病態生化学分野　Division of Pathogenic Biochemistry

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◇研究目的

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，がん，免疫疾患などを中心にして検討を行っている。

◇研究概要

Ⅰ）和漢薬に関する基礎的研究

1)　漢方方剤およびその構成成分によるがん転移抑制とその機構
2)　和漢薬による免疫応答および免疫疾患の制御に関する研究

Ⅱ）がんの増殖・転移機構の解明とその制御

1)　薬剤併用による細胞死誘導効果とその分子機構の解明
2)　上皮間葉転換 (Epitherial Mesenchymal Transition; EMT) の制御機構の解析と阻害剤の探索
3)　がん転移病態モデルを用いての転移阻害効果の解析

Ⅲ）ストレス応答シグナルによる病態制御機構の解析

1)　プロテインキナーゼ TAK1 によるがん悪性化の分子機構の解明
2)　がん分子標的治療に関与する細胞内シグナルの制御に関する研究

◇著書

1)　Yokoyama S. and Fisher D.E.: Chapter 5. Transcriptional Regulation in Melanoma. Melanoma Development. (Ed.) Bosserhoff A., Springer Wien New York, USA, 2011, pp79-104

◇原著論文

1)　**Waiwut P., Shin M.S., Inujima A., Zhou Y., Koizumi K., Saiki I., and Sakurai H.: Gomisin N enhances TNF-α-induced apoptosis via inhibition of NF-κB and EGFR survival pathways. Mol. Cell. Biochem., 350: 169-175, 2011.**

Abstract: Tumor necrosis factor (TNF-α) is a pleiotropic cytokine that plays an important role in the control of cell proliferation, differentiation, and apoptosis. TNF-α-induced apoptosis is limited by TAK1-mediated activation of NF-κB (mainly p65-p50 hetrodimer) signaling pathway. We have recently reported that TAK1 regulates phosphorylation of EGFR at Ser-1046/7 through p38 MAPK, which cooperates with NF-κB in TNF-α-induced apoptosis. The present study investigated the effect of gomisins A and N, dibenzocyclooctadiene lignans isolated from the fruit of Schisandra chinensis, on TNF-α-induced apoptosis in HeLa cells. Gomisins A and N strongly promoted TNF-α-induced cleavage of caspase-3 and PARP-1, which are key markers of apoptosis. We found that gomisin N, but not gomisin A, inhibited the TNF-α-induced activation of NF-κB by suppressing the activation of IKKα. Gomisin N also inhibited p38-mediated phosphorylation of the EGFR at Ser-1046/7 and subsequent endocytosis of EGFR, another prosurvival pathway. The findings suggested that gomisin N enhanced TNF-α-induced apoptosis by suppressing of NF-κB and EGFR signaling pathways.

2) **Prangsaengtong O., Koizumi K., Senda K., Sakurai H., and Saiki I.: eNOS and HSP90 interaction directly correlates with lymphatic tube formation. Lymph. Res. Biol., 9: 53-59, 2011.**

Abstract: Endothelial nitric oxide synthase (eNOS) and heat shock protein 90 (Hsp90) have been reported to contribute to angiogenesis and lymphangiogenesis. However, the functions of these proteins during lymphangiogenesis are unclear. In the present study, we first observed the cord formation pattern of human dermal microvascular lymphatic endothelial cells (HMVEC-dLy) on Matrigel over 2 to 8 h. The length of cord formation increased, peaked at 4 h, and then started to decline after 6 to 8 h of incubation. siRNA-targeted NOS3 significantly reduced the cord formation ability of HMVEC-dLy cells by 27% relative to control. This result confirmed the importance of eNOS in cord formation by human lymphatic endothelial cells. In addition, immunoprecipitation and Western blotting indicated that the interaction between eNOS and Hsp90 was maximal at 4 h, and then the proteins dissociated. This interaction correlated with the observation of cord formation of human lymphatic endothelial cells on Matrigel. Moreover, we found that the eNOS level decreased as the eNOS and Hsp90 complex disassociated during the late stage of cord formation. An Hsp90 inhibitor, 17-DMAG, was able to inhibit the eNOS and Hsp90 interaction, decrease the level of eNOS, and significantly inhibit cord formation to 38% of the level observed in the control. For the first time, we report that the interaction between eNOS and Hsp90 plays an important role in determining eNOS levels and in regulating cord formation of human lymphatic endothelial cells *in vitro*.

3) **Mizumoto Y., Kyo S., Kiyono T., Takakura M., Nakamura M., Maida Y., Mori N., Bono Y., Sakurai H., and Inoue M.: Activation of NF-κB is a novel target of KRAS-induced endometrial carcinogenesis. Clin. Cancer Res., 17: 1341-1350, 2011.**

Abstract: PURPOSE: Although the KRAS mutation is one of critical genetic alterations in endometrial carcinogenesis, the downstream targets are not known.
EXPERIMENTAL DESIGN: In this study, we investigated the molecular targets of KRAS signals, using tumorigenic cells with oncogenic KRAS mutation established from telomerase reverse transcriptase (TERT)-immortalized endometrial epithelial cells.
RESULTS: We first confirmed that the RAF-ERK pathway, but not the PI3K-Akt pathway, was activated in KRAS tumorigenic cells. However, the introduction of constitutively active MAP/ERK kinase into immortalized cells to mimic RAF-ERK activation failed to obtain tumorigenic phenotypes, indicating the existence of other carcinogenic pathways triggered by KRAS. Recent evidence suggestive of linkage with KRAS signals prompted us to examine the involvement of NF-κB in endometrial carcinogenesis. We found that the DNA-binding activity of NF-κB was markedly elevated in KRAS tumorigenic cells compared with TERT-immortalized cells. Furthermore, the ability of NF-κB to activate the target gene promoters significantly increased in KRAS tumorigenic cells. Introduction of a mutant IκB that is resistant to degradation and thereby enhances the inhibitory effect on NF-κB largely abrogated the transformed phenotypes of KRAS tumorigenic cells. Thus, oncogenic KRAS signals contributed to the tumorigenic phenotypes of endometrial cells by activating the transcription function of NF-κB.
CONCLUSIONS: These findings clearly show that NF-κB activation is a novel target of oncogenic KRAS in endometrial carcinogenesis, implying the potential utility of NF-κB inhibitors for endometrial cancer chemoprevention, especially with KRAS mutation.

4) **Oka H., Goto H., Koizumi K., Nakamura S., Tsuneyama K., Zhou Y., Jo M., Sakurai H., Shibahara N., Saiki I., and Shimada Y.: Effect of hachimijiogan against renal dysfunction and involvement of hypoxia inducible factor-1 in the remnant kidney model. Evid Based Complement Alternat Med, Volume 2011, ArticleID 348686, 9pages, 2011.**

Abstract: In chronic renal failure, hypoxia of renal tissue is thought to be the common final pathway leading to end-stage renal failure. In this study the effects of hachimijiogan, a Kampo formula, were studied with respect to hypoxia-inducible factor (HIF). Using remnant kidney rats, we studied the effects of hachimijiogan on renal function in comparison with angiotensin II receptor blocker. The result showed that oral administration of hachimijiogan for seven days suppressed urinary protein excretion and urinary 8-OHdG, a marker of antioxidant activity, equally as well as oral administration of candesartan cilexetil. In contrast, the protein volume of HIF-1α in the renal cortex was not increased in the candesartan cilexetil group, but that in the hachimijiogan group was increased. In immunohistochemical studies as well, the expression of HIF-1α of the high-dose hachimijiogan group increased compared to that of the control group. Vascular endothelial growth factor and glucose transporter 1, target genes of HIF-1α, were also increased in the hachimijiogan group. These results suggest that hachimijiogan produces a protective effect by a mechanism different from that of candesartan cilexetil.

5) **Igarashi Y., Yanase S., Sugimoto K., Enomoto M., Miyanaga S., Trujillo M.E., Saiki I., and Kuwahara S.: Lupinacidin C, an Inhibitor of Tumor Cell Invasion from Micromonospora lupini. J. Nat. Prod., 74: 862-865, 2011.**

Abstract: A new anthraquinone derivative, lupinacidin C (1), was isolated from the endophytic actinomycete Micromonospora lupini. The structure was elucidated on the basis of spectroscopic analyses, and the absolute configuration was determined by total synthesis. Lupinacidin C (1) exhibited the most potent inhibitory effects among the congeners on the invasion of murine colon carcinoma cells into the reconstituted basement membrane.

6) **Jiang Y.L., Tang L.Q., Miyanaga S., Igarashi Y., Saiki I., Liu Z.P.: Synthesis and evaluation of trehalose-based compounds as anti-invasive agents. Bioorg Med Chem Lett., 21: 1089-1091, 2011.**

Abstract: Brartemicin is a trehalose-based inhibitor of tumor cell invasion produced by the actinomycete of the genus Nonomuraea. In order to explore the preliminary structure-activity relationship and obtain more potent inhibitors, a series of brartemicin analogs were synthesized through the Mitsunobu coupling of the secondary hydroxyls benzyl protected α, α-D-trehalose with benzoic acid derivatives, followed by modification of functional groups and deprotection. These compounds were evaluated for their inhibitory activity against invasion of murine colon 26-L5 carcinoma cells *in vitro*. Among the synthetic analogs tested, 6,6'-bis(2,3-dimethoxybenzoyl)-α,α-D-trehalose (5e) was found to be the most potent anti-invasive agent, exhibited a 2.6-fold improvement with regard to the parent natural product brartemicin, and it is considered to be a promising lead molecule for the anti-metastasis.

7) **Thanaketpaisarn O., Waiwut P., Sakurai H., and Saiki I.: Artesunate enhances TRAIL-induced apoptosis in human cervical carcinoma cells through inhibition of the NF-κB and PI3K/Akt signaling pathways. Int. J. Oncol., 39: 279-285, 2011.**

Abstract: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis and kills cancer cells with little or no adverse effects on normal cells. TRAIL is relatively safe for clinical applications. However, TRAIL resistance is widely found in cancer cells leading to limitations in utilizing TRAIL as a therapeutic agent for cancer treatment. Recently, artesunate, an effective and safe anti-malarial drug, was also described as a promising candidate for cancer therapy. It would be of importance to determine whether combination treatment of TRAIL together with artesunate could overcome drug-resistance of tumors. Here, we demonstrate the first evidence that artesunate effectively enhances TRAIL-mediated cytotoxicity by suppressing pro-survival proteins, such as survivin, XIAP and Bcl-XL. Upon treatment with artesunate, the levels of survival proteins were strongly suppressed in HeLa cells. The down-regulation of these survival proteins could be regulated by repressing activation of NF-κB and Akt. Artesunate also inhibited TRAIL-induced transcriptional activity of NF-κB. In addition, this

substance significantly enhanced both extrinsic and intrinsic apoptosis, which were induced by TRAIL. Taken together, the results of the present study suggest that artesunate exhibits an ability to overcome TRAIL resistance and combination treatment of TRAIL together with artesunate may be an effective strategy for cancer therapy.

8) **Refaat A., Zhou Y., Suzuki S., Takasaki I., Koizumi K., Yamaoka S., Tabuchi Y., Saiki I., and Sakurai H.: Distinct roles of TAK1-c-REL and IRF4 pathways in HTLV-1 transformed Th17-like cells producing IL-9. J. Biol. Chem., 286: 21092-21099, 2011.**

Abstract: Investigation of helper T cell markers in HTLV-1-transformed cell lines demonstrated that HuT-102 has an IL-9-producing Th17 phenotype. We confirmed the vital role of retinoic acid-related orphan receptor C, a Th17 transcription factor, in the expression of IL-17. Interferon regulatory factor 4 (IRF4), a transcription factor overexpressed in all HTLV-1-infected cells, regulated IL-17 and IL-9 concomitantly. We further demonstrated a novel pathway for the regulation of Tax-induced cytokines, IL-9 and IL-6, through TAK1-mediated nuclear accumulation of c-Rel. A microarray analysis for IRF4 knocked down HuT-102 cells showed a significant up-regulation in the set of genes related to Th1, mainly IFN-γ and several transcription factors. T-bet and IRF1, but not STAT1 and IRF9, participated in counteracting the inhibitory effect of IRF4 on the production of IFN-γ. Finally, suppression of both IRF4 and c-Rel resulted in the reduced proliferation. Collectively, these findings indicate that TAK1-c-Rel and IRF4 pathways play distinct roles in the maintenance of IL-9-producing Th17 phenotype of HTLV-1-transformed cells.

9) **Waiwut P., Inujima A., Inoue H., Saiki I., and Sakurai H.: Bufotalin sensitizes death receptor-induced apoptosis via Bid- and STAT1-dependent pathway. Int. J. Oncol., 40: 203-208, 2011.**

Abstract: Tumor necrosis factor-alpha (TNF-α) and TNF-related apoptosis-inducing ligand (TRAIL) are apoptosis-inducing ligands that stimulate death receptors. In this study, we investigated the effects of bufotalin, a major compound in toad venom, on sensitizing TNF-α and TRAIL-induced apoptosis of HeLa cells. Bufotalin promoted death receptor-mediated cell death, especially TRAIL-induced apoptosis, through activation of caspase-3 and PARP-1. Mitochondrial Bid-dependent pathway was activated in TNF-α-induced cell death. Cotreatment of bufotalin with TRAIL resulted in the downregulation of anti-apoptotic proteins, including Bcl-XL, Mcl-1, survivin and XIAP, and the up-regulation of MAPKs and TRAIL receptor DR5. In addition, phosphorylation of STAT1 was strongly inhibited by bufotalin. Moreover, DR5 expression was induced by knocking down the STAT1 expression. Moreover, the TRAIL-induced apoptotic response was promoted by STAT1 siRNA. Our results demonstrated that bufotalin is a powerful sensitizer of death receptor-induced apoptosis in cancer cells.

10) **Feige E., Yokoyama S., Levy C., Khaled M., Igras V., Lin R.J., Lee S., Widlund H.R., Granter S.R., Kung A.L., Fisher D.E.: Hypoxia-induced transcriptional repression of the melanoma- associated oncogene MITF. Proc. Natl. Acad. Sci. USA, 108: E924-933, 2011.**

Abstract: Microphthalmia-associated transcription factor (MITF) regulates normal melanocyte development and is also a lineage-selective oncogene implicated in melanoma and clear-cell sarcoma (i.e., melanoma of soft parts). We have observed that MITF expression is potently reduced under hypoxic conditions in primary melanocytes and melanoma and clear cell sarcoma cells through hypoxia inducible factor 1 (HIF1)-mediated induction of the transcriptional repressor differentially expressed in chondrocytes protein 1 (DEC1) (BHLHE40), which subsequently binds and suppresses the promoter of M-MITF (melanocyte-restricted MITF isoform). Correspondingly, hypoxic conditions or HIF1α stabilization achieved by using small-molecule prolyl-hydroxylase inhibitors reduced M-MITF expression, leading to melanoma cell growth arrest that was rescued by ectopic expression of M-MITF *in vitro*. Prolyl hydroxylase inhibition also potently suppressed melanoma growth in a mouse xenograft model. These studies illuminate a physiologic hypoxia response in pigment cells leading to M-MITF suppression, one that suggests a potential survival advantage mechanism for MITF amplification in metastatic melanoma and offers a small-molecule strategy for suppression of the MITF oncogene *in vivo*.

11) **Yokoyama S., Wood S.L., Boyle G.M., Aoude L.G., MacGregor S., Zismann V., et al.: A novel recurrent mutation in MITF predisposes to familial and sporadic melanoma. Nature, 480:**

99-103, 2011.

Abstract: So far, two genes associated with familial melanoma have been identified, accounting for a minority of genetic risk in families. Mutations in CDKN2A account for approximately 40% of familial cases, and predisposing mutations in CDK4 have been reported in a very small number of melanoma kindreds. Here we report the whole-genome sequencing of probands from several melanoma families, which we performed in order to identify other genes associated with familial melanoma. We identify one individual carrying a novel germline variant (coding DNA sequence c.G1075A; protein sequence p.E318K; rs149617956) in the melanoma-lineage-specific oncogene microphthalmia-associated transcription factor (MITF). Although the variant co-segregated with melanoma in some but not all cases in the family, linkage analysis of 31 families subsequently identified to carry the variant generated a log of odds (lod) score of 2.7 under a dominant model, indicating E318K as a possible intermediate risk variant. Consistent with this, the E318K variant was significantly associated with melanoma in a large Australian case-control sample. Likewise, it was similarly associated in an independent case-control sample from the United Kingdom. In the Australian sample, the variant allele was significantly over-represented in cases with a family history of melanoma, multiple primary melanomas, or both. The variant allele was also associated with increased naevus count and non-blue eye colour. Functional analysis of E318K showed that MITF encoded by the variant allele had impaired sumoylation and differentially regulated several MITF targets. These data indicate that MITF is a melanoma-predisposition gene and highlight the utility of whole-genome sequencing to identify novel rare variants associated with disease susceptibility.

12) Oka H., Goto H., Koizumi K., Nogami T., Watari H., Nakamur S., Zhou Y., Sakurai H., Shibahara N., Saiki I., Shimada Y.: Cinnamaldehyde and paeonol increase HIF-1α activity in proximal tubular epithelial cells under hypoxia. J. Tad. Med., 28: 149-157, 2011.

13) Wolf A., Beuerlein K., Eckart C., Weiser H., Dickkopf B., Muller H., Sakurai H., Kracht M.: Identification and functional characterization of novel phosphorylation sites in TAK1-binding protein (TAB) 1, PLoS ONE, 6: e29256, 2011.

Abstract: TAB1 was defined as a regulatory subunit of the protein kinase TAK1, which functions upstream in the pathways activated by interleukin (IL)-1, tumor necrosis factor (TNF), toll-like receptors (TLRs) and stressors. However, TAB1 also functions in the p38 MAPK pathway downstream of TAK1. We identified amino acids (aa) 452/453 and 456/457 of TAB1 as novel sites phosphorylated by TAK1 as well as by p38 MAPK in intact cells as well as *in vitro*. Serines 452/453 and 456/457 were phosphorylated upon phosphatase blockade by calyculin A, or in response to IL-1 or translational stressors such as anisomycin and sorbitol. Deletion or phospho-mimetic mutations of aa 452-457 of TAB1 retain TAB1 and p38 MAPK in the cytoplasm. The TAB1 mutant lacking aa 452-457 decreases TAB1-dependent phosphorylation of p38 MAPK. It also enhances TAB1-dependent CCL5 secretion in response to IL-1 and increases activity of a post-transcriptional reporter gene, which contains the CCL5 3' untranslated region. These data suggest a complex role of aa 452-457 of TAB1 in controlling p38 MAPK activity and subcellular localization and implicate these residues in TAK1- or p38 MAPK-dependent post-transcriptional control of gene expression.

◇総　説

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2) 済木育夫：特集：エビデンスと臨床経験にがん領域の漢方治療，がん領域で有効な漢方薬–「補剤」のしくみと使い方，薬局 10 月号，62(11): 42-51，2011.
3) Koizumi K., Kato S., Sakurai H., Hashimoto I., Yasumoto K., and Saiki I.: Therapeutics target of CXCR4 and its downstream in peritoneal carcinomatosis of gastric cancer, Frontier in Bioscience, in press, 2011.

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4) Zhou Y., Refaat A., Suzuki S., Takasaki I., Koizumi K., Tabuchi Y., Yamaoka S., Saiki I., Sakurai H.: HTLV-1 manipulates interferon regulatory signals by activating TAK1-IRF3 pathway and controlling negative factor IRF4. 日本分子生物学会第 11 回春季シンポジウム, 2011. 5. 25-26, 金沢.

5) 申明淑，佐藤佳奈絵，河西美保，済木育夫，櫻井宏明：EGF 受容体のスレオニンリン酸化によるチロシンキナーゼ活性の抑制機構，日本生化学会北陸支部第 29 回大会，2011. 5. 28，金沢.

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◇その他

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◇研究費取得状況

1) 平成 23 年度 厚生労働省科学研究費 医薬技術実用化総合研究事業（代表：済木育夫）「漢方薬によるワクチンアジュバント効果の検討と臨床応用」（H22. 4. 1～H25. 3. 31）
2) 平成 23 年度厚労科研補助金 創薬基盤推進研究事業（分担：済木育夫）「漢方薬に使用される薬用植物の総合情報データーベース構築のための基盤整備に関する研究」（H23. 4. 1～）
3) 平成 23 年度文部科学省科学研究費補助金 基盤研究（C）（分担：櫻井宏明）「ケモカイン機能を利用したがん細胞呼び込み型 DDS 型剤の開発と腹膜播種治療への応用」
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◇学位（修士，博士）取得者

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