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日中笹川医学奨学金制度
第45期＜共同研究コース＞
研究者集会

主　催：公益財団法人　日中医学協会
　　笹川医学奨学金進修生同学会

開催日：2024年9月4日

会　場：日本財団ビル大会議室

Program

研究者集会（14：30～17：40　日本財団ビル2階　大会議室）

開会宣言　小川　秀興　日中医学協会会長

挨　　拶　跡見　　裕　日中医学協会理事長

趙　　群　笹川医学奨学金進修生同学会理事長

祝　　辞　呉　　江浩　中華人民共和国駐日本国特命全権大使

尾形　武寿　日本財団理事長

研究発表

座　長　林﨑　良英　日中医学協会理事、

日中医学（日中医学協会-日本財団）協力委員会委員長

発表者　9組（第45期研究者・日本側共同研究者）

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発表①

^{211}At radiolabeling chemistry and pharmacodynamics for cancer-targeted alpha particle therapy

がん標的アルファ線治療のためのアスタチン-211標識化学とその薬力学

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【Abstract】

^{211}At has been regarded as one of the most promising radionuclides for targeted alpha particle therapy. Fukushima Medical University and Sichuan University are two institutes available for producing ^{211}At at the medically-used level and have been performing long-term investigations of radioastatinated compounds. However, both institutions are discouraged by the same issues about ^{211}At-based radiopharmaceuticals: their low radiolabeling efficiency and the unsatisfactory radiochemical stability in vivo. Through the collaboration funded by the Japan-China Sasakawa Medical Fellowship, we have managed to design two strategies to address above problems. In the first strategy, we utilized the strong binding between astatine and silver to achieve highly efficient conjugation between ^{211}At and Ag-based nanoparticles. ^{211}At@Ag-PEG-FA was obtained via a one-pot assembly of ^{211}At, Ag, and SH-PEG-FA in extremely high radiochemical yield (RCY, > 95%) within 15 min, and it maintained its excellent stability in physiochemical media. The prepared ^{211}At@Ag-PEG-FA demonstrated specific binding to 4T1 cells (breast cancer) with a high endocytosis rate and excellent antitumor effect that completely inhibited tumor growth during the first week. It could effectively prolong the median survival of subjected mice to 44 days relative to 16 days in the control group. All the treated mice exhibited minimal side effects of @Ag-PEG-FA during the experiment, indicating its acceptable biosafety. In the second strategy, a multifunctional binding agent was introduced to simultaneously achieve ^{211}At radiolabeling and the prolongation of tumor retention of the corresponding radiolabeled drug in tumor cells. ^{211}At-IPBA-FAPI was successfully synthesized by conjugating ^{211}At with a satisfactory RCY of > 60% within 1.5 h. ^{211}At-IPBA-FAPI exhibited extraordinary in vitro stability, significant tumor affinity, and a specific killing effect on FAP-positive U87MG cells (glioma) , showing markedly longer tumor retention than that in previous work. As a result, ^{211}At-IPBA-FAPI induced a more pronounced tumor inhibition without noticeable biotoxicity toward the main healthy organs/tissues. All these results indicate that introducing a multifunctional binding agent can effectively enhance the utilization of FAPI for ^{211}At conjugation and realize the tumoricidal effect. Moreover, we have been working on a newly modified compound, ^{211}At-PSMA, with great potential in the treatment of metastatic castration-resistant prostate cancer. We also have recently developed radioimmunotherapy for acute myelogenous leukemia using ^{211}At-CD82 monoclonal antibody targeting CD82 to eradicate leukemia stem cells. Our work can provide valuable insights into the ^{211}At radiolabeling of general compounds and may promote the translation of ^{211}At-related radiopharmaceuticals.

発表②

Intensive care of Post cardiac arrest patients
心停止後症候群患者における集中治療

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【Abstract】

Background:Therapeutic temperature management (TTM) is the standard treatment protocol for unconscious post-resuscitation patients. However, there is still controversy about the ideal targeted temperature of mild hypothermia therapy. Additionally, studies about protective therapy for post-resuscitation intestinal injury are very limited. Therefore, this study was performed to explore: 1) whether mild hypothermia therapy can exert a protective effect on post-resuscitation intestinal injury; 2) the protective effect of different targeted temperatures on post-resuscitation intestinal injury and the ideal targeted temperature; 3) the potential protective mechanism of mild hypothermia therapy for post-resuscitation intestinal injury.

Methods:Ventricular fibrillation was electrically induced and untreated for 6 min while defibrillation was attempted after 8 min of cardiopulmonary resuscitation in 15 rats. After successful resuscitation, animals were randomized into three groups: (i) control; (ii) TTM-35; (iii) TTM-33. In animals of the control group, temperature was maintained at 37 ± 0.2 ˚C for 6 hours. In animals of the two TTM groups, temperature was maintained at 33 ± 0.2 ˚C or 35 ± 0.2 ˚C for 6 hours, respectively. During mild hypothermia therapy, intestinal microcirculation was measured at 60, 240, and 360 min after resuscitation. Animals were euthanized 6.5 h after resuscitation. The morphological changes in the intestinal tissue, systemic and local inflammatory factors, and intestinal injury markers were measured and analyzed. The tight junction proteins in the intestinal epithelium, cell-cell contact protein E-cadherin expression, myosin light chain (MLC) and myosin light chain kinase (MLCK) levels, and the NF-κB p65 signaling pathway were analyzed by western blotting.

Results:Compared with results in the control group, mild hypothermia therapy (TTM-33 and TTM-35 groups) significantly improved post-resuscitation intestinal microcirculation and pathological scores, decreased systemic and local intestinal tissue inflammatory factor levels, inhibited the NF-κB signaling pathway and downstream MLC phosphorylation, and significantly decreased MLC phosphorylation-associated loss of intestinal tight junction proteins and E-cadherin ($P<0.05$). A 33 ℃ target temperature could exert more protective effects than 35 ℃ on post-resuscitation intestinal injury, such as improving intestinal microcirculation, decreasing intestinal ischemia factor iFABP and plasma endotoxin levels, inhibiting the NF-κB signaling pathway and downstream MLC phosphorylation, and suppressing the loss of intestinal tight junctions and E-cadherin ($P<0.05$). Conclusions: Mild hypothermia therapy can improve post-resuscitation intestinal injury, and a targeted temperature of 33 ℃ may confer more benefit for mitigation of intestinal injury as compared with a targeted temperature of 35 ℃.

発表③

Identification of a novel autophagic inhibitor
新規オートファジー阻害剤の同定

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【Abstract】

Autophagy is a self-degradative process that targets cytosolic components and organelles for lysosomal degradation. This process is crucial for maintaining cellular homeostasis and is implicated in the pathogenesis of various diseases. Notably, excessive autophagy is associated with numerous conditions, including cancer and autoimmune diseases. Therefore, small chemical molecules that can modulate autophagy may offer significant therapeutic potential for these conditions.

In our research, we employed a high-content screening assay utilizing green fluorescent protein-tagged microtubule-associated protein 1 light chain 3 (GFP-LC3) and green fluorescent protein-tagged syntaxin 17 (GFP-STX17). Through this approach, we identified a novel chemical compound, referred to as #524, capable of inhibiting autophagy, likely at its late stage.

Our findings suggest that compound #524 has significant potential as a therapeutic agent. By inhibiting excessive autophagy, it could play a crucial role in the treatment of autophagy-related diseases such as cancer and autoimmune disorders. Further research is needed to elucidate the precise mechanisms by which #524 modulates autophagy and to assess its efficacy and safety in various disease models.

Moreover, we aim to investigate the compound's effect on various cellular pathways involved in autophagy to better understand its broad therapeutic implications. Preclinical studies, including in vivo models, will be essential to establish the pharmacokinetics and pharmacodynamics of #524. Additionally, we plan to explore the potential synergistic effects of #524 when combined with existing therapeutic agents, which could enhance its efficacy and broaden its application in treating complex diseases.

In conclusion, our study identifies compound #524 as a novel autophagy inhibitor, highlighting its potential as a therapeutic candidate for managing diseases characterized by excessive autophagy. The development of such inhibitors could open new avenues for the treatment of complex diseases, providing a targeted approach to restore cellular balance and improve patient outcomes. Further research and clinical trials will be crucial in translating this potential into effective treatments.

発表④

An artificial intelligence model for lymphoid malignancies immune cell therapy sensitivity based on immunomics

リンパ系悪性腫瘍の免疫細胞治療感受性のための免疫オミクスに基づく人工知能モデル

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【Abstract】

Chimeric antigen receptor (CAR)-T cell therapy is a revolutionary new method in lymphoid malignancies therapy. Although treatment with CAR-T cells has produced remarkable clinical responses, many challenges limit the therapeutic efficacy of CAR-T cells .The host and tumor microenvironment interactions with CAR-T cells critically alter CAR-T cell function. Furthermore, a complex workforce is required to develop and implement these treatments. Dr. Wang and Dr. YASUI have been working on immunotherapy-related research for lymphoid malignancies for many years, and in this project, they will jointly try to delineate immunomics changes before and after lymphoid malignancies diagnosis and immune cell therapy, and try to apply artificial intelligence to establish early prediction models of treatment effectiveness and find new targets for immunotherapy. The cooperation between China and Japan can further verify the accuracy of our AI models so that they can be translated into applications around the world.

発表⑤

Exploration of mechanistic insights into the potential alleviating effects of sulforaphane in atopic dermatitis

アトピー性皮膚炎におけるスルフォラファンの緩和効果に関する研究

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【Abstract】

Atopic dermatitis (AD) is one of the most common chronic, recurrent inflammatory dermatoses, arising from multifactorial genetic predispositions, a compromised epidermal barrier, and immunological dysregulation. As a leading non-fatal health burden among skin diseases, AD necessitates the exploration of effective and safe treatment modalities through a detailed understanding of its pathogenesis. Sulforaphane (SFN), a bioactive compound derived from broccoli, is renowned for its antioxidant, anti-tumor, anti-angiogenic, and anti-inflammatory activities. However, the effects of SFN on skin inflammatory conditions such as AD have not been fully elucidated. This study aimed to illustrate the potential effects and molecular mechanisms of SFN on AD by employing network analysis. Using databases such as Swiss Target Prediction, DisGeNET, GeneCards, and STRING, we identified overlapping targets between "SFN" and "AD", including NOS2, NOS3, EGFR, DUSP1, MAPK1, MAPK14, JAK1, JAK2, and TYK2. Further analysis through the Metascape database and KEGG pathway enrichment revealed several pathways, particularly highlighting the AGE/RAGE/MAPK signaling pathway. Additionally, in vitro studies using normal human epidermal keratinocytes treated with IL-4 and IL-13, LPS or poly I:C showed that SFN downregulated the mRNA expression of inflammatory cytokines IL-6 and IL-33, and the expression of multiple antimicrobial peptides such as hBD2. Concurrently, SFN enhanced the expression of barrier-related gene TJP1. Additionally, SFN inhibited mast cell degranulation via both IgE-mediated and non-IgE-mediated pathways. In summary, these findings suggest that SFN might exert an anti-inflammatory effect by modulating the expression of key cytokines from keratinocytes implicated in the pathogenesis of AD , and by inhibiting mast cell activity, potentially through the regulation of the AGE/RAGE/MAPK signaling pathway. Further studies are needed to better elucidate the role of SFN in the pathogenesis of AD.

発表⑥

Discovery of novel IgA type autoantibodies against mesangial autoantigen in patients with IgA nephropathy
IgA腎症における標的メサンギウム抗原の探索

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【Abstract】

Introduction:IgA nephropathy (IgAN) is the most common primary form of glomerular disease worldwide with a complex pathogenesis involving abnormal immune responses and carries a high lifetime risk of kidney failure. Recently, we have reported novel IgA-type autoantibodies against mesangial cell autoantigens, βII-spectrin and CBX3, in the serum of IgAN patients (Science Advances, 2023. Life Sci. Alliance 2024). About half of IgAN patients were positive for serum anti-βII-spectrin and/or anti-CBX3 IgA, suggesting the existence of other undiscovered autoantigens. The aim of this study is to systematically screen and identify novel autoantigens in IgAN to further elucidate the immunopathological mechanisms of IgAN and provide new targets for clinical diagnosis and treatment.

Methods:Collect kidney samples from patients diagnosed with βII-spectrin-negative and CBX3-negative IgAN and control subjects and isolate glomerular mesangial cells from the kidney samples by engineering techniques or laser microdissection. Use high-throughput proteomic techniques (e.g., LC-MS/MS) combing with bioinformatics analysis to analyze the mesangial cells protein expression profiles of patients and control groups to identify proteins that are significantly expressed or modified in IgAN patients. Validate the candidate proteins by Western blotting, immunofluorescence, immunohistochemistry and ELISA. Use immunoprecipitation to verify the binding of candidate proteins to IgA antibodies from patients. In clinical experiments, we will assess the correlation between IgA autoantibodies against the newly identified autoantigens and clinical parameters of IgAN (e.g., proteinuria, serum creatinine levels, renal function) and analyze the expression and antibody response differences in various subtypes of IgAN.

Expected Outcomes:Identification of multiple novel autoantigens that are significantly expressed and bind to IgA-type autoantibodies in IgAN patients. Elucidation of the potential roles of these novel autoantigens in the pathogenesis of IgAN. Provision of potential biomarkers for early diagnosis and monitoring of IgAN. Identification of new molecular targets for the targeted therapy of IgAN.

Significance:This study aims to systematically screen and identify novel autoantigens in the serum of IgAN patients, thereby revealing further insights into the immunopathological mechanisms of IgAN. The results are expected to provide new targets for early diagnosis, prognosis evaluation, and personalized treatment of IgAN.

発表⑦

Evolution of the Stromal Component in Bladder Cancer Leading to Cancer Cell Infiltration and Metastasis
膀胱癌における間質成分の進化ががん細胞の浸潤と転移に与える影響の研究

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【Abstract】
The breakthrough of the submucosal or stromal layer in bladder cancer can significantly alter treatment approaches and prognosis. The infiltration of cancer cells into the fibroblast-rich stroma remains poorly understood. We conducted multi-omics analysis on tissue from a patient with muscle-invasive bladder cancer. Spatial transcriptomics revealed heterogeneity between cancer cells and stromal cells, while spatial metabolomics captured tissue images depicting cancer cells breaking through the stromal layer to invade muscle tissues. Spatially-aware nearest shrunken centroids clustering in metabolomics further distinguished cancer and stromal cells based on differential metabolism. Metabolite differentiation analysis across different clusters revealed metabolic disparities both between cancer cells and within the stromal matrices themselves. Single-cell sequencing identified subsets of cancer cells and stromal cells, highlighting differentiated cells where some exhibited convergent cellular characteristics. This finding aligns with spatial metabolomic observations, indicating distinct metabolic profiles among differentiated cells. Single-cell sequencing also pinpointed specific genes in cancer cells and fibroblasts responsible for mutual homogenization. Differential metabolites derived from these genes likely mediate this process. Our integrated approach combining spatial multi-omics analysis and single-cell sequencing provides insights into key differentiating genes and metabolites crucial for understanding cancer cell infiltration and proliferation within the stroma.

発表⑧

Molecular mechanisms by which cancer-associated fibroblasts affect treatment resistance in thyroid cancer
甲状腺癌における癌関連線維芽細胞が治療抵抗性に及ぼす影響とその分子機構の解明

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【Abstract】

Most papillary thyroid carcinomas (PTCs) have an indolent clinical course, but some exhibit aggressive behavior with loco-regional or even distant metastases. The role of cancer-associated fibroblasts (CAFs) in thyroid cancer (TC) is not fully understood. Limited studies have indicated that CAFs are associated with lymph node metastasis, invasiveness, and dedifferentiation of TC, but these studies have only investigated α-SMA as the CAF marker. CAFs are known to be heterogeneous, and the CAF expressing α-SMA is called myCAF, which is one type of different CAFs. There is one PTC study that investigates various CAF marker proteins; therefore, the issue remains inconclusive. More importantly, the relationship between CAFs and treatment response in TC is not thoroughly understood.

So far, the research team in China has studied the expression of α-SMA and FAP in thyroid cancer tissues, as well as the co-culture of CAFs and thyroid cancer cells, showing that CAFs enhance the proliferation, migration, and invasion capabilities of thyroid cancer cells. On the other hand, the Japanese research team has extensive experience in analyzing molecular mechanisms in thyroid cancer and responses to radiation, including DNA damage response.

In this research project, we aim to study how co-culture with CAFs affects the radiation response in thyroid cancer cells. Initially, thyroid cancer cells will be co-cultured with normal fibroblasts to serve as a control group. Subsequently, thyroid cancer cells will be co-cultured with activated fibroblasts, which will be induced to become myCAF and/or iCAF. The activation of these fibroblasts will be confirmed by the expression of various markers, including FAP, α-SMA, IL-6, CXCL12, IL-11, and PDGFR. We will then investigate the differences in cell growth, migration, apoptosis, and radiation sensitivity of thyroid cancer cells induced by these co-culture combinations. The effect of CAFs on TC radiation sensitivity in vivo will also be studied. Radiation will be implemented on different mixture of cells (CAFs cells and/or TC cells). After the observation, the tumor tissues will be dissected for further analysis. By comparing these parameters, we aim to elucidate the mechanisms by which CAFs influence these aspects of thyroid cancer biology. Understanding these interactions will provide insights into the role of CAFs in treatment resistance and could inform the development of new therapeutic strategies for thyroid cancer.

This experiment aims to serve as a starting point for understanding the relationship between treatment resistance and CAFs in thyroid cancer. By elucidating the molecular mechanisms involved, we hope to identify potential targets for enhancing the effectiveness of existing treatments and improving patient outcomes.

発表⑨

Analysis of surgical approaches for elderly patients with colorectal cancer liver metastases in Japan and China
日中両国における高齢の大腸癌肝転移患者における外科的治療法の比較検討

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【Abstract】
More than 1.9 million new cases of colorectal cancer(CRC) and 904,000 deaths were estimated to occur in 2022 all around the world, which ranks in third place in terms of incidence but second in terms of mortality. China placed first worldwide in the number of new CRC cases (517,100) and CRC-related deaths (240,000) because of its comparatively large population. About 15% to 25% of CRC patients have liver metastases (CRLM) at the time of diagnosis, while another 15% to 25% will develop liver metastases after radical surgery for CRC. CRLM is the main cause of death in CRC patients, and represents a severe threat to the health of population as well as a heavy economic burden on the society and individuals.

Therefore, proper treatment and surveillance are of great importance to the outcome of CRLM patients. In Japan, the Standardized treatment, surveillance, and the deployment of state-of-the-art theories and techniques have boosted the prognosis of CRLM patients. Additionally, the Japanese population is aging rapidly, and it is also essential to apply the therapeutic approach for CRLM patients considering their age.

In order to further improve the therapeutic protocol of CRLM in China, we intend to compare the clinical characteristics, treatment strategy and short/long term prognosis of CRLM patients receiving liver resection in two surgical departments in Japan and China; Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Graduate School of Medicine, the University of Tokyo and Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University. We will also compare the differences of guidelines in treating CRLM between two countries.

Given the serious problem of rapid aging in China as well as Japan, the aim of this project is to compare the impact of treatment protocols on short-term and long-term prognosis and survival rates especially in very elderly CRLM patients (≥80 years old, mainly octogenarians), as well as the correlation between guideline adherence and clinical effectiveness.

日中笹川医学奨学金制度
学位取得コース・ポストドクターコース
第45期研究者名簿

第45期＜学位取得コース＞研究者

学位取得コース紹介

氏　名	所　属　機　関	受　入　機　関	指導責任者
	研究テーマ	取得学位 専攻分野	
袁　野	遵義医科大学附属医院 研修医	筑波大学医学医療系 神経内科学	斉木　臣二 教授
	A study based on functional magnetic resonance imaging to investigate the relationship between abnormal functional connectivity and long-term functional prognosis and cognitive function in PD patients	課程博士 医学	
阿布力米提 穆姬莎	中国医学科学院腫瘤医院深圳医院 主治医師	筑波大学医学医療系 放射線腫瘍学	櫻井　英幸 教授
	Proton beam therapy for children: Artificial intelligence and radiomic predict brain damage in children and AYAs treated with proton beam therapy	課程博士 医学	
李　博倫	自治医科大学 博士課程学生	自治医科大学大学院医学研究科 形成外科学	吉村　浩太郎 教授
	培養上清を用いた慢性潰瘍治療の研究	課程博士 医学	
張　含煙	西安培華学院 日本語教師	杏林大学大学院国際協力研究科	宮首　弘子 教授
	日中医療通訳者の役割意識及び通訳効果との関連性	課程博士 学術	
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	Muller-Weiss Disease: The Descriptive Factors of Failure Midfoot Arthrodesis	課程博士 医学	
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	External and Internal Exposure Dose Estimation and Visual Analysis at Restricted areas around the Fukushima Daiichi Nuclear Power Plant	課程博士 医学	

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