Press Release

Keio University

July 19, 2019

Keio University School of Medicine

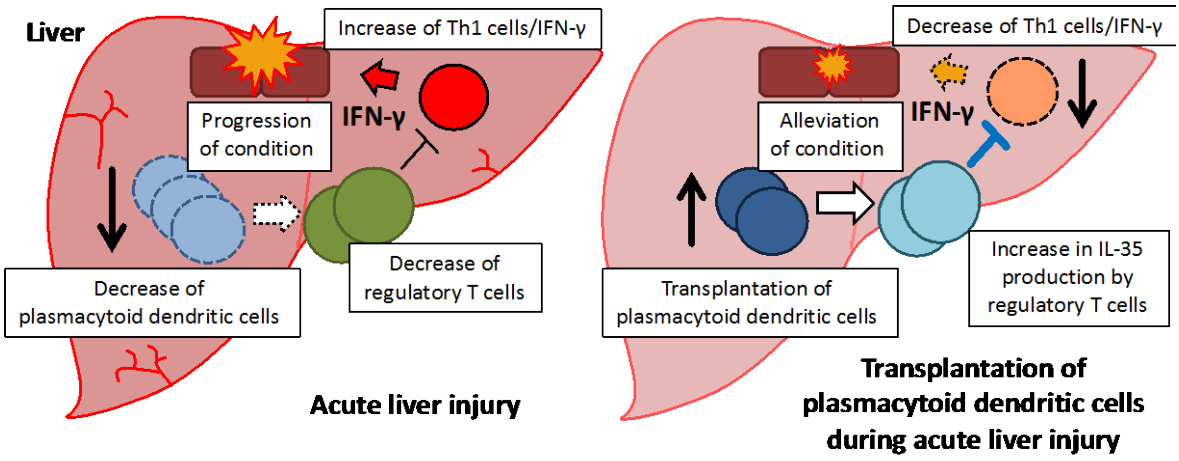
Discovery of New Immune Cells that Suppress Acute Liver Failure —Expectations in the Development of New Treatments for Acute Liver Failure—

A research group comprising Professor Takanori Kanai and Associate Professor Nobuhiro Nakamoto of the Keio University School of Medicine, Department of Internal Medicine Division of Gastroenterology and Hepatology, and Yuzo Koda, a joint researcher, discovered that plasmacytoid dendritic cells (*1), which are a type of immune cell, were significantly reduced in the liver and blood of patients suffering from acute liver failure, a liver disease that has a high mortality rate and for which there are few effective treatments other than a liver transplant.

Furthermore, it was found that developing acute hepatitis in mice by inducing a deficiency in plasmacytoid dendritic cells worsened their condition, while transplanting plasmacytoid dendritic cells in mice that had developed acute hepatitis improved their condition, leading to the conclusion that plasmacytoid dendritic cells play a protective role against acute hepatitis. In addition, it was also found that plasmacytoid dendritic cells increase the immunosuppressive cytokine IL-35 (*2) produced by regulatory T cells, which suppresses Th1 cells (*3) and a substance they produce that aggravates hepatitis, IFN-γ (figure 1).

These results show the possibility of plasmacytoid dendritic cells protecting the liver from rapidly progressing hepatitis as well as the details of its protective role through regulatory T cells and IL-35. There are expectations that these findings will lead to the development of new treatments and diagnostic agents for acute hepatitis and acute liver failure using plasmacytoid dendritic cells.

The outcomes of this research were published in the online version of the international academic publication, “Journal of Clinical Investigation” on July 2, 2019 (Eastern Standard Time).



【Figure 1】Overview of results

1. Background of research

Acute liver failure (fulminant hepatitis) is a liver disease that causes severe inflammation of the liver and rapidly destroys liver cells. It is a highly fatal disease where the abnormal functioning of the liver progresses, affecting other organs throughout the body and leading to the failure of multiple organs. There are few effective treatments for this disease other than a liver transplant, but the difficulty in securing donors for transplantations is another problem that arises.

Various types of acute hepatitis such as viral hepatitis, drug-induced hepatitis, and autoimmune hepatitis increase in severity and lead to acute liver failure, but their detailed mechanisms had remained unclear.

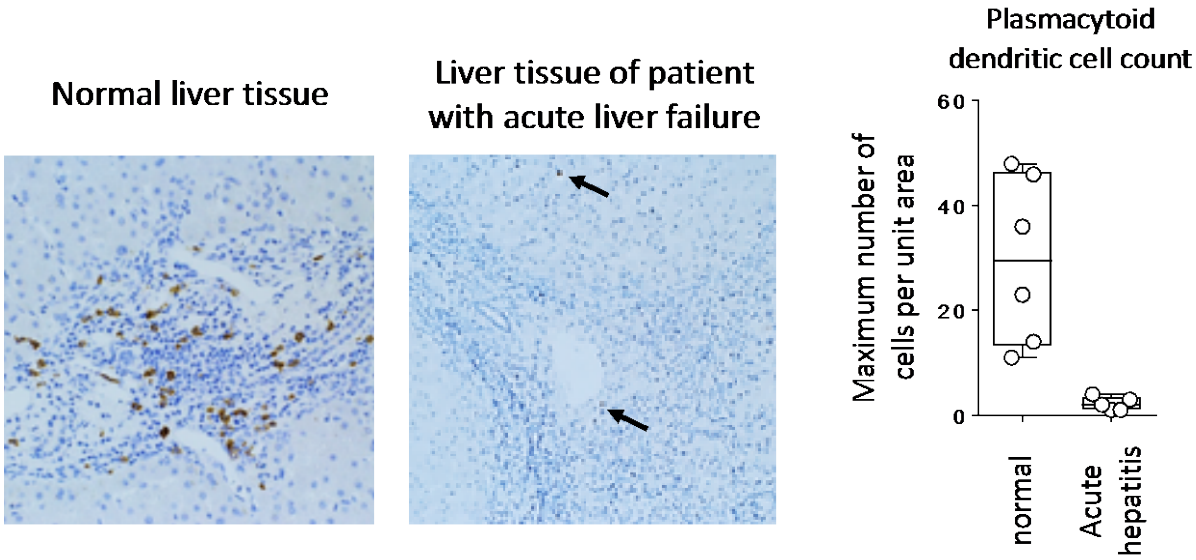
Autoimmune hepatitis, which is one of the causes of acute liver failure, has been recognized as a designated intractable disease by the Japanese government. It has been suggested that abnormalities of the immune system contribute to the condition. However, there are many uncertainties regarding the immune cells that are involved in the pathology of this disease. In this study, the types of immune cells in the bloods of patients with acute hepatitis, which causes acute liver failure, were therefore analyzed, and attempts were made to identify the immune cells that contribute to the condition.

2. Results of research

The research group used flow cytometry (*4) to analyze the types of immune cells in the blood of each patient with acute hepatitis. From the results of the analyses, it was found that “plasmacytoid dendritic cells,” which are a type of dendritic cell, were significantly reduced in patients in the acute stages of autoimmune hepatitis when compared with healthy people.

In addition, liver tissue samples of patients with acute liver failure caused by autoimmune hepatitis were used to analyze the changes of plasmacytoid dendritic cells in liver tissue. Results showed that even in liver tissue of patients with acute liver failure, the proportion of plasmacytoid dendritic cells was significantly reduced when compared with liver tissue samples of healthy people. These findings suggest that plasmacytoid

dendritic cells are involved in both autoimmune hepatitis and the pathology of acute liver failure caused by autoimmune hepatitis (figure 2).

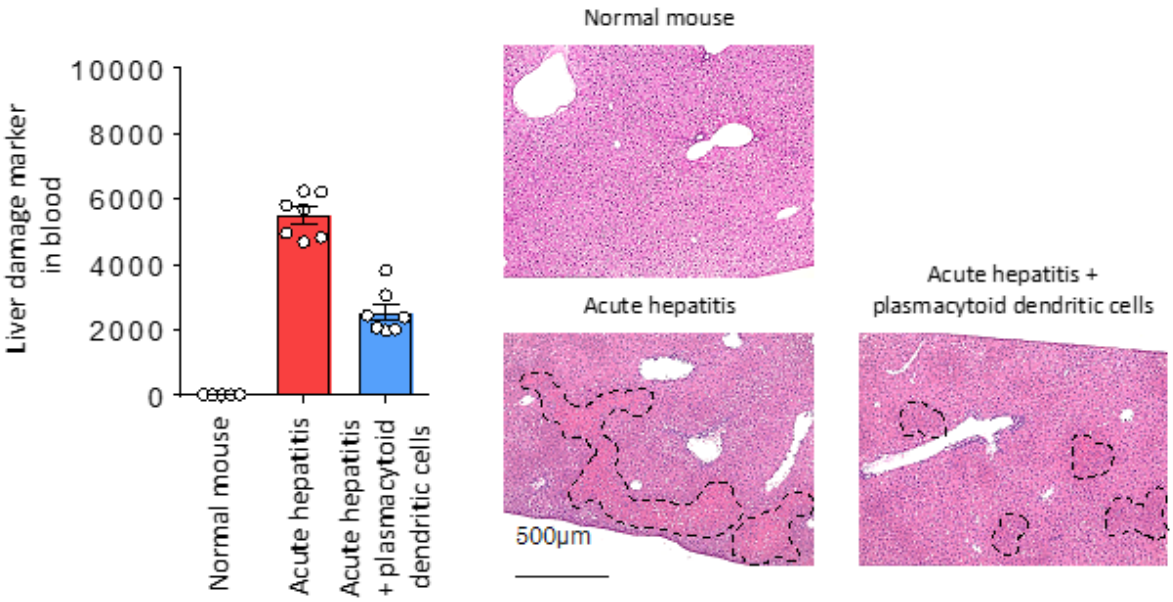


【Figure 2】Number of plasmacytoid dendritic cells in liver tissue of a patient with acute liver failure caused by autoimmune hepatitis

Immunohistochemical staining was used to stain the plasmacytoid dendritic cells in the liver tissue of patients with acute liver failure. While many plasmacytoid dendritic cells (brown) are found in normal liver tissue, these are very scarce in the liver tissue of patients with acute liver failure.

Furthermore, attempts were made to elucidate the role of plasmacytoid dendritic cells in this disease using autoimmune hepatitis model mice. When the effects on the pathology of the disease were examined using ConA-induced hepatitis (*5) mice whose plasmacytoid dendritic cells were deleted using gene modification techniques, a significant deterioration in their conditions was observed when compared with healthy mice induced with hepatitis. In addition, when plasmacytoid dendritic cells prepared by mass culture of bone marrow cells were transplanted into mice with ConA-induced hepatitis, significant improvements were seen in the condition (figure 3).

These results indicated that plasmacytoid dendritic cells play a protective role in the model mice. In other words, it suggests that the transplantation of plasmacytoid dendritic cells or other methods that will induce the proliferation of these cells could possibly be a new way to treat autoimmune hepatitis and acute liver failure caused by autoimmune hepatitis.



【Figure 3】Effect of plasmacytoid dendritic cells on hepatitis

Alleviation in the state of the disease was observed in hepatitis model mice transplanted with plasmacytoid dendritic cells cultured and grown from bone marrow cells when compared with mice that had not received a transplant.
Serum marker indicating the extent of the hepatitis condition (left).
H&E staining of the liver tissue shows a significant reduction of necrotic areas inside the black dotted lines (right).

Additionally, the research group investigated the detailed mechanism of how plasmacytoid dendritic cells suppress acute liver injury.

A comprehensive analysis of cytokine levels in the blood serums of ConA-induced hepatitis mice with plasmacytoid dendritic cells transplanted and mice with ConA-induced hepatitis but without transplantation was carried out. This revealed that there was a significant increase of IL-35, an immunosuppressive cytokine, in the blood serums of mice that received plasmacytoid dendritic cells transplantation.

The cytokine called IL-35 is known to suppress interferon gamma (IFN-γ), which acts as an adverse component of hepatitis. In this study, in addition to IFN-γ, a significant reduction of Th1 cells in the liver, which produce IFN-γ, was also seen in blood serums of mice transplanted with plasmacytoid dendritic cells.

Furthermore, when mice that received plasmacytoid dendritic cell transplantations were administered with an antibody that counteracts the activities of IL-35 or an antibody that eliminates regulatory T cells, which are the main cells that produce IL-35, the suppressive effects that plasmacytoid dendritic cells had on hepatitis were lost.

From these findings, it can be said that plasmacytoid dendritic cells increase IL-35 produced by regulatory T cells, and IL-35 reduces the number of Th1 cells in the liver, thereby decreasing the production of IFN-γ, the adverse component. This shows that liver inflammation can be suppressed.

3. Future developments

This study found evidence of plasmacytoid dendritic cells functioning to protect the liver, and that reductions in the number of plasmacytoid dendritic cells may possibly cause the onset of acute liver failure and be a factor that worsens the pathology of the disease.

Currently, no effective treatments for acute liver failure other than liver transplants have been reported. Based on the findings of this study, the group plans to carry out detailed investigations using human-derived plasmacytoid dendritic cells. There are expectations that the outcomes of this research will lead to the development of new treatments, such as cell therapy for acute liver failure and hepatitis.

4. Special note

This research was supported by the Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Scientific Research (KAKENHI) Grant Number JP16K09374.

5. Details of original paper

Title: Plasmacytoid dendritic cells protect against immune-mediated acute liver injury via IL-35

Authors: Yuzo Koda, Nobuhiro Nakamoto, Po-Sung Chu, Aya Ugamura, Yohei Mikami, Toshiaki Teratani, Hanako Tsujikawa, Syunsuke Shiba, Tomohisa Sujino, Kentaro Miyamoto, Nobuhito Taniki, Takahiro Suzuki, Akihiro Yamaguchi, Rei Morikawa, Katsuaki Sato, Michiie Sakamoto, Takayuki Yoshimoto, Takanori Kanai

Journal: Journal of Clinical Investigation

【Glossary】

∗1 Plasmacytoid dendritic cell: A type of dendritic cell known to play an important role protecting against viral infections. When stimulated by viral components, etc., these cells become active and produce IFN-α/ß. In recent years, it has also become clear that these cells have immunosuppressive abilities, and analyses of these functions are being carried out.

∗2 Interleukin 35 (IL-35): A new immunosuppressive cytokine that was recently discovered. It is a heterodimer composed of IL12A and EBI3, and it is reported that these are mainly produced by regulatory T cells.

∗3 Th1 cell: A type of CD4-positive helper T cell that mainly produces IFN-γ. IFN-γ is known to be important to protect against bacterial infections as well as for antitumor immunity, but when it is excessively produced it becomes the cause of or an exacerbating factor in inflammatory diseases.

∗4 Flow cytometer: A device that can simultaneously measure multiple molecules (mainly proteins) of a cell at high speed, as well as analyze the distribution of multiple types of cells. After marking the surface of the cell or the molecules within a cell with a fluorescent substance, what molecules the cell has can be analyzed by detecting the fluorescence

wavelength that is generated when laser beams of a specific wavelength are directed at each cell. It is used to analyze the increase or decrease of cell populations that are present at a given site as well as the expression levels of functional molecules.

*5 ConA-induced hepatitis: Administering Concanavalin A (ConA), a substance that stimulates the immune system, through the tail vein of mice induces hepatitis that is mediated by the immune system such as T cells. It is widely used in experiments to bring about acute liver failure and acute hepatitis.

*Please direct any requests or inquires to the contact information provided below in advance.

【Inquiries about this announcement】
Keio University School of Medicine
Department of Internal Medicine
Division of Gastroenterology and Hepatology
Professor Takanori Kanai
Tel: +81(0)3-5363-3790
Fax: +81(0)3-3353-6247
E-mail: takagast@z2.keio.jp

【Inquiries about press release】
Keio University Shinanomachi Campus
Office of General Affairs: Suzuki, Yamazaki
35 Shinanomachi, Shinjuku-ku, Tokyo
160-8582
Tel: +81(0)3-5363-3611
Fax: +81(0)3-5363-3612
E-mail: med-koho@adst.keio.ac.jp
http://www.med.keio.ac.jp/
*If you would like a color version of this press release, please contact the above.