Clodronate Liposomes

Abstracts

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HYGIEIA BIOSCIENCE
株式会社 ヒュギエイアバイオサイエンス

目次

Stem Cell Reports. 2013 Dec 5;1(6):499-508.

Immortalization of Erythroblasts by c-MYC and BCL-XL Enables Large-Scale Erythrocyte Production from Human Pluripotent Stem Cells.

Sho-ichi Hirose, Naoya Takayama, Sou Nakamura, Kazumichi Nagasawa, Kiyosumi Ochi, Shinji Hirata, Satoshi Yamazaki, Tomoyuki Yamaguchi, Makoto Otsu, Shinya Sano, Nobuyasu Takahashi, Akira Sawaguchi, Mamoru Ito, Takashi Kato, Hiromitsu Nakauchi, Koji Eto

Laboratory of Stem Cell Therapy, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan,
Clinical Application Department, Center for iPS Cell Research and Application, Kyoto University, Kyoto 606-8507, Japan.

Abstract

The lack of knowledge about the mechanism of erythrocyte biogenesis through self-replication makes the in vitro generation of large quantities of cells difficult. We show that transduction of c-MYC and BCL-XL into multipotent hematopoietic progenitor cells derived from pluripotent stem cells and gene overexpression enable sustained exponential self-replication of glycophorin A+ erythroblasts, which we term immortalized erythrocyte progenitor cells (imERYPCs). In an inducible expression system, turning off the overexpression of c-MYC and BCL-XL enabled imERYPCs to mature with chromatin condensation and reduced cell size, hemoglobin synthesis, downregulation of GCN5, upregulation of GATA1, and endogenous BCL-XL and RAF1, all of which appeared to recapitulate normal erythropoiesis. imERYPCs mostly displayed fetal-type hemoglobin and normal oxygen dissociation in vitro and circulation in immunodeficient mice following transfusion. Using critical factors to induce imERYPCs provides a model of erythrocyte biogenesis that could potentially contribute to a stable supply of erythrocytes for donor-independent transfusion.

Scientific Reports 2014 Nov 11;4:6997

From cartoon to real time MRI: in vivo monitoring of phagocyte migration in mouse brain.

Yuki Mori, Ting Chen, Tetsuya Fujisawa, Syoji Kobashi, Kohji Ohno, Shinichi Yoshida, Yoshiyuki Tago, Yutaka Komai, Yutaka Hata, Yoshichika Yoshioka

Biofunctional Imaging,WPI Immunology Frontier Research Center (WPI IFReC), Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan, Center for Information and Neural Networks (CiNet), National Institute of Information and Communications Technology (NICT) and Osaka University, 1-4 Yamadaoka, Suita, Osaka 565-0871, Japan.

Abstract

Recent studies have demonstrated that immune cells play an important role in the pathogenesis of many neurological conditions. Immune cells constantly survey the brain microvasculature for irregularities in levels of factors that signal homeostasis. Immune responses are initiated when necessary, resulting in mobilisation of the microglial cells resident in the central nervous system (CNS) and/or of infiltrating peripheral cells. However, little is known about the kinetics of immune cells in healthy and diseased CNS, because it is difficult to perform long-term visualisation of cell motility in live tissue with minimal invasion. Here, we describe highly sensitive in vivo MRI techniques for sequential monitoring of cell migration in the CNS at the single-cell level. We show that MRI combined with intravenous administration of super-paramagnetic particles of iron oxide (SPIO) can be used to monitor the transmigration of peripheral phagocytes into healthy or LPS-treated mouse brains. We also demonstrate dynamic cell migration in live animal brains with time-lapse MRI videos. Time-lapse MRI was used to visualise and track cells with low motility in a control mouse brain. High-sensitivity MRI cell tracking using SPIO offers new insights into immune cell kinetics in the brain and the mechanisms of CNS homeostasis.

Transl Vis Sci Technol. 2015 Mar 10;4(2):6. eCollection 2015.

Suppression of Laser-Induced Choroidal Neovascularization by the Oral Medicine Targeting Histamine Receptor H4 in Mice.

Ryo Ijima, Hiroki Kaneko, Fuxiang Ye, Kei Takayama, Yosuke Nagasaka, Keiko Kataoka, Yasuhito Funahashi, Takeshi Iwase, Shu Kachi[1], Seiichi Kato, HirokoTerasaki

Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Abstract

PURPOSE: This study aimed to examine relationship of histamine receptor H4 (HRH4) and the pathogenesis of laser-induced choroidal neovascularization (laser-CNV) and to determine whether oral administration of HRH4 antagonists suppressed laser-CNV in mice.

METHODS: Laser photocoagulation was performed in mice to induce the laser-CNV. Histamine was administered intravitreously, and CNV volume was measured. Laser photocoagulation and intravitreous injection of HRH4 antagonist JNJ7777120 were performed after intraperitoneal injection of clodronate liposome, which depletes circulating monocyte-derived macrophages; CNV volume was compared with that in mice injected with control (dimethyl sulfoxide [DMSO]/PBS). Three days after laser-CNV, the F4/80+CD11b+ macrophage population in retinal pigment epithelium (RPE)/choroid complex was quantified with flow cytometry in wild-type and Hrh4-/- mice. The long-acting HRH4 antagonist JNJ28307474 was then administrated periorally, and the laser-CNV volume was compared with controls.

RESULTS: Intravitreous injection of histamine did not affect laser-CNV volume. The laser-CNV from the eye injected with JNJ7777120 was equivalent to that injected with the DMSO/PBS in mice that had intraperitoneally received clodronate liposome. Flow cytometry after laser-CNV induction revealed a smaller F4/80+CD11b+ macrophage population in the RPE/choroid complex of Hrh4-/- mice than in wild-type mice. Oral administration of JNJ28307474 significantly reduced laser-CNV volume in wild-type mice.

CONCLUSIONS: Our results suggested that HRH4-positive macrophages played an important role in the pathogenesis of laser-CNV and that they require a different ligand from that of histamine. The oral administration of an HRH4 antagonist successfully reduced laser-CNV.

TRANSLATIONAL RELEVANCE: Our results indicate that drugs targeting HRH4 are potentially a novel oral treatment for age-related macular degeneration.

Nature Communications 2015 Feb 26;6:6241.

Complement C1q-induced activation of b-catenin signalling causes hypertensive arterial remodelling.

Tomokazu Sumida, Atsuhiko T. Naito, Seitaro Nomura, Akito Nakagawa, Tomoaki Higo, Akihito Hashimoto, Katsuki Okada, Taku Sakai, Masamichi Ito, Toshihiro Yamaguchi, Toru Oka, Hiroshi Akazawa, Jong-Kook Lee, Tohru Minamino, Stefan Offermanns, Tetsuo Noda, Marina Botto, Yoshio Kobayashi, Hiroyuki Morita, Ichiro Manabe, Toshio Nagai, Ichiro Shiojima, Issei Komuro

Department of Cardiovascular Medicine, The University of Tokyo Graduate School of Medicine, Tokyo 113-8655, Japan, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka 565-0871, Japan.

Abstract

Hypertension induces structural remodelling of arteries, which leads to arteriosclerosis and end-organ damage. Hyperplasia of vascular smooth muscle cells (VSMCs) and infiltration of immune cells are the hallmark of hypertensive arterial remodelling. However, the precise molecular mechanisms of arterial remodelling remain elusive. We have recently reported that complement C1q activates β-catenin signalling independent of Wnts. Here, we show a critical role of complement C1-induced activation of β-catenin signalling in hypertensive arterial remodelling. Activation of β-catenin and proliferation of VSMCs were observed after blood-pressure elevation, which were prevented by genetic and chemical inhibition of β-catenin signalling. Macrophage depletion and C1qa gene deletion attenuated the hypertension-induced β-catenin signalling, proliferation of VSMCs and pathological arterial remodelling. Our findings unveil the link between complement C1 and arterial remodelling and suggest that C1-induced activation of β-catenin signalling becomes a novel therapeutic target to prevent arteriosclerosis in patients with hypertension.

Elife. 2015 Aug 11;4. doi: 10.7554/eLife.08733.

A pain-mediated neural signal induces relapse in murine autoimmune encephalomyelitis, a multiple sclerosis model.

Yasunobu Arima, Daisuke Kamimura, Toru Atsumi, Masaya Harada, Tadafumi Kawamoto, Naoki Nishikawa, Andrea Stofkova, Takuto Ohki, Kotaro Higuchi, Yuji Morimoto, Peter Wieghofer, Yuka Okada, Yuki Mori, Saburo Sakoda, Shizuya Saika, Yoshichika Yoshioka, Issei Komuro, Toshihide Yamashita, Toshio Hirano, Marco Prinz, Masaaki Murakami

Division of Molecular Neuroimmunology, Institute for Genetic Medicine, Graduate School of Medicine, Hokkaido University, Sapporo, Japan.

Abstract

Although pain is a common symptom of various diseases and disorders, its contribution to disease pathogenesis is not well understood. Here we show using murine experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis (MS), that pain induces EAE relapse. Mechanistic analysis showed that pain induction activates a sensory-sympathetic signal followed by a chemokine-mediated accumulation of MHC class II+CD11b+ cells that showed antigen-presentation activity at specific ventral vessels in the fifth lumbar cord of EAE-recovered mice. Following this accumulation, various immune cells including pathogenic CD4+ T cells recruited in the spinal cord in a manner dependent on a local chemokine inducer in endothelial cells, resulting in EAE relapse. Our results demonstrate that a pain-mediated neural signal can be transformed into an inflammation reaction at specific vessels to induce disease relapse, thus making this signal a potential therapeutic target.

Arterioscler Thromb Vasc Biol. 2015 Jun;35(6):1423-33.

Identification of Pathogenic Cardiac CD11c+ Macrophages in Nod1-Mediated Acute Coronary Arteritis.

Yoshitomo Motomura, Shunsuke Kanno, Kenichi Asano, Masato Tanaka, Yutaka Hasegawa, Hideki Katagiri, Takashi Saito, Hiromitsu Hara, Hisanori Nishio, Toshiro Hara, Sho Yamasaki

The Division of Molecular Immunology, Research Center for Infectious Diseases, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan.
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Abstract

OBJECTIVE: Nod1 is an intracellular pattern recognition receptor for bacterial peptidoglycan fragments. We previously reported that a synthetic Nod1 ligand, FK565, induced acute coronary arteritis in mice similar to that of Kawasaki disease. However, the molecular mechanisms underlying this characteristic inflammation have remained elusive.

APPROACH AND RESULTS: We found that CD11c(+)MHC class II(+) cells accumulated in the heart of FK565-treated mice before arteritis development. Morphological features and gene expression signatures of the cardiac CD11c(+)MHC class II(+) cells suggested that this population is closely related to macrophages, and thus, we designated them cardiac CD11c(+) macrophages. Nod1 in nonhematopoietic cells, rather than hematopoietic cells, was required for the increase of cardiac CD11c(+) macrophages and arteritis development. Among nonhematopoietic cells, cardiac endothelial cells produced a large amount of chemokines in response to FK565. Endothelial cell-specific blockade of Nod1 signaling suppressed FK565-induced expression of these chemokines, accumulation of cardiac CD11c(+) macrophages, and subsequent coronary arteritis development. We also found that CCR2(+)Ly6C(hi) inflammatory monocytes in peripheral blood supplied precursors of cardiac CD11c(+) macrophages. CCR2-deficient mice or pertussis toxin-treated mice exhibited decreased numbers of cardiac CD11c(+) macrophages and reduced arteritis.

CONCLUSIONS: These results suggest that Ly6C(hi) monocytes are recruited to FK565-activated endothelial cells to generate cardiac CD11c(+) macrophages,

which play a pivotal role in the pathogenesis of acute coronary arteritis.

European Journal of Immunology 2016 May;46(5):1214-23.

Monocyte infiltration into obese and fibrilized tissues is regulated by PILRα.

Kohyama M, Matsuoka S, Shida K, Sugihara F, Aoshi T, Kishida K, Ishii KJ, Arase H

Laboratory of Immunochemistry, Immunology Frontier Research Center, Osaka University, Suita, Osaka, Japan, Department of Immunochemistry, Research Institute for Microbial Diseases, Osaka University, Suita, Osaka, Japan, Laboratory of Biofunctional Imaging, Immunology Frontier Research Center, Osaka University, Suita, Osaka, Japan, Laboratory of Vaccine Science, Immunology Frontier Research Center, Osaka University, Suita, Osaka, Japan, Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation (NIBIO), Ibaraki, Osaka, Japan.

Abstract

Paired immunoglobulin-like type 2 receptor α (PILRα) is an inhibitory receptor that is mainly expressed on myeloid cells, and negatively regulates neutrophil infiltration during inflammation. However, PILRα role on monocyte has not been described. Under both steady-state and inflammatory conditions, monocytes migrate into tissues and differentiate into macrophages. Macrophages in adipose and liver tissues play important roles in tissue homeostasis and pathogenesis of metabolic diseases. Here, we found that PILRα controls monocyte mobility through regulating integrin signaling and inhibiting CD99-CD99 binding. Moreover, we found that Pilra(-/-) mice developed obesity and hepatomegaly with fibrosis, and the numbers of macrophages in adipose and liver tissues are significantly increased in Pilra(-/-) mice. These data suggest that immune inhibitory receptor, PILRα, plays an important role in the prevention of obesity and liver fibrosis.

Oncotarget. 2016; 7:48860-48869.

Circulating nano-particulate TLR9 agonist scouts out tumor microenvironment to release immunogenic dead tumor cells

Yuji Kitahata1,2, Tomohiro Kanuma1,3, Masayuki Hayashi1, Nobuyoshi Kobayashi1, Koji Ozasa1,5, Takato Kusakabe1,3, Burcu Temizoz3, Etsushi Kuroda3, Hiroki Yamaue2, Cevayir Coban4, Takuya Yamamoto1,3, Kouji Kobiyama1,3, Taiki Aoshi1,3 and Ken J. Ishii1,3

1 Labotatory of Adjuvant Innovation, National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Osaka, Japan
2 2nd Department of Surgery, Wakayama Medical University, Wakayama, Japan
3 Laboratory of Vaccine Science, WPI Immunology Frontier Research Center (IFReC), Osaka University, Osaka, Japan
4 Laboratory of Malaria Immunology, WPI Immunology Frontier Research Center, Osaka University, Osaka, Japan
5 Department of Pediatrics, Yokohama City University, Yokohama, Japan

Abstract

Recent evidence suggest that a β-glucan derived from mushroom Schizophyllan(SPG) complexed with a humanized TLR9 agonistic CpG DNA, K3 (K3-SPG) is a promising vaccine adjuvant that induces robust CD8 T cell responses to co-administered antigen. However, it has not been investigated whether K3-SPG alone can act as an anti-cancer immunotherapeutic agent or not. Here, we demonstrate that intravenous injection of K3-SPG, but not CpG alone, is accumulated in the tumor microenvironment and triggered immunogenic cell death (ICD) of tumor cells by local induction of type-I interferon (IFN) as well as IL-12. Resultant innate immune activation as well as subsequent tumor-specific CD8 T cell responses were contributed the tumor growth suppression. This anti-tumor effect of K3-SPG monotherapy was also confirmed by using various tumor models including pancreatic cancer peritoneal dissemination model. Taken together, nano-particulate TLR9 agonist injected intravenously can scout out tumor microenvironment to provoke local innate immune activation and release dead tumor cells into circulation that may induce broader and protective tumor antigen-specific CD8 T cells.

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NK cells activated by Interleukin-4 in cooperation with Interleukin-15 exhibit distinctive characteristics.

Tsuyoshi Kiniwa, Yutaka Enomoto, Natsumi Terazawa, Ai Omi, Naoko Miyata, Kenji Ishiwata and Atsushi Miyajima

Laboratory of Cell Growth and Differentiation, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Bunkyo-ku, Tokyo 113-0032, Japan and Department of Tropical Medicine, The Jikei University School of Medicine, Minato-ku, Tokyo 105-8461, Japan

Abstract

Natural killer (NK) cells are known to be activated by Th1-type cytokines, such as IL-2, -12, or -18, and they secrete a large amount of IFN-γ that accelerates Th1-type responses. However, the roles of NK cells in Th2-type responses have remained unclear. Because IL-4 acts as an initiator of Th2-type responses, we examined the characteristics of NK cells in mice overexpressing IL-4. In this study, we report that IL-4 overexpression induces distinctive characteristics of NK cells (B220high/CD11blow/IL-18Rαlow), which are different from mature conventional NK (cNK) cells (B220low/CD11bhigh/IL-18Rαhigh). IL-4 overexpression induces proliferation of tissue-resident macrophages, which contributes to NK cell proliferation via production of IL-15. These IL-4–induced NK cells (IL4-NK cells) produce higher levels of IFN-γ, IL-10, and GM-CSF, and exhibit high cytotoxicity compared with cNK cells. Furthermore, incubation of cNK cells with IL-15 and IL-4 alters their phenotype to that similar to IL4-NK cells. Finally, parasitic infection, which typically causes strong Th2-type responses, induces the development of NK cellswith characteristics similar to IL4-NK cells. These IL4-NK–like cells do not develop in IL-4Rα KO mice by parasitic infection. Collectively, these results suggest a novel role of IL-4 in immune responses through the induction of the unique NK cells.

Cancer Medicine 2016; 5(10):2920–2933

CCL2 as a potential therapeutic target for clear cell renal cell carcinoma

Ryuichiro Arakaki1, Toshinari Yamasaki1, Toru Kanno1, Noboru Shibasaki1, Hiromasa Sakamoto1,Noriaki Utsunomiya1, Takayuki Sumiyoshi1, Shinsuke Shibuya2, Tatsuaki Tsuruyama2, Eijiro Nakamura3, Osamu Ogawa1 & Tomomi Kamba1

1Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan
2Department of Diagnostic Pathology, Kyoto University Graduate School of Medicine, Kyoto, Japan
3Laboratory for Malignancy Control Research/Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

Abstract

We previously reported that the pVHL-atypical PKC-JunB pathway contributed to promotion of cell invasiveness and angiogenesis in clear cell renal cell carcinoma (ccRCC), and we detected chemokine (C-C motif) ligand-2 (CCL2) as one of downstream effectors of JunB. CCL2 plays a critical role in tumorigenesis in other types of cancer, but its role in ccRCC remains unclear. In this study, we investigated the roles and therapeutic potential of CCL2 in ccRCC. Immunohistochemical analysis of CCL2 expression for ccRCC specimens showed that upregulation of CCL2 expression correlated with clinical stage, overall survival, and macrophage infiltration. For functional analysis of CCL2 in ccRCC cells, we generated subclones of WT8 cells that overexpressed CCL2 and subclones 786-O cells in which CCL2 expression was knocked down. Although CCL2 expression did not affect cell proliferation in vitro, CCL2 overexpression enhanced and CCL2 knockdown suppressed tumor growth, angiogenesis, and macrophage infiltration in vivo. We then depleted macrophages from tumor xenografts by administration of clodronate liposomes to confirm the role of macrophages in ccRCC. Depletion of macrophages suppressed tumor growth and angiogenesis. To examine the effect of inhibiting CCL2 activity in ccRCC, we administered CCL2 neutralizing antibody to primary RCC xenografts established from patient surgical specimens. Inhibition of CCL2 activity resulted in significant suppression of tumor growth, angiogenesis, and macrophage infiltration. These results suggest that CCL2 is involved in angiogenesis and macrophage infiltration in ccRCC, and that CCL2 could be a potential therapeutic target for ccRCC.

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Possible Involvement of Liver Resident Macrophages (Kupffer Cells) in the Pathogenesis of Both Intrahepatic and Extrahepatic Inflammation

Yuki Kakinuma, Takuya Kimura, and Yoshifumi Watanabe

Department of Pharmaceutical Sciences, Musashino University, Tokyo 202-0023, Japan

Abstract

Liver resident macrophages designated Kupffer cells (KCs) formthe largest subpopulation of tissuemacrophages. KCs are involved in the pathogenesis of liver inflammation. However, the role of KCs in the systemic inflammation is still elusive. In this study, we examined whether KCs are involved in not only intrahepatic inflammation but also extrahepatic systemic inflammation. Administration of clodronate liposomes resulted in theKCdeletion and in the suppression of liver injury inTcell-mediated hepatitis by ConA as a local acute inflammation model, while the treatment did not influence dextran sulfate sodium-(DSS-) induced colitis featured byweight loss, intestinal shrink, and pathological observation as an ectopic local acute inflammationmodel. In contrast,KC deletion inhibited collagen-induced arthritis as amodel of extrahepatic, systemic chronical inflammation. KC deleted mice showed weaker arthritic scores, less joint swelling, and more joint space compared to arthritis-induced control mice. These results strongly suggest that KCs are involved in not only intrahepatic inflammatory response but also systemic (especially) chronic inflammation.

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Macrophage Infiltration Is a Causative Factor for Ligamentum Flavum Hypertrophy through the Activation of Collagen Production in Fibroblasts

Takeyuki Saito,1a Masamitsu Hara,1a Hiromi Kumamaru,1 Kazu Kobayakawa,1 Kazuya Yokota,2 Ken Kijima,1a Shingo Yoshizaki,1a Katsumi Harimaya,1 Yoshihiro Matsumoto,1 Kenichi Kawaguchi,1 Mitsumasa Hayashida,1 Yutaka Inagaki,34 Keiichiro Shiba,2 Yasuharu Nakashima,1 and Seiji Okada1a

From the Departments of Advanced Medical Initiatives[a] and Orthopaedic Surgery,[1] Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; the Department of Orthopaedic Surgery,[2] Spinal Injuries Center, Fukuoka, Japan; the Center for Matrix Biology and Medicine,[3] Graduate School of Medicine, and the Department of Regenerative Medicine,[4] School of Medicine, Tokai University, Isehara, Japan

Abstract

Ligamentum flavum (LF) hypertrophy causes lumbar spinal canal stenosis, leading to leg pain and disability in activities of daily living in elderly individuals. Although previous studies have been performe on LF hypertrophy, its pathomechanisms have not been fully elucidated. In this study, we demonstrated that infiltrating macrophages were a causative factor for LF hypertrophy. Induction of macrophages into the mouse LF by applying a microinjury resulted in LF hypertrophy along with collagen accumulation and fibroblasts proliferation at the injured site, which were very similar to the characteristics observed in the severely hypertrophied LF of human. However, we found that macrophage depletion by injecting clodronate-containing liposomes counteracted LF hypertrophy even with microinjury. For identification of fibroblasts in the LF, we used collagen type I α_2 linked to green fluorescent protein transgenic mice and selectively isolated green fluorescent protein positive fibroblasts from the microinjured LF using laser microdissection. A quantitative RT-PCR on laser microdissection samples revealed that the gene expression of collagen markedly increased in the fibroblasts at the injured site with infiltrating macrophages compared with the uninjured location. These results suggested that macrophage infiltration was crucial for LF hypertrophy by stimulating collagen production in fibroblasts, providing better understanding of the pathophysiology of LF hypertrophy.

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Oncostatin M Causes Liver Fibrosis by Regulating Cooperation Between Hepatic Stellate Cells and Macrophages in Mice

Michitaka Matsuda,1 Shinya Tsurusaki,1,3 Naoko Miyata,1 Eiko Saijou,2 Hitoshi Okochi,1 Atsushi Miyajima,2 and Minoru Tanaka1,3

1Department of Regenerative Medicine, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;
2Laboratory of Cell Growth and Differentiation, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan
3Laboratory of Stem Cell Regulation, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan.

Fibrosis is an important wound-healing process in injured tissues, but excessive fibrosis is often observed in patients with chronic inflammation. Although oncostatin M (OSM) has been reported to play crucial roles for recovery from acute liver injury by inducing tissue inhibitor of metalloproteinase 1 (Timp1) expression, the role of OSM in chronic liver injury (CLI) is yet to be elucidated. Here, we show that OSM exerts powerful fibrogenic activity by regulating macrophage activation during CLI. Genetic ablation of the OSM gene alleviated fibrosis in a mouse model of chronic hepatitis. Conversely, continuous expression of OSM in a normal mouse liver by hydrodynamic tail vein injection (HTVi) induced severe fibrosis without necrotic damage of hepatocytes, indicating that OSM is involved in the fundamental process of liver fibrosis (LF) after hepatitis. In a primary coculture of hepatic stellate cells (HSCs) and hepatic macrophages (HMs), OSM up-regulated the expression of fibrogenic factors, such as transforming growth factor-b and platelet-derived growth factor in HMs, while inducing Timp1 expression in HSCs, suggesting the synergistic roles of OSM for collagen deposition in the liver. Fluorescence-activated cell sorting analyses using OSM-HTVi and OSM knockout mice have revealed that bone-marrow−derived monocyte/macrophage are responsive to OSM for profibrotic activation. Furthermore, depletion or blocking of HMs by administration of clodronate liposome or chemokine inhibitor prevented OSM-induced fibrosis. Conclusion: OSM plays a crucial role in LF by coordinating the phenotypic change of HMs and HSCs. Our data suggest that OSM is a promising therapeutic target for LF.