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TGF-β-driven reduction of cytoglobin is associated with oxidative DNA damage of stellate cells in non-alcoholic steatohepatitis

Osaka, April 21, 2020 – This study shows the molecular regulatory mechanism of TGF-β-induced downregulation of cytoglobin (CYGB) expression in human hepatic stellate cells (HSCs), leading to the loss of cellular tolerance to exogenous oxidative stress and oxidative DNA damage in activated HSCs in human non-alcoholic steatohepatitis (NASH) with advanced fibrosis. Our findings published in the *Journal of Hepatology*, provide new insights into the relationship between CYGB expression and the pathophysiology of NASH fibrosis in the human liver.

A research group led by Professor Norifumi Kawada from the Department of Hepatology in Osaka City University Graduate School of Medicine, Japan reported a new insight into the pathophysiology of human NASH with fibrosis and suggested a possibility of the new therapy using CYGB inducer for clinical application.

Liver fibrosis is a common pathological feature of chronic liver diseases including viral infection, alcohol-related damage and metabolic syndromes and ultimately progresses to cirrhosis and increases the risk of developing hepatocellular carcinoma.

Although the number of patients with viral hepatitis has been reduced due to the development of antiviral therapy, NASH with liver fibrosis caused by metabolic syndrome has been increasing in recent years. However, evidence-based treatment for pathophysiology of NASH with liver fibrosis has not been established yet.

When the liver is damaged, HSCs, one of the liver constituent cells, are activated and collagen production is accelerated. If the cause is not eliminated, it progresses to cirrhosis, which causes scarring of tissues and markedly reduces liver function.

Moreover, severe hepatic fibrosis and hepatocellular carcinoma are estimated to cause 3.5% of all deaths worldwide, indicating a need for new anti-fibrotic therapies based on a detailed mechanistic understanding of liver diseases.

Therefore, activated HSCs have recently been focused on as a target cell for anti-fibrotic therapy and research on HSC is being actively pursued worldwide.

It is widely accepted that transforming growth factor beta (TGF-β), a cytokine, triggers a strong fibrogenic response through activation of HSCs.

CYGB, a mammalian globin discovered by researchers, that uniquely expresses in HSCs in the liver. Previously, researchers have reported that CYGB suppresses liver damage caused by oxidative stress and is expected to have a protective effect on hepatic parenchymal cells.

This study shows the molecular regulatory mechanism of TGF-β-induced downregulation of CYGB in human HSCs, leading to the loss of cellular tolerance to exogenous oxidative stress and oxidative DNA damage in activated HSCs in human NASH with advanced fibrosis. Moreover, researchers revealed the new function of CYGB for the first time that CYGB can inhibit oxidative DNA damage by scavenging hydroxyl radicals.

The article is "TGF-β-driven reduction of cytoglobin leads to oxidative DNA damage in stellate cells during non-alcoholic steatohepatitis," by Yoshinori Okina, Misako Sato-Matsubara, Tsutomu Matsubara, Atsuko Daikoku, Lisa Longato, Krista Rombouts, Le Thi Thanh Thuy, Hiroshi Ichikawa, Yukiko Minamiyama, Mitsutaka Kadota, Hideki Fujii, Masaru Enomoto, Kazuo Ikeda, Katsutoshi Yoshizato, Massimo Pinzani, and Norifumi Kawada (https://doi.org/10.1016/j.jhep.2020.03.051). It appears in the *Journal of Hepatology* published by Elsevier.

This work was supported by a Grant-in-Aid for Scientific Research (C) from JSPS KAKENHI 15K08314 (to MSM) and by a Grant-in-Aid for Scientific Research (B) from JSPS KAKENHI 16H05290 and a Grant for Research Program on Hepatitis from the Japan Agency for Medical Research and Development (AMED – 18fk0210004h0003 and 19fk0210050h0001) (to NK).

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OCU is composed of eight faculties and ten graduate schools (Business, Economics, Law, Literature and Human Sciences, Science, Engineering, Medicine, Nursing, Human Life Science and Urban Management). It has about 8,000 students and 700 academic staff members. OCU has two Nobel Prize winners; Dr. Yoichiro NAMBU and Dr. Shinya YAMANAKA.

As an urban-based university, OCU emphasizes studies and research relevant to the integrated issues that modern cities have. Three of OCU's leading interdisciplinary research programs focus on next-generation energy problems, health science and disaster prevention issues. OCU is proud of its top-class research reputation underlain by the number of research projects granted by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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