様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

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研究課題名（和文）Cytoglobin overexpression inhibits liver fibrosis and cancer development via anti-oxidant function

研究課題名（英文）Cytoglobin overexpression inhibits liver fibrosis and cancer development via anti-oxidant function

研究代表者
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研究成果の概要（和文）：チオアセトアミド（TAA）注射の10週間後、またはコリン欠乏アミノ酸（CDAA）の16週間の摂食後、これらのモデルはすべて、Cygb欠損マウスでは重度の肝障害と線維症を示しましたが、Cygb過剰発現マウスでは減弱した。培養HSCでは、6Hisタグ付き組換えヒトCYGB（His-CYGB）がクラスリン媒介経路を介してエンドサイトーシスされた。 His-CYGBはROS形成を著しく阻害し、I型コラーゲンα1の産生を抑制した。静脈内His-CYGBは、TAAまたはDDCで治療したマウスの肝臓の炎症、線維症、および酸化的細胞損傷を有意に抑制した。

研究成果の学術的意義や社会的意義
抗線維化療法は、ヒトの慢性肝疾患において満たされていない医学的ニーズのままです。 現在、線維症の理解に大きな進歩があり、肝線維形成の根底にある複数のメカニズムが明らかにされていますが、特定の効果的な抗線維化療法はとらえどころのないままです。 損傷後の肝臓の修復は高度に調整された調整されたプロセスであり、線維症を抑制することで肝臓を健康な状態に戻すことができます。 価値のある治療法を見つけるためのこれらの取り組みにおいて、肝硬変および癌の発症におけるCYGBの保護的役割は有望なものとなる可能性があります。

研究成果の概要（英文）：We have investigated the role of endogenous CYGB on liver diseases using CYGB deficient (Cygb-KO) mice and CYGB transgenic (Cygb-TG) mice under 10 weeks after thioacetamide (TAA) injection, or 16 weeks of choline deficient amino acid define diet (CDAA) feeding. These all models showed that absence of Cygb significantly exacerbated liver damage, fibrosis and reactive oxygen species (ROS) formation which were attenuated in Cygb-overexpressing mice. We have produced 6His-tagged recombinant human CYGB (His-CYGB). In cultured HSCs, His-CYGB was endocytosed and accumulated in endosomes via clathrin-mediated pathway. His-CYGB significantly impeded ROS formation spontaneously or in the presence of ROS inducers in HSCs, thus leading to the attenuation of collagen type I alpha 1 production and alpha-smooth muscle actin expression. Intravenously injected His-CYGB markedly suppressed liver inflammation, fibrosis and oxidative cell damage in TAA- or DDC-administered mice without adverse effects.

研究分野：Hepatology

キーワード：Liver fibrosis　Hepatic stellate cells　Cytoglobin　Antioxidant

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

More than 130 different proteins or peptides have been approved for clinical use by the US Food and Drug Administration to treat or alleviate diseases, including insulin, growth hormone, factor VIII, human albumin and (rh) interferons. However, many anti-fibrotic therapeutic agents cannot be clinically applied because they do not target hepatic stellate cells (HSCs) and are toxic to parenchymal cells. Furthermore, many proteins are larger than the typical pore sizes between endothelial cells, and therefore, the distribution of proteins is limited to the vascular space in the absence of specific protein receptors. However, interestingly, peroxidases, such as catalase, myeloperoxidase and heme proteins with peroxidase activity, including haemoglobin, myoglobin and cytochrome c, have been extensively used in studies to trace the capillary permeability of various tissues. Cytoglobin (CYGB) is the fourth member of globin family, uniquely express in HSCs. Here, we investigate the anti-fibrosis effect of CYGB in vitro and in vivo.

２．研究の目的

We aim to assess the effect of Cygb overexpression and recombinant human CYGB on the development of liver injuries including liver fibrosis, steatohepatitis induced by
different etiologies.

３．研究の方法

(a) Assess the effect of Cygb-overexpressing in HSCs on the development of liver injuries in mice. Perform mouse bile duct ligation (BDL) studies, choline-deficient amino acid-define (CDAA) diet administration, His-CYGB treatment in normal WT mice, PXB mice, thioacetamide (TAA)-treated mice, or 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet-fed mice. Blood and tissues were collected for further analysis.
(b) Cell culture and treatment: Human hepatic stellate cells (HHSteCs) were culture and treated with rhCYGB under different challenging factors including ROS inducer, TGFβ1 cytokine. Molecular and mechanism analysis are performed.

４．研究成果

We have completed investigating the role of endogenous CYGB on liver diseases using CYGB deficient (Cygb-KO) mice and CYGB transgenic (Cygb-TG) mice. We have completed 3 models of liver injuries using wild-type (WT), Cygb transgenic (TG), and knockout (KO) mice. Mice were sacrificed at 10 weeks after thioacetamide (TAA) injection, 16 weeks after choline deficient amino acid define diet (CDAA) feeding plus 4 weeks recovery or 12 months after diethylnitrosamine (DEN) treatment. These all three models showed that despite of different etiologies, absence of Cygb significantly exacerbated liver damage, fibrosis and reactive oxygen species (ROS) formation. All these manifestations were attenuated in Cygb-overexpressing mice. We have further produced 6His-tagged recombinant human CYGB (His-CYGB), traced its bio-distribution in vitro, and assessed its function in suppressing fibrosis synthesis in cultured human hepatic stellate cells (HHSteCs).
We have performed (1) comprehensive whole transcriptomic analysis by RNA sequencing usig rhCYGB treated HHSteCs, (2) mechanism analysis of CYGB signaling; (3) biodistribution and safety assay of rhCYGB in vivo; (4) anti-fibrotic therapy using

mice with advanced liver cirrhosis under thioacetamide (TAA) or 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) treatment. Here we showed:

His-CYGB triggers the deactivation of HSCs and suppresses collagen production in vitro

We investigated the effects of exogenous His-CYGB on cultured HHSteCs. The addition of His-CYGB (5-80 μg/mL, for 1-48 h) markedly suppressed the protein levels of HSC activation markers, including COL1A1 and αSMA (Fig. 1).

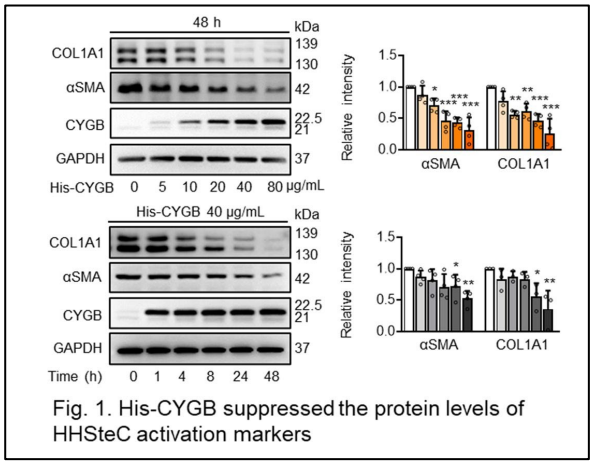

Fig. 1. His-CYGB suppressed the protein levels of HHSteC activation markers

To examine changes in gene expression associated with the activation of HSCs and the function of His-CYGB, we performed RNA-seq analysis of three untreated and three His-CYGB-treated HHSteC samples. RNA-seq data revealed the downregulation of extracellular matrix-encoding and fibrosis-related genes, such as COL21A1, COL13A1, COL14A1 and □SMA, and the upregulation of antioxidant and matrix metalloproteinase (MMP)-1 gene in response to the His-CYGB treatment (Fig. 2). Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) confirmed the significant downregulation of fibrosis-related mRNA expression, such as □SMA(50%), COL1A1 (84%), COL3A1 (66%), TIMP-1 (64%) and TGF-□1 (64%); meanwhile, MMP-1 expression increased by 32-fold (Fig. 3).

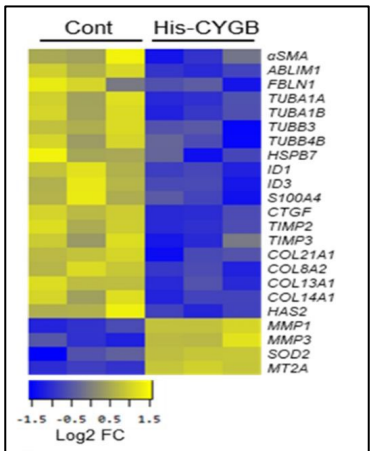

Fig. 2. Heatmap analysis of fibrosis- and anti-oxidant-related genes that were 2-fold changed significantly in HHSteCs treated with His-CYGB (80 μg/mL, 48 h) compared to untreated controls by RNA-Seq (n = 3).

His-CYGB scavenges ROS and attenuates ROS-induced HSC activation and collagen

Synthesis CYGB is involved in the detoxification of ROS, nitric oxide (NO) metabolism and lipid metabolism, which are all associated with HSC activation and liver fibrogenesis. Herein, we directly demonstrated the ROS-scavenging function of His-CYGB. In a cell-free system, the total antioxidant capacity (TAC) of His-CYGB was equivalent to that of 1,094 nmol/μg of Trolox, a water-soluble vitamin E analogue (Fig. 4A, left). His-CYGB-treated HHSteCs demonstrated a significant TAC increase (by 2-fold) when compared with untreated controls (Fig. 4A, right). During the spontaneous, culture-dependent

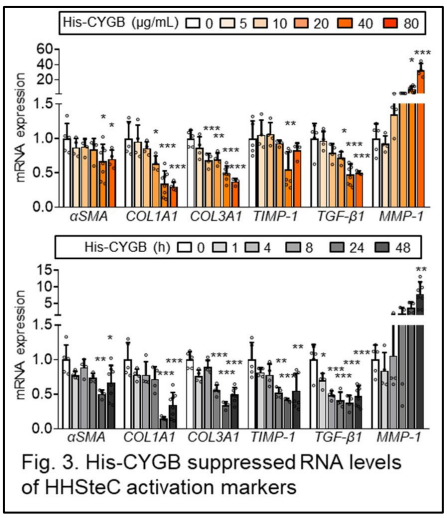

Fig. 3. His-CYGB suppressed RNA levels of HHSteC activation markers

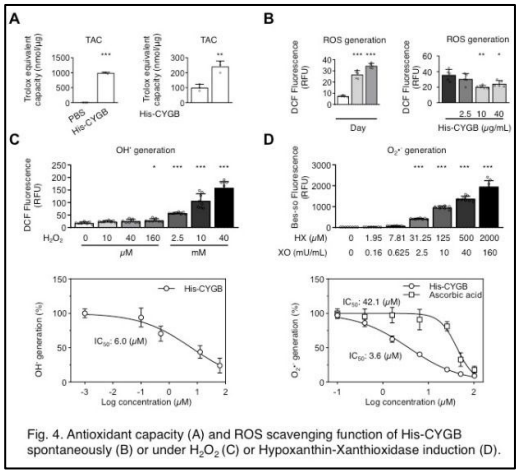

Fig. 4. Antioxidant capacity (A) and ROS scavenging function of His-CYGB spontaneously (B) or under H_2O_2 (C) or Hypoxanthin-Xanthioxidase induction (D).

scavenged by His-CYGB (Fig. 4C, bottom). activation of HHSteCs, cellular ROS formation, which was measured using a 2′,7′-dichlorofluorescein diacetate (DCFDA)-based assay, increased in a time-dependent manner, demonstrating a 5-fold increase on day 3 (Fig. 4B, left). The His-CYGB treatment suppressed ROS generation in a dose-dependent manner (Fig. 4B, right). H2O2 administration in HHSteCs induced a dose-dependent increase in hydroxyl radical (OH·)levels (Fig. 4C, top), which were

Hypoxanthine-xanthine oxidase (HX-XO) treatment increased superoxide anion radical ($O_2^{\cdot-}$) levels in a dose-dependent manner as measured by the BES-So assay in a cell-free system (Fig. 4D, top). The addition of His-CYGB reduced more than 90% of the $O_2^{\cdot-}$-released by the HX-XO reaction, which was a stronger effect than that observed for ascorbic acid at the same concentration (Fig. 4D, bottom). These results suggested that His-CYGB could scavenge endogenous and exogenous ROS, resulting in the prevention of HSC activation.

In addition, His-CYGB treatment affects IFN secretion in HSCs. RNA-Seq analysis of His-CYGB-treated HHSteC samples in comparison with controls revealed the upregulation of the IFN-stimulated genes. Next, the applicability of His-CYGB as protein therapy against liver injury and fibrosis was tested using in vivo mouse models. The appropriate dose of His-CYGB was first determined by evaluating liver cirrhosis in mice that had already developed severe liver fibrosis by the injection of TAA for ten weeks. His-CYGB at 2 mg/kg bode weight was tail vein injection at the last 2 or 5 weeks of TAA injection.

Serum levels of AST, ALT and lactate dehydrogenase (LDH) were all significantly diminished following the His-CYGB treatment (Fig. 5A). Histological analysis revealed that the His-CYGB treatment inhibited the infiltration of neutrophils and CD68+ macrophages in the liver when compared with controls (Fig. 5B). RNA-seq analysis revealed that similar to RNA-seq results in vitro, here we also found that all of the typical fibrosis-related genes and genes associated with inflammatory cytokines, chemokines and oxidative stress response were significantly downregulated (Fig. 5C), which was confirmed by qRT-PCR analysis (Fig. 5D). Furthermore, it significantly suppressed up to 72% of COL1A1 and 78% of □SMA at protein and RNA levels and 43% of Tgf-□1, 53% of Tgf-□3 and 79% of Timp-1 mRNA expression (Fig. 5D). Reduced glutathione (GSH) is among the most important ROS scavengers, and the ratio of GSH to oxidised glutathione (GSSG) is widely used in clinical practice to evaluate the oxidative stress status of biological samples.

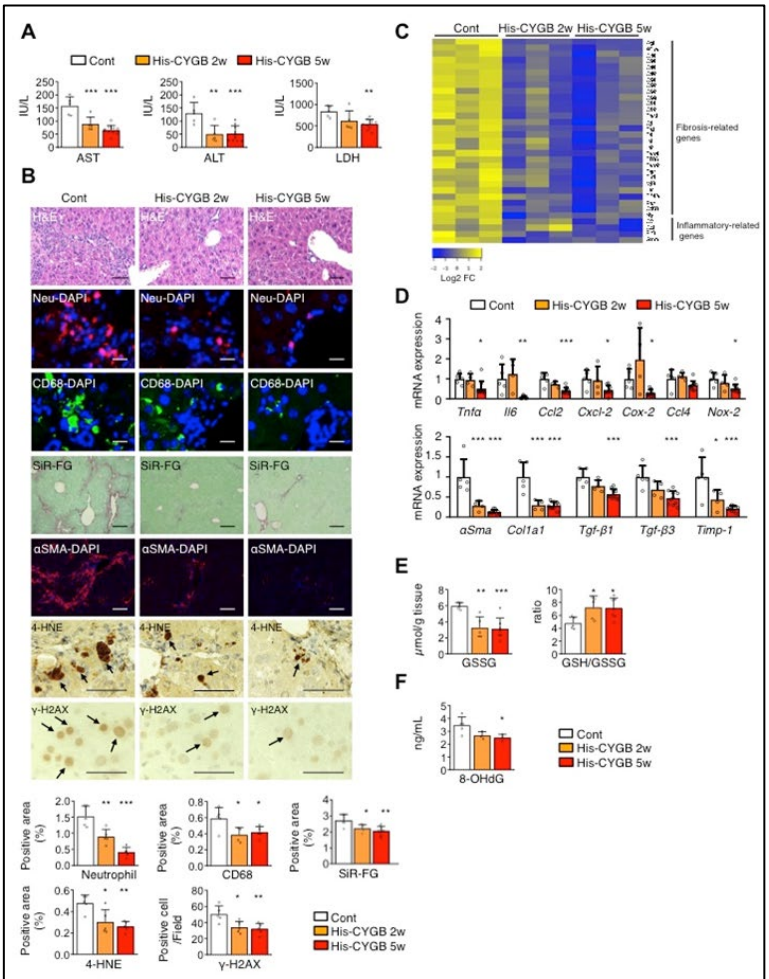

Fig. 5. Intravenously injected His-CYGB markedly suppressed liver inflammation, fibrosis and oxidative cell damage in TAA administered mice

Safety and distribution of His- CYGB in vivo

The safety of His-CYGB was assessed in vivo in both WT and PXB mice. The serum levels of mouse AST and ALT during the acute (1-48 h) or chronic phases (2 weeks) in WT mice and human albumin and ALT in humanized liver chimeric PXB mice did not change following the tail-vein injection of His-CYGB, suggesting that His-CYGB administration
resulted in negligible side effects for both mouse and human HCs .
The in vivo and ex vivo analysis of the injected Alexa 488-His-CYGB conjugates revealed the significant accumulation of the fluorescence signal in the liver, kidney, pancreas, fat, intestine, colon, stomach and bladder but not in the brain for both normal WT and TAA-induced liver fibrosis WT mice when assessed between 1 h and 48 h after injection. To our surprise, at the liver tissue level, Alexa 488-His-CYGB accumulated in hepatic sinusoidal cells, colocalised with desmin-positive HSCs and partially colocalised with CD31-positive endothelial cells but did not colocalise with CD68-positive macrophages. To verify these findings, Cygb-deficient mice were injected with His-CYGB, and its distribution was determined using an anti-CYGB antibody. Consistently, His-CYGB was found in HSCs and endothelial cells but not macrophages in both untreated and CDAA-treated Cygbdeficient mice. The injected His-CYGB predominantly localised to HSCs but not to macrophages suggesting specific targeting effects. See detail in our published paper Hepatology 2021 Jun;73(6):2527-2545. doi: 10.1002/hep.31752.
Conclusions: His-CYGB could have anti-fibrotic clinical applications for human chronic liver diseases.

５．主な発表論文等

〔雑誌論文〕　計9件（うち査読付論文　9件／うち国際共著　5件／うちオープンアクセス　7件）

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３．雑誌名 Oncogenesis	６．最初と最後の頁 0-0
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3．雑誌名 Antioxid Redox Signal	6．最初と最後の頁 -
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2．論文標題 Clinical significance of circulating soluble immune checkpoint proteins in sorafenib-treated patients with advanced hepatocellular carcinoma	5．発行年 2020年
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1．発表者名 Minh Phuong Dong, Le Thi Thanh Thuy, Hoang Hai, Vu Ngoc Hieu, Dinh Viet Hoang, Sawako Uchida-Kobayashi, Masaru Enomoto, Akihiro Tamori and Norifumi Kawada
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１．発表者名
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２．発表標題
Organize Committee, Scientific secretary

３．学会等名
the Asian Pacific Association for the Study of the Liver, Single Topic Conference (APASL STC) in Osaka（国際学会）

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Circulating soluble immune checkpoint proteins as biomarkers for predicting the outcome of antiviral treatment of chronic hepatitis B

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1.Vu Ngoc Hieu, Ninh Quoc Dat, Le Thi Thanh Thuy, Hoang Hai, Dinh Viet Hoang, Katsutoshi Yoishizato and Norifumi Kawada.

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Recombinant human Cytoglobin Deactivates Hepatic Stellate Cells and Prevents Fibrosis Aggravation by Scavenging ROS and Inducing Interferon-Beta

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１．発表者名
Le Thi Thanh Thuy

２．発表標題
Chairman for the session of Biology and Medicine

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２．発表標題 Chairman for the session of Biology and Medicine
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〔図書〕　計1件

１．著者名 Le Thi Thanh Thuy, Hoang Hai, Vu Ngoc Hieu, Ninh Quoc Dat, Dinh Viet Hoang, and Norifumi Kawada.	４．発行年 2019年
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３．書名 The Evolving Landscape of Liver Cirrhosis Management. Chapter 16: Antifibrotic therapy for liver cirrhosis.	

〔出願〕　計1件

産業財産権の名称 肝星細胞の活性化並びに肝炎・肝線維化を抑制するサイトグロビン関連ペプチド	発明者 河田　則文，LE THI THANH THUY	権利者 同左
産業財産権の種類、番号 特許、2019-087681	出願年 2019年	国内・外国の別 国内

〔取得〕　計1件

産業財産権の名称 肝星細胞の活性化並びに肝炎;肝線維化を抑制するサイトグロビン関連ペプチド	発明者 河田　則文，LE THI THANH THUY	権利者 同左
産業財産権の種類、番号 特許、2020-566309	取得年 2021年	国内・外国の別 国内

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関