IPRF2013

International Pancreatic Research Forum

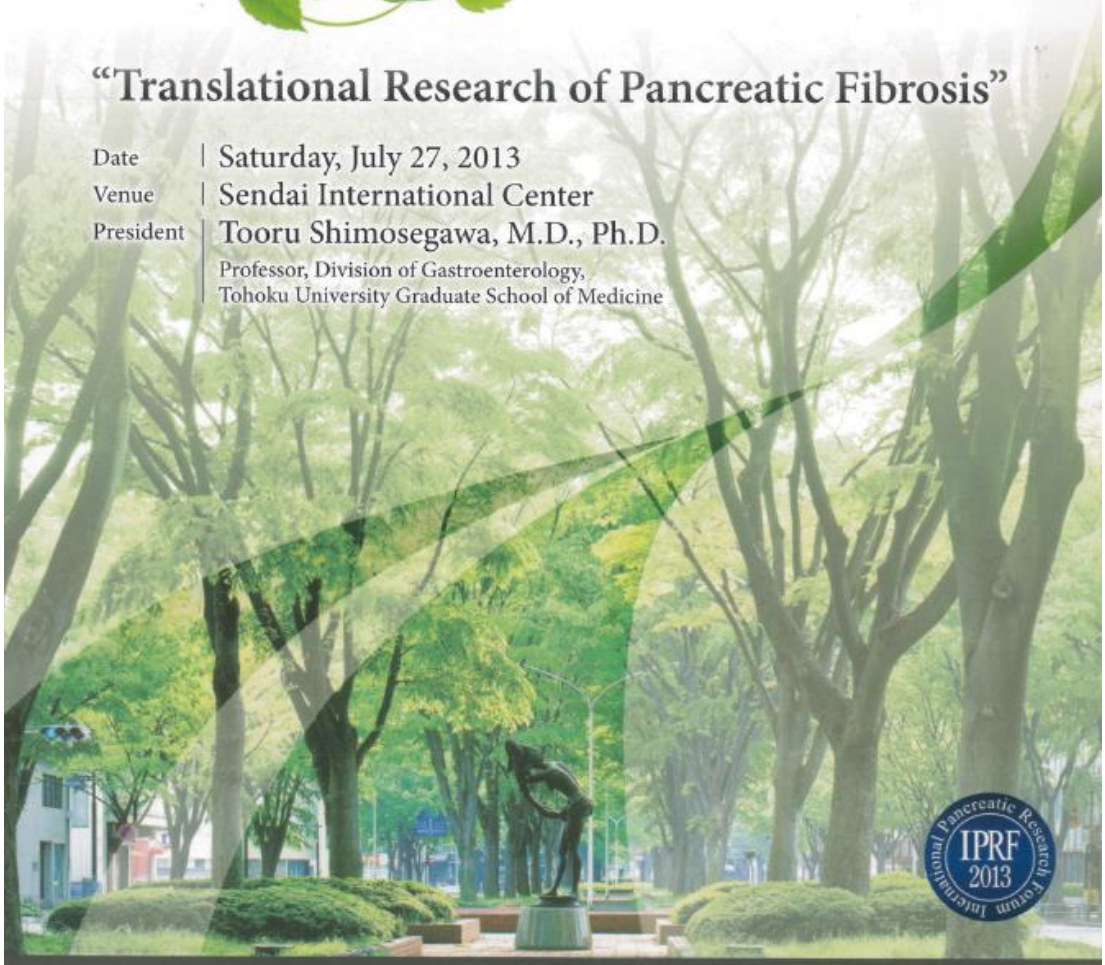
"Translational Research of Pancreatic Fibrosis"

Date | Saturday, July 27, 2013

Venue | Sendai International Center

President | Tooru Shimosegawa, M.D., Ph.D.

Professor, Division of Gastroenterology,
Tohoku University Graduate School of Medicine



Pancreas Research Foundation of Japan

Welcome Message

I am Tooru Shimosegawa, the congress President of the 44th annual meeting of the Japan Pancreas Society (JPS). It is my great pleasure to host the International Research Forum in Sendai 2013 in conjunction with the 44th JPS annual meeting. The International Research Forum was planned to stimulate scientific activities in the next generation of JPS members, to promote the academic connection with foreign researchers, and deepen mutual friendships. This symposium has been prepared by the efforts of Dr. Atsushi Masamune, Associate Professor of Tohoku University and Dr. Kyoko Shimizu, Associate Professor of Tokyo Women's Medical University, and is supported by the Japan Pancreas Research Foundation (Suizobyo Kenkyu Zaidan). I express my sincere thanks to Drs. Masamune and Shimizu, and Professor emeritus Tadashi Takeuchi, President of the Japan Pancreas Research Foundation.

We selected "Translational Research of Pancreatic Fibrosis" for the title of this symposium, a hot topics not only in academic field but also in clinical practice of pancreatic diseases. Very fortunately, we could invite this time Dr. Minoti Apte, Professor of Medicine at the University of New South Wales in Sydney, the world famous authority in this field. She takes the trouble to fly from London for us to join in this International Research Forum.

As seen in this program, so many very active and top-ranked young investigators in this field responded to our invitation, thus ensuring high level contents of this forum from scientific aspects. I hope that all attendees will fully participate in the discussions and enjoy the recent global advances in this scientific field. It is my sincere wish that the International Research Forum in Sendai 2013 will be fruitful and help young JPS investigators to find new provisions for future developments.

Tooru Shimosegawa, M.D., Ph.D.

President, International Pancreatic Research Forum 2013

Professor, Division of Gastroenterology,
Tohoku University Graduate School of Medicine

General Information

Date & Time

9:00 – 12:00, Saturday, July 27, 2013

Venue

Sendai International Center, 3F "Shirakashi"
URL: www.sira.or.jp/icenter/english/index.html

Theme

Translational Research of Pancreatic Fibrosis

Official Language

English

Organized by

Pancreas Research Foundation of Japan

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Japan Pancreas Society

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Tooru Shimosegawa, M.D., Ph.D.
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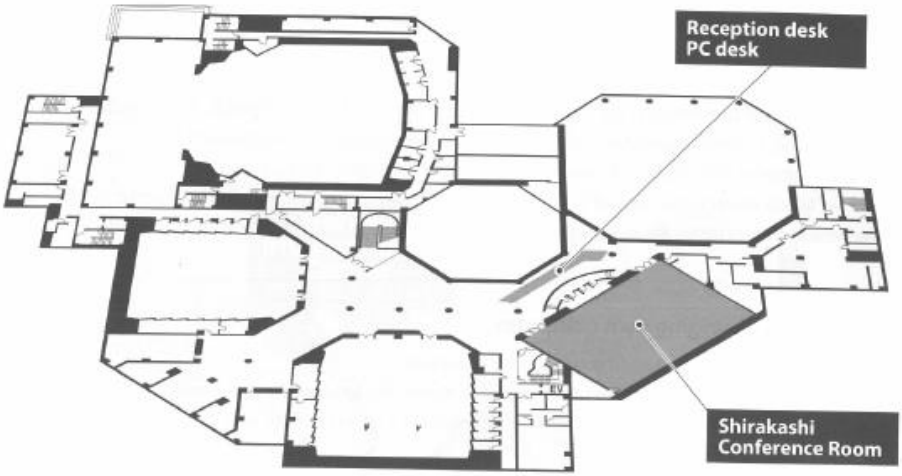
Floor Map

Sendai International Center

3F



Information for Participants

Please stop by the reception desk when you come to the venue. The reception desk opens at 8:30am.

Information for Chairperson, Moderators, and Commentators

Please be seated in the next to the chairperson's seat 10 min. prior to the beginning of your session.

Information for Speakers

Preview / Submit Presentation Data

Please be done preview/submit your presentation data at least 30 min. prior to the beginning of your presentation at the PC desk in front of the Shirakashi Conference Room. The PC desk opens at 8:30am.

For a Next Presenter

Please be seated in a next to the presenter's seat 10 min. prior to the beginning of your speech.

Presentation Instructions

- The only equipment provided for presentation will be a PC projector. There will be no other projectors such as 35mm slide projector.
- During your presentation, you can forward your presentation slide by yourself by using a keyboard and a mouse on the podium.
- Please register Presentation Data with your own computer OR with a USB memory stick or a CD-R.
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  OS: Windows XP, Vista, Windows 7
  Applications: Power Point 2003, 2007, 2010
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- All the copied data will be deleted by organizers appropriately after the congress ended.

Discussion time

Individuals wishing to ask questions will be line up at the microphone provided in the session room. They should give their name and affiliation before starting question. Question should be brief and simple.

Forum Venue

Sendai International Center, Sendai, Japan

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Phone: +81-22-265-2211
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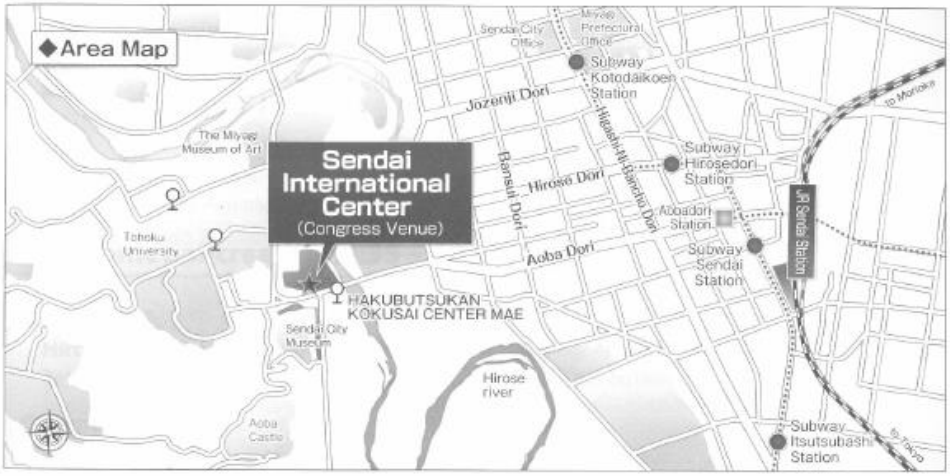

◆Access

Opening Remarks (9:00 ~ 9:05)

OR-1 **Tooru Shimosegawa** (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

1. Keynote lecture (9:05 ~ 9:35)

Chair:

Atsushi Masamune (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

K-1 **Pancreatic Stellate Cells (PSCs) : A Starring Role in Healthy, Inflamed and Cancerous Pancreas**

Minoti Apte, Zhihong Xu, Ron Pirola, Jeremy Wilson

Faculty of Medicine, University of New South Wales and Ingham Institute for Applied Medical Research, Sydney, Australia

2. Chronic pancreatitis (9:35 ~ 10:20)

Moderators:

Hirohide Ohnishi (Department of Gastroenterology and Neurology, Akita University)
Tetsuhide Ito (Department of Medicine and Bioregulatory Science, Kyushu University)

Commentators:

Akira Andoh (Shiga University of Medical Science Graduate School of Medicine)
Yusuke Tando (Hirosaki University Graduate School of Health Sciences, Division of Medical Life Sciences, Department of Biomedical Sciences)
Minoti Apte (South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales)

CP-1 **ERK pathway and sheddases play an essential role in ethanol-induced CX3CL1 release in pancreatic stellate cells**

Masahiko Uchida[1], Tetsuhide Ito[1], Taichi Nakamura[1,2], Hisato Igarashi[1], Masayuki Hijioka[1], Yusuke Niina[1], Lingaku Lee[1], Robert T. Jensen[2], Ryoichi Takayanagi[1]

[1]Department of Medicine and Bioregulatory Science, Kyushu University, Fukuoka, Japan, [2]Department of Cell Biology Section, NIDDK, National Institutes of Health, Bethesda, Maryland, United States

CP-2 **Treatment of pancreatic fibrosis with siRNA against a collagen-specific chaperone in vitamin A-coupled liposomes**

Yoshiro Niitsu[1], Hirotoshi Ishiwatari[2], Yasushi Sato[2], Kazuyuki Murase[2], Akihiro Yoneda[1], Ryosuke Fujita[1], Hiroki Nishita[1], Naoko Kubo Birukawa[1], Tsuyoshi Hayashi[2], Tsutomu Sato[2], Koji Miyanishi[2], Rishu Takimoto[2], Masayoshi Kobune[2], Shigenori Ota[3], Yasutoshi Kimura[3], Koichi Hirata[3], Junji Kato[2]

[1]Department of Molecular Target Exploration, Sapporo Medical University, Sapporo, Japan, [2]Fourth Department of Internal Medicine, Sapporo Medical University, Sapporo, Japan, [3]First Department of Surgery Sapporo Medical University, Sapporo, Japan

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EU-1 **Estimation of EUS features of chronic pancreatitis in comparison with clinical symptoms**

Masayuki Kitano, Kumpei Kadosaka, Hiroki Sakamoto, Hajime Imai, Ken Kamata, Takeshi Miyata, Shunsuke Omoto, Kentaro Yamao, Masatoshi Kudo

Department of Gastroenterology and Hepatology, Kinki University Faculty of Medicine, Japan

EU-2 **EUS-elastography in the quantitative analysis of pancreatic fibrosis with special emphasis on comparison with surgical specimens**

Yoshiki Hirooka[1], Akihiro Itoh[2], Hiroki Kawashima[2], Eizaburo Ohno[1], Yuya Itoh[2], Hiroyuki Sugimoto[2], Hajime Sumi[2], Daijuro Hayashi[2], Takamichi Kuwahara[2], Tomomasa Morishima[2], Kohei Funasaka[1], Masanao Nakamura[2], Ryoji Miyahara[2], Hidemi Goto[1,2]

[1]Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan, [2]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

EU-3 **Role of CD133 in amelioration of fibrosis of type 1 autoimmune pancreatitis**

Nobumasa Mizuno

Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan

Closing Remarks (11:50 ~ 11:55)

CR-1 **Tadashi Takeuchi** (Pancreas Research Foundation of Japan)

K-1

Pancreatic Stellate Cells (PSCs) : A Starring Role in Healthy, Inflamed and Cancerous Pancreas

Minoti Apte, Zhihong Xu, Ron Pirola, Jeremy Wilson

Faculty of Medicine, University of New South Wales and Ingham Institute for Applied Medical Research, Sydney, Australia

While the morphology and function of most of the cells of the exocrine and endocrine pancreas have been well described over several centuries, one important cell type in the gland, the pancreatic stellate cell (PSC), was first described only as recently as 30 years ago. Furthermore, it was to be another 16 years before the biology of these cells could begin to be studied because it was only in 1998 that methods were developed to isolate and culture PSCs from rodent and human pancreas. PSCs are now known to be key players in pancreatic fibrosis, a predominant histological feature of two major diseases of the pancreas - chronic pancreatitis and pancreatic cancer. In health, PSCs are in their quiescent phase and are characterised by abundant vitamin A storing lipid droplets in their cytoplasm. The cells are responsible for maintaining normal pancreatic architecture via regulation of the synthesis and degradation of extracellular matrix (ECM) proteins. Recently, PSCs have also been implicated in other functions as progenitor/stem cells, as immune cells and as intermediaries in exocrine pancreatic secretion in humans.

During pancreatic injury, PSCs change to an activated, myofibroblast-like phenotype, characterised by loss of the vitamin A stores and the synthesis of excessive amounts of ECM proteins resulting in the fibrosis of chronic pancreatitis and pancreatic cancer. The central role of PSCs in the fibrosis of chronic pancreatitis and pancreatic cancer, as well as their demonstrated role in cancer progression, makes these cells an important therapeutic target to improve the outcome of these diseases. While several exciting therapeutic approaches have been developed using appropriate experimental animal models, the challenge that remains is to translate these pre-clinical developments into clinically applicable treatments for patients with chronic pancreatitis and pancreatic cancer.

CP-1

ERK pathway and sheddases play an essential role in ethanol-induced CX3CL1 release in pancreatic stellate cells

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[1]Department of Medicine and Bioregulatory Science, Kyushu University, Fukuoka, Japan, [2]Department of Cell Biology Section, NIDDK, National Institutes of Health, Bethesda, Maryland, United States

Background and AIM

Chronic pancreatitis (CP) worsens with drinking, and pancreatic stellate cells (PSCs) play an important role in the pathogenesis of alcoholic CP. Fractalkine is chemokines, and membrane type and soluble type is present. A membrane-bound extracellular region is cut by sheddase, and soluble type fractalkine shows migration activity for the inflammatory cell with CX3CR1 (fractalkine receptor). Serum levels of fractalkine (CX3CL1) are elevated in patients with alcoholic CP, however the mechanism remains unclear. This study aims to determine the effects of cytokines, pathogen-associated molecular patterns (PAMPs), and ethanol and its metabolites on CX3CL1 secretion by PSCs.

Methods

Male Wistar/Bonn Kobori (WBN/Kob) rats were used as models of CP in vivo. PSCs were isolated from 6-week-old male Wistar rats. The effects of cytokines, PAMPs, and ethanol and its metabolites on chemokine production and activation of signaling pathways in PSCs in vitro were examined by real-time reverse transcription-polymerase chain reaction (RT-PCR), western blotting, and enzyme-linked immunosorbent assay.

Results

Expression of CX3CL1 and matrix metalloprotease (MMP)-2 was increased in the pancreas of WBN/Kob rats. The rat PSCs expressed CX3CL1, MMP-2, and a disintegrin and metalloprotease domain (ADAM) 17. Cytokines and PAMPs induced CX3CL1 release. CX3CL1 release was suppressed by specific inhibitors of extracellular signal-regulated kinase (ERK), MMP, and ADAM, and ERK was associated with CX3CL1 transcription. Ethanol synergistically increased CX3CL1 release via ERK and ADAM17 activation in PSCs.

Conclusion

We demonstrated for the first time that ethanol synergistically increased CX3CL1 release from PSCs in part through activation of ERK and ADAM17. This might be one of the mechanisms of serum CX3CL1 elevation and disease progression in patients with alcoholic CP.

CP-1

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CP-2

Treatment of pancreatic fibrosis with siRNA against a collagen-specific chaperone in vitamin A-coupled liposomes

Yoshiro Niitsu[1], Hirotoshi Ishiwatari[2], Yasushi Sato[2], Kazuyuki Murase[2], Akihiro Yoneda[1], Ryosuke Fujita[1], Hiroki Nishita[1], Naoko Kubo Birukawa[1], Tsuyoshi Hayashi[2], Tsutomu Sato[2], Koji Miyanishi[2], Rishu Takimoto[2], Masayoshi Kobune[2], Shigenori Ota[3], Yasutoshi Kimura[3], Koichi Hirata[3], Junji Kato[2]

[1]Department of Molecular Target Exploration, Sapporo Medical University, Sapporo, Japan, [2]Fourth Department of Internal Medicine, Sapporo Medical University, Sapporo, Japan, [3]First Department of Surgery Sapporo Medical University, Sapporo, Japan

Fibrosis associated with chronic pancreatitis is an irreversible lesion that can disrupt pancreatic exocrine and endocrine function.Currently, there are no approved treatments for this disease. We previously showed that siRNA against collagen-specific chaperone protein gp46, encapsulated in vitamin A-coupled liposomes (VA-lip-siRNAgp46), resolved fibrosis in a model of liver cirrhosis. This treatment was investigated for pancreatic fibrosis induced by dibutyltin dichloride (DBTC) and cerulein in rats.

Specific uptake of VA-lip-siRNAgp46,conjugated with 60-carboxyfluorescein (FAM) by activated pancreatic stellate cells (aPSCs), was analysed by fluorescence activated cell sorting (FACS). Intracellular distribution of VA-lip-siRNAgp46-FAM was examined by fluorescent microscopy. Suppression of gp46 expression by VA-lip-siRNAgp46 was assessed by immunoblotting.Collagen synthesis in aPSCs was assayed by dye-binding.

Specific delivery of VA-lip-siRNAgp46 to aPSCs in DBTC rats was verified following intravenous VA-lip-siRNA-FAM and 3H-VA-lip-siRNAgp46. The effect of VA-lip-siRNA on pancreatic histology in DBTC- and cerulein-treated rats was determined by Azan-Mallory staining and hydroxyproline content.

FACS analysis revealed specific uptake of VA-lipsiRNAgp46-FAM through the retinol binding protein receptor by aPSCs in vitro. Immunoblotting and collagen assay verified knockdown of gp46 and suppression of collagen secretion, respectively, by aPSCs after transduction of VA-lip-siRNAgp46. Specific delivery of VAlip-siRNAgp46 to aPSCs in fibrotic areas in DBTC rats was confirmed by fluorescence and radioactivity 24 h after the final injection. 10 systemic VA-lip-siRNAgp46 treatments resolved pancreatic fibrosis, and suppressed tissue hydroxyproline levels in DBTC- and cerulein-treated rats.

These data suggest the therapeutic potential of the present approach for reversing pancreatic fibrosis.

CP-3

Use of nanoparticle to analyze vasculature in diseases

Mitsunobu R Kano

Department of Pharmaceutical Biomedicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan

Effective treatment of "intractable" solid tumors is one of important goals of chemotherapy using nano drug delivery system (nanoDDS). To realize this, we need to investigate why intractable tumors, such as pancreatic cancer, are "intractable". Our study suggests that the structure of vasculature in those tumors is different from what we observe in popular tumor animal models.

We used xenografts of BxPC3 cell line derived from pancreatic cancer as a model of intractable cancer, and those of C26 cell line derived colon cancer as an ordinary cancer model, and compared them. The BxPC3 model has more fibrotic stromal components, whereas the C26 model has less. Moreover, the former has more pericyte-covered vasculature than the latter. As a result, nanoparticle accumulated autonomously in the latter, whereas it accumulated hardly in the former.

To overcome this difficulty in accumulation in the pancreatic cancer model, which is a factor of intractability, we used TGF-beta inhibitor. The inhibitor reduces pericytes, and increased accumulation of nanoparticle in the model and led to significant growth-inhibitory effect. Yet, use of VEGF inhibitor, reported to normalize vasculature, did not increase accumulation in the stroma rich models. VEGF inhibitor did, however, increase distribution of nanoparticle in the colon cancer model, although TGF-beta inhibitor did not in the model.

We further analyzed vascular structure in human tissues of pancreatic or colon cancers. Vasculature in pancreatic cancer was firmly covered by pericytes, whereas that in colon cancer was not covered by pericytes, as in the animal models.

According to these observations, we may need to know the structure of tumor vasculature in various cancers, and to optimize it to maximize the effect of nanoDDS.

References

[1] Kano M R, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M, Fujii T, Komuro A, Kiyono K, Kaminishi M, Hirakawa K, Ouchi Y, Nishiyama N, Kataoka K, Miyazono K. Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. Proc Natl Acad Sci U S A 2007; 104: 3460-3465.

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[3] Cabral H, Matsumoto Y, Mizuno K, Chen Q, Murakami M, Kimura M, Terada Y, Kano MR, Miyazono K, Uesaka M, Nishiyama N, Kataoka K. Accumulation of sub-100 nm polymeric micelles in poorly permeable tumours depends on size. Nat Nanotechnol. 2011; 6(12):815-23.

[4] Zhang L, Nishihara H, Kano MR. Pericyte-coverage of human tumor vasculature and nanoparticle permeability. Biol Pharm Bull. 2012; 35(5):761-6.

PK-1

Pancreatic stellate cell contributes to the maintenance of cancer stem cell-like phenotype in pancreatic cancer cells

Shin Hamada[1], Atsushi Masamune[1], Kennichi Satoh[2], Tooru Shimosegawa[1]

[1]Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan, [2]Division of cancer stem cell, Miyagi Cancer Center Research Institute, Natori, Miyagi, Japan

Background;

Formation of metastasis, invasive growth and chemoresistance contribute to the dismal prognosis of pancreatic cancer, and these characteristics are also cancer stem cell (CSC)-like phenotypes. On the other hand, recent researches have uncovered that tumor stroma itself forms cancer promoting microenvironment by yielding growth support and physical barrier of cancer cells. Pancreatic stellate cells (PSCs) play pivotal role during the formation of pancreatic fibrosis, including cancer-associated desmoplasia. Interaction between cancer cells and stromal cells promotes invasive growth and chemoresistance, but the detailed contribution of PSCs in the maintenance of CSC-like phenotype has not yet clarified.

Methods;

The human pancreatic cancer cell lines SUIT-2 and AsPC-1 were indirectly co-cultured with human PSC cell line hPSC21-S/T. Cell growth and spheroid formation under the co-culture condition were compared with mono-culture condition. The expression of epithelial-mesenchymal transition (EMT) marker *Snail*, putative stem cell markers *ABCG2*, *LIN28* and *Nestin* expressions were quantified by real-time RT-PCR. The subcutaneous xenograft tumors in nude mice were transplanted by injecting AsPC-1 ($1x10^6$ cells) with or without hPSC21-S/T ($1x10^6$ cells). These mice were subjected to the olmesartan administration and histopathological examination of subcutaneous tumor.

Results;

The indirect co-culture of SUIT-2 and AsPC-1 with hPSC21-S/T increased the spheroid formation without affecting cell growth. SUIT-2 and AsPC-1 under the co-culture also revealed the phenotypic changes compatible with EMT. According to these morphological and functional changes, the EMT marker *Snail*, putative stem cell markers *ABCG2*, *LIN28* and *Nestin* expressions were increased in co-cultured SUIT-2 and AsPC-1. Furthermore, co-injection of hPSC21-S/T with AsPC-1 increased the growth of the subcutaneous tumor in nude mice. An angiotensin receptor blocker (ARB) olmesartan administration attenuated the growth of the subcutaneous tumor derived from AsPC-1 / hPSC21-S/T co-injection, suggesting therapeutic application as a PSC-targeting therapy.

Conclusion;

Indirect co-culture of pancreatic cancer cell lines with PSCs resulted in the increased CSC-like phenotypes *in vitro*. PSCs also supported the tumor formation *in vivo*, and targeting PSCs by ARB attenuated this phenomenon. These interactions could be novel therapeutic targets.

PK-2

Modeling pancreatic cancer and the tumor microenvironment by using genetically-engineered mice

Hideaki Ijichi[1], Motohisa Tada[1,2], Koji Miyabayashi[1], Ryota Takahashi[1], Dai Mohri[1], Yosuke Nakai[1], Hiroyuki Isayama[1], Minoru Tada[1], Kazuhiko Koike[1]

[1]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Japan, [2]Department of Gastroenterology, Graduate School of Medicine and Clinical Oncology, Chiba University, Japan

Pancreatic cancer is one of the most deadly cancers with 5 year survival rate around 5%. To conquer this cancer, a better understanding of this disease is inevitably required. For this purpose, we have established a genetically-engineered murine pancreatic cancer model of pancreatic epithelium-specific mutant Kras expression plus knockout of TGF-beta receptor 2 (Tgfbr2). This model demonstrated rapidly progressive pancreatic cancer formation with 100% penetrance and a median survival of 59 days. In addition, this model recapitulated histological features of human pancreatic cancer, ductal adenocarcinoma with abundant stroma, including marked fibrosis called as desmoplasia. Compared with other reported models, this model can be one of the closest approximation of human pancreatic cancer.

The dense stroma might be contributing to the poor prognosis of this disease, by disturbing drug delivery to the cancer cells, and also providing a tumor microenvironment in favor of cancer cells through the tumor-stromal interaction. Therefore, analysis of anti-tumor effect of therapeutic methods and associated changes of tumor microenvironment is to be performed by using genetically-engineered models

Through the analysis of tumor-stromal interaction in this model, we found that CXC chemokine/CXCR2 axis is promoting the tumor progression and blocking the axis can be a potent therapeutic option for pancreatic cancer. We also treated the model mice with several molecular targeting drugs and some of them significantly extended the survival. According to the results, targeting tumor microenvironment, in combination with conventional chemotherapeutic reagents, is important for the therapy of pancreatic cancer.

PK-3

Possible development of pancreatic cancer therapy regulating desmoplasia by targeting pancreatic stellate cells

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Pancreatic stellate cells (PSCs), which are related with desmoplasia in pancreatic cancer, contribute to enhancement of aggressiveness of pancreatic cancer cells (PCCs) and resistance to traditional treatments. Hence we conducted comprehensive studies on PSCs to develop a new therapeutic strategy against pancreatic cancer. In this conference we'll present the results of our two recent studies. First, we revealed that PSCs consisted of various phenotypes with different functions, similar to cancer stem cells. *In vitro*, $CD10^+$ PSCs promoted the invasiveness of PCCs, compared with $CD10^-$ PSCs. $CD10^+$ PSCs significantly increased the tumor growth in a murine co-transplantation model. $CD10^+$ PSCs secreted higher levels of matrix metalloproteinase 3 than did $CD10^-$ PSCs and decreased the promoting effect on the invasion of PCCs by knockdown of matrix metalloproteinase 3. $CD10^+$ PSCs may be a candidate for selective therapeutic targeting in the treatment of pancreatic cancer. Second, we indentified that the antifibrotic agent, pirfenidone, could suppress desmoplasia and exert anti-tumor effects against pancreatic cancer. *In vitro*, pirfenidone inhibited the proliferation and invasiveness of PSCs and tumor-stromal interaction between PSCs and PCCs. Oral administration of pirfenidone to mice implanted with PCCs and PSCs significantly reduced tumor growths. Pirfenidone also decreased the proliferation of PSCs and the deposition of collagen type I and periostin in tumors. Pirfenidone in combination with gemcitabine more effectively suppressed tumor growth and incidence of distant metastasis compared with pirfenidone or gemcitabine alone. These findings indicate that pirfenidone is a promising antitumor agent for pancreatic cancer, owing to its suppression of desmoplasia through regulating PSCs.

EU-1

Estimation of EUS features of chronic pancreatitis in comparison with clinical symptoms

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Background: EUS findings were reported to play an important role in detecting chronic pancreatitis. In the present study, we investigated the clinical significance of EUS imaging findings of early chronic pancreatitis.

Patients and Methods: Recorded movie images of the pancreatic parenchyma in the 3168 cases who underwent EUS from March 2009 to May 2012 were evaluated whether they had EUS imaging findings of early chronic pancreatitis. In cases with clinical features of chronic pancreatitis, such as (1) repeated upper abdominal pain, (2) abnormality of pancreatic enzymes, (3) drinking history lasting more than 80g per day, (4) diabetes, rates of EUS imaging findings of early chronic pancreatitis were assessed.

Results: 13.1% of the 3168 cases had the EUS imaging findings of early chronic pancreatitis. Patients with repeated upper abdominal pain, abnormality of pancreatic enzymes or drinking history had significantly more positive items of EUS imaging findings than patients without these clinical features. Patients with abnormality of pancreatic enzymes and diabetes had significantly higher incidences of hyperechoic foci without shadowing than those without these clinical findings. Patients with repeated upper abdominal pain had significantly higher incidence of lobularity, strands and hyperechoic MPD margin than those without repeated upper abdominal pain.

Conclusion: The number of EUS image findings are correlated well with the severity of chronic pancreatitis. The results in the present study suggest that strands and hyperechoic MPD margin were related to the activity of pancreatitis while hyperechoic foci without shadowing are associated with the endocrine dysfunction.

EU-2

EUS-elastography in the quantitative analysis of pancreatic fibrosis with special emphasis on comparison with surgical specimens

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Background

An accurate diagnosis of pancreatic fibrosis is clinically important, and may have potential for staging chronic pancreatitis. The aim of this study was to diagnose the pancreatic fibrosis through a quantitative analysis of endoscopic ultrasound elastography (EUS-EG).

Methods

Fifty-eight consecutive patients examined by EUS-EG for both pancreatic tumors and their upstream pancreas before pancreatectomy were enrolled. Preoperative EUS-EG images in the upstream pancreas were statistically quantified, and the results were retrospectively compared with postoperative histological fibrosis in the same area. For the quantification of EUS-EG images, 4 parameters (mean, standard deviation, skewness, and kurtosis) were calculated using novel software. Histological fibrosis was graded into 4 categories (normal, mild fibrosis, marked fibrosis, and severe fibrosis) according to a previously reported scoring system.

Results

The fibrosis grade in the upstream pancreas was normal in 24 patients, mild fibrosis in 19, marked fibrosis in 6, and severe fibrosis in 9. Fibrosis grade was significantly correlated with all 4 quantification parameters. According to the receiver operating characteristic (ROC) analysis, the mean was the most useful parameter for diagnosing pancreatic fibrosis.

Conclusions

An accurate diagnosis of pancreatic fibrosis may be possible by analyzing EUS-EG images.

EU-3

Role of CD133 in amelioration of fibrosis of type 1 autoimmune pancreatitis

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Histological findings of type-1 autoimmune pancreatitits (AIP) are characterized by diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis (storiform fibrosis), acinar atrophy, and obliterative phlebitis. Endoscopic ultrasound (EUS)-guided fine needle aspiration and/or core biopsy is useful for the histological diagnosis of AIP, as well as for distinguishing it from pancreatic cancer. Corticosteroids ameliorate the histological abnormalities seen in AIP. However, the precise mechanism of this benefit is unclear. We studied pancreatic tissue obtained by EUS-guided core biopsy before and after treatment with corticosteroids in patients with type 1 AIP. Before treatment, CD133 - a marker of pancreatic stem/progenitor cells, was only detected focally in the apical membrane of small interlobular ducts. In areas where most of the pancreatic acini had disappeared and were replaced by fibrosis, CD133 staining was not seen. Short-term treatment with corticosteroids caused clustered regeneration of acinar cells and amelioration of fibrosis. CD133 immuno-labeling was detected in the apical membrane of most of the ductal structures surrounded by regenerated acinar cells. On the other hand, no post-treatment CD133 labeling was detected in the residual fibrotic areas, where acinar cell regeneration was not found. These findings suggest that CD133 positive cells play an important role in regeneration of acinar cells and subsequent amelioration of pancreatic fibrosis in patients with type 1 AIP.


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