-101 alone and 5-fluorouracil/leucovorin (5-FU/LV) significantly inhibited the intrahepatic growth of L5 tumors ($P=0.002$, 0.001, respectively), while 5-FU alone did not ($P=0.088$). When TAC-101 was administered with 5-FU/LV, marked enhancement of antitumor activity was observed (95% inhibition, $P<0.001$). This enhanced antitumor effect was also observed in experiments using Co-3 human colon adenocarcinoma. Concurrent treatment with TAC-101 and 5-FU/LV or sequential treatment with 5-FU/LV followed by TAC-101 resulted in significant augmentation of antitumor activity against Co-3 (overall $P=0.007$ and 0.015, respectively). These findings indicate that TAC-101 inhibits tumor angiogenesis and suggested that it may be effective against hepatic metastasis of colon cancer.

8) **Xu Q., Wu F., Cao J., Chen T., Jiang J., Saiki I. and Koda A.: Astilbin selectively dysfunction of liver-infiltrating cells -novel protection from liver damage. Eur. J. Pharmacol., 377 : 93–100, 1999.**

Abstract : The present study aimed to examine the effect of astilbin, a flavanoid, on liver injury. When administered during the effector but not induction phase, astilbin significantly decreased the liver injury induced by delayed-type hypersensitivity to picryl chloride in mice. The pretreatment of nonparenchymal cells but not hepatocytes with astilbin *in vitro* caused a concentration- and time-dependent inhibition against the damage. Nonparenchymal cells isolated from astilbin-administered mice also showed a significant incompetence of hepatotoxicity, correlated with the inhibition of serum transaminase elevation. However, astilbin did not protect from CCl4-induced liver damage. Furthermore, the flavanoid markedly promoted the apoptosis of nonparenchymal cells from liver-injured mice, whereas did

not influence those from naive mice. These results suggest that astilbin provides improvement against liver injury through a selective dysfunction of liver-infiltrating cells rather than by protecting the hepatocyte membrane. Such characteristics will be of significance to pave a new way for treating immunologically related liver diseases and for developing new drugs.

9) **Murakami K., Yamada Y., Saiki I., Matsuura T., Hasumura S., and Nagamori S.: Gene expression in human hepatocellular carcinoma cell lines. Tiss. Cult. Res. Commun., 18 : 221–228, 1999 (in Japanese).**

Abstract : Established hepatocellular carcinoma (HCC) cell lines have many functions and show the hepatocyte-like properties such as secretin of plasma proteins and activities of metabolic enzymes, and therefore they have been considered to be useful for the analysis of liver cell functions. On the other hand, HCC cell lines may have some properties as tumor cells because they show the autocrine growth in the serum-free condition. In this study, we investigated the gene expression of growth factors and receptors in JHH-5, JHH-6 and JHH-7 using RT-PCR. JHH-5 and JHH-7 showed a marked increase of the expression of mRNA for insulin-like growth factor-II (IGF-II). The proliferation of JHH-7 was inhibited by anti-IGF-II antibody. HCC cell lines also expressed mRNAs for angiogenic factors including vascular endothelial growth factor (VEGF) and fibroblast growth factor. JHH-7-induced migration of endothelial cell was significantly inhibited by anti-VEGF antibody. These findings suggest that established HCC cell lines have some HCC properties and may be beneficial to analyze the molecular mechanism of hepatocarcinogensis.

10) **Murakami K., Yamaura T., Suda K., Ohie S., Shibata J., Toko T., Yamada Y. and Saiki I.: TAC-101 inhbits spontaneous mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma. Jpn. J. Cancer Res., 90 : 1254 –1261, 1999.**

Abstract : The anti-tumor and anti-metastatic effects of 4-[3,5-bis(trimethyl-silyl) benzamido] benzoic acid (TAC-101) was investigated using our established lung cancer model. Orthotopic implantation of Lewis lung carcinoma (LLC) cells into the lung parenchyma produced a solitary tumor nodule in the lung followed by the formation of mediastinal lymph node metastasis. Daily oral administration of TAC-101 at the doses ranging from 4 to 16 mg/kg resulted in a significant inhibition of lymphatic metastasis (inhibition rate = 57 to 76 %), while only 16 mg/kg TAC-101 significantly inhibited tumor growth at the implanted sites (inhibition rate = 46 %). Combined treatment of CDDP with TAC-101 (8 mg/kg, p.o., daily) enhanced anti-tumor effect of CDDP (7 mg/kg, i.v., bolus) against both the growth of implanted tumor and lymphatic metastasis. In addition, this combined treatment significantly prolonged the survival time of LLC tumor-bearing mice as compared with each alone. Anti-AP-1 activity of TAC-101 caused inhibition of LLC cell invasion through the repression of urokinase-type plasminogen activator and its receptor production.

Anti-invasive activity of TAC-101 may be involved in *in vivo* anti-metastatic activity. These findings suggest that TAC-101 is a novel anti-cancer agent and may improve therapeutic modality for lung cancer patient with metastatic disease.

11) **Ogasawara M., Murata J., Kamitani Y., Hayashi K. and Saiki I.: Inhibition by vasoactive intestinal polypeptide (VIP) of angiogenesis induced by murine colon 26-L5 carcinoma cell metastasized in liver. Clin. Exp. Metastasis, 17 : 283–291, 1999.**

Abstract : We investigated the effect of VIP on the liver metastases and angiogenesis by Colon 26-L5 carcinoma cells in mice. Daily systemic administration of VIP, beginning 3 days after tumor inoculation into a portal vein of mice, inhibited significantly the development of their liver metastases. Immunohistochemical staining for factor VIII-related antigen in the sections of liver metastases showed that the systemic administration of VIP caused significant prevention of angiogenesis within tumor masses. VIP (10-(10) to 10(-6) M) inhibited the invasion of reconstituted basement membrane (Matrigel) by hepatic sinusoidal endothelial (HSE) cells in a concentration-dependent manner in a Transwell chamber assay *in vitro* and achieved approximately 50% reduction of control at 10(-6) M. VIP (10(-6) M) also significantly suppressed the haptotactic migration of HSE cells to fibronectin, laminin or type I collagen substrates with a similar inhibition rate to the invasion assay. Exposure of VIP to HSE cells induced accumulation of intracellular cAMP in a concentration-dependent manner. The inhibitory effect of VIP (10(-6) M) on HSE cell migration was significantly abrogated in the presence of 3 x 10(-6) M H-89, a cAMP-dependent protein kinase inhibitor. VIP (10(-6) M) inhibited the morphogenesis of HSE cells into capillary-like structures on Matrigel-coated wells. VIP did not affect the proliferation of HSE cells and the production of gelatinases in HSE cells *in vitro* at the concentrations used in the invasion assay. These observations suggest that the anti-metastatic effect of VIP on liver metastases by Colon 26-L5 carcinoma cells in mice is partly due to the prevention of tumor angiogenesis probably through suppression of the motility of endothelial cells.

12) **Tahara E., Satoh T., Watanabe C., Nagai H., Shimada Y., Itoh T., Terasawa K. and Saiki I.: A third phase cutaneous response (very late phase response; vLPR) after the elicitation of DNFB in passively or actively sensitized mice. Allergology. Int., 48 : 265–273,1999.**

Abstract : Previous studies have reported that the mice passively sensitized with anti-DNP IgE antibody exhibited IgE-mediated cutaneous reaction with an immediate phase response (IPR) at 1 h and a late phase response (LPR) at 24 h after the challenge of DNFB. We found that the third phase inflammatory reaction with intense and persisting infiltration of eosinophils, named "very late phase reaction (vLPR)", was induced following IPR and LPR in response to DNFB in actively and passively sensitized mice, and that the peak response of vLPR was at 8 day after the challenge. This reaction was slightly observed in non-sensitized

mice. Since the accumulation of eosinophils in vLPR was markedly observed as compared with that of LPR at 24 h, the vLPR may be an important reaction in allergic diseases. The development of vLPR was partly decreased in mast cell-deficient WBB6F1-W/Wv mice and was absent in T cell-deficient BALB/c-nu/nu mice in passively sensitization. These results indicate that the vLPR in the triphasic cutaneous reaction may be mainly mediated by T cells and partially mast cells and/or IgE antibody, and consequently lead to an intense ear swelling accompanying massive infiltration of eosinophils.

13) **Stampoulis P., Tezuka Y., Banskota A.H., Tran K. Q., Saiki I. and Kadota S.: Staminolactone A, B and Norstaminol A: Oxygenated Staminane-type diterpenes from Orthosiphon stamineus. Organic Letts, 1 : 1367–1370, 1999.**

Abstract : Staminolactones A (1) and B (2) and norstaminol A (3), three highly oxygenated staminane-type diterpenes having mild cytotoxic activities against highly liver-metastatic colon 26-L5 carcinoma cells, were isolated from the aerial part of the Vietnamese medicinal plant *Orthosiphon stamineus* (Lamiaceae). Their structures were elucidated on the basis of the extensive spectral analyses.

14) **Xu Q., Cao J., Wu F., Hayakawa Y., Saiki I. and Koda A.: Role of Th1 and Th2 cytokines in regulating the liver injury induced by delayed-type hypersensitivity to picryl chloride. Liver, 19 : 473–480, 1999.**

Abstract : *Aims/Background*: We have previously reported that a new model of liver injury induced in mice by delayed-type hypersensitivity (DTH) to picryl chloride (PCl) mimicks the pathogenesis of human hepatitis. This liver injury is mediated by $CD4^+$ T cells. The interaction between lymphocyte function associated antigen 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) is an essential process for hepatocyte (HC) damage. The present study was undertaken to reveal the role of Th1 and Th2-like cytokines in regulating liver injury. *Methods*: The kinetics of cytokine production were examined by ELISA and RT-PCR after the elicitation of liver injury for both serum protein and liver mRNA expression, respectively. A co-culture assay between liver nonparenchymal cells (NPC) and HC was couducted to evaluate the cytokine regulation on the cell-cell interaction. Expression of LFA-1 on NPC and ICAM-1 on HC were examined by FACScan and ELISA, respectively. *Results*: serum IL-2 and IFN-γ showed a peak production at 6 and 12 h, while IL-5 and IL-4 reached their maximum levels at 18 and 24 h after induction of liver injury, respectively. Liver mRNA expression of IFN-γ and IL-4 had a similar time course to their corresponding products. Both recombinant murine IFN-γ and IL-2 triggered the hepatotoxicity of NPC or spleen cells at 0 h. In this case, an increased expression of both LFA-1 on NPC and ICAM-1 on HC was also observed. In contrast, IL-4 and IL-5 completely abolished the hepatotoxicity of NPC at 12 h without influencing the adhesion moecules. *Conclusion*: Th1 and Th2 may be involved in regulating liver injury. Th1/Th2 balance may critically contribute to the production of the liver injury or recovery from it.

15) **Gewali M. B., Tezuka Y., Banskota A. H., Ali M.S., Saiki I., Dong H and Kadota S.: Epicalyxin F and calyxin I: Two novel antiproliferative diarylheptanoids from the seeds of *Alpinia blepharocalyx*. Organic Letts, 1 : 1733–1736, 1999.**

Abstract: Epicalyxin F (1) and calyxin I (2), two novel diaryheptanoids, were isolated from a residul fraction of an EtOH extract of *Alpinia blepharocalyx*. Calyxin I (2) represented a new carbon skeleton, and epicalyxin F (1) possessed potent antiproliferative activity toward HT-1080 fibrosarcoma and colon 26-L5 carcinoma with ED_{50} values of 1.71 and 0.89 μM, respectively.

16) **Koketsu M., Ishihara H., Wu W., Murakami K. and Saiki I: 1,3-Selenazine derivatives induce cytotoxicity and DNA fragmentation in human HT-1080 fibrosarcoma cells. Eur J. Pharm. Sci., 9 : 157–161, 1999.**

Abstract: The inhibitory effects of aseries of 5,6-dihydro-4H-1,3-se;emazome derivatives, 1,3-selenazole, and 5,6-dihydro-4H-1,3-thiazine derivatives on the proliferation of human HT-1080 fibrosarcoma cells were investigated. The compounds 4-ethyl-4-hydroxy-2-p-tolyl-5,6-dihydro-4H-1,3-selenazine (TS-2) and 4-hydroxy-4-methyl-6-propyl-2-p-tolyl-5,6-dihydro-4H-1,3-selenazine (TS-6) exhibited the strongest inhibotory effect amound 1,3-selenazine derivatives, and the EC_{50} of TS-2 and TS-6 was 7.76 and 8.40 μM, respectively. On the other hand, 1,3-selenazole and 5,6-dihydro-4H-1,3-thiazines had no inhibitoryu effects. TS-2 and TS-6 inhibited the proliferation of HT-1080 cells time- and dose-dependently. They induced dose-dependent DNA fragmentation in HT-1080 cells, revealing a typical apoptosis characteristics. The present study demonstrated that TS-2 and TS-6 inhibited HT-1080 proliferation through the induction of DNA fragmentation.

17) **Murakami K., Sakukawa R., Ikeda T., Matsuura T., Hasumura T., Nagamori S. Yamada Y. and Saiki I.: Invassiveness of hepatocarcinoma cell lines: Contributions of associated molecules. Neoplasia, 1: 424-430, 1999.**

Abstract: Intrahepatic metastasis is one of the malignant features of hepatocellular carcinoma (HCC). Matrix metalloproteoinases (MMPs) and urokinase-type plasminogen activator (u-PA)/plasmin, are known to be associated with the invasive properties of various types of tumor cells. In this study, we examined which proteinases play a role in the metastatic invasion of human HCC cell lines. JHH-5 and JHH-6 cells constitutively expressed mRNAs for both membrance-type 1 matrix metalloproteinase (MT1-MMP) and u-PA and invaded through recomstituted MATRIGEL *in vitro*, whereas JHH-7 cells expressed u-PA mRNA but not MT1-MMP and did not invade. However, hepatocyte growth factor (HGF) induced MT1-MMP expression on the surface of JHH-7 cells and markedly increased invasiveness of JHH-7 in a concentration-dependent manner. Moreover, cleavage activity for pro-MMP-2 was induced in HGF-treated JHH-7 cells. MMP inhibitor, rather than serine proteinase inhibitor, potently inhibited HCC cell invasion. Intrahepatic injection of HCC cell lines into athymic nude mice caused visible intrahepatic metastases *in vivo*. Moreover, JHH-7 tumors

showed expression of MT1-MMP mRNA, while *in vitro* cultured JHH-7 cells did not. These findings suggest that MT1-MMP plays an important role in the invasive properties of HCC cells, and that HGF modifies the invasive properties of nonivasive HCC cells.

18) **Nagakawa O., Murakami K., Ogasawara M., Murata J., Fuse H. and Saiki I.: Effect of chromogranin A (pancreastatin) fragment on invasion of prostate cancer cells. Cancer Letts, 147: 204-213, 1999.**

Abstract: We investigated the effect of chromogranin A (pancreastatin) fragment on the invasion of PC-3, DU-145 and LNCaP prostate cancer cells through a reconstituted basement membrane (Matrigel) using a Transwell cell culture chamber assay. Chromogranin A fragment increased the invasive capacity of both PC-3 and DU-145 cells, whereas it had no significant effect of LNCaP cells. Chromogranin A fragment also increased the haptotactic migration of both PC-3 and DU-145 cells to fibronectin. Furthermore chromogranin A fragment increased the fibrinolytic activities of urokinase-type plasminogen activator (u-PA) in fibrin zymograms of both PC-3 and DU-145 cells and the expression of u-PA mRNA of PC-3 cells. However, the growth of these tumor cells was not affected by chromogranin A fragment at any concentrations used in this study. These results indicate that chromogranin A fragment increased the invasive potential of both PC-3 and DU-145 cells probably through enhancement of cell motility and the production of u-PA.

19) **Tahara E., Satoh T., Toriizuka K., Nagai H., Shimada Y., Itoh T., Terasawa K. and Saiki I.: Effect of Shimotsu-to (a Kampo medicine, Si-Wu-Tang) and its constituents on triphasic cutaneous reaction in passively sensitized mice. J. Ethnopharmacol., 68 : 219–228, 1999.**

Abstract: Pervious studies have reported that mice passively sensitized with anti-DNP (dinitrophenol) IgE antibody exhibited IgE-mediated skin reaction with an immediate phase response (IPR) at 1 h and a late phase response (LPR) at 24 h after the challenge of DNFB (dinitrofluorobenzene). We recently found that a third phase inflammatory reaction with intense and persisting infiltration of eosinophils, named very late phase response (vLPR), was induced by DNFB challenge peaking at 8 days. In this study, we examined the effects of a Kampo medicine, Shimotsu-to (Si-Wu-Tang), and its constituent crude drugs on triphasic skin reaction in passively sensitized mice. Shimotsu-to inhibited ear swelling in LPR and vLPR after DNFB challenge in a dose-dependent manner, and slightly diminished the scratching behavior considered to be associated with pruritis in IPR. The inhibitory effect on LPR and vLPR was partly due to Cnidii Rhizoma (Senkyu) in Shimotsu-to formulation, especially its fraction 5 containing cnidilide. On the other hand, Angelicae Radix (Toki) rather than Cnidii Rhizoma (Senkyu) in Shimotsu-to, inhibited the scratching behavior, although it did not inhibit the ear swelling in IPR. These findings indicate that the Shimotsu-to formulation is useful for the inhibition of cutaneous inflammatory diseases.

20) **Wu W., Murakami K., Koketsu M., Yamada Y. and Saiki I.: Induction of apoptosis in human gastric adenocarcinoma cells by two novel organoselenium compounds, TS-2 and TS-6.**

Abstract: Two new organoselenium compounds, 4-ethyl-4-hydroxy-2-p-tolyl-4H-5,6-dihydro-1,3-selenazine (TS-2) and 4-hydroxy-4-methyl-6-propyl-2-p-tolyl-4H-5,6-dihydro-1,3-selenazine (TS-6) were investigated for their inhibitory effect on the growth of 8 human tumor cell lines, including stomach, lung, prostate and colon cancer cell lines, in vitro. Both TS-2 and TS-6 exhibited the strongest cytotoxicity against a gastric adenocarcinoma (TMK-1) among 8 human tumor cell lines, and their IC_{50} were 2.38 μM and 2.78 μM, respectively. Twenty-four-h exposure of TMK-1 cells to TS-2 or TS-6 (0.1-100 μM) in the absence of serum led to a concentration-dependent increase of cytotoxicity. Exposure of TMK-1 cells toTS-2 or TS-6 (5, 10 or 20 μM) in the presence of 5% serum resulted in significant inhibition of TMK-1 cell proliferation in a concentration- and time-dependent manner. Morphological changes including shrinkage of the nucleus, and DNA ladder fragmentation, which are considered to be the typical features of apoptosis, were observed in TMK-1 cells in response to TS-2 or TS-6. Furthermore, the caspase-3 activity in TMK-1 cells treated with TS-2 or TS-6 was also found to be increased in a time-dependent manner, in parallel with the induction of DNA fragmentation. Taken together, the results of the present study suggest that the inhibition of growth of TMK-1 cells by TS-2 and TS-6 is mediated by the induction of apoptosis.

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◇研究費取得状況

1）文部省科学研究費，がん重点領域研究支援委員会（分担：済木育夫）「制癌剤スクリーニング」，（分担課題）基底膜浸潤阻害物質の検定
2）文部省科学研究費，重点領域研究（1）（分担：済木育夫）「宿主因子を重視した転移の分子生物学」，（課題番号０９２５４１０１）（分担課題）免疫誘導による転移形成の制御
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