# Elucidation of the mechanism of liver cancer progression focusing on tumor microenvironment and its clinical application

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## Abstract

Cancers contain not only cancer cells but also various stromal cells such as immune cells, fibroblasts, and vascular endothelial cells. These cells interact with cancer cells to form an environment favorable for cancer progression, which is called the tumor microenvironment. We are working to elucidate the molecular mechanisms of liver cancer progression in the tumor microenvironment. We have found and reported that GDF15 (3), IL-6 family cytokines (1), and CTGF (1,4) are important molecules for the interaction between liver cancer cells and stromal cells in the liver tumor microenvironment.

Meanwhile, we are also working on the development of new biomarkers to stratify patients with high and low risk of future liver carcinogenesis. We found that GDF15, found in the liver tumor microenvironment, is elevated in sera of patients with chronic hepatitis. We found that patients with high serum GDF15 are more likely to develop liver cancer even after elimination of hepatitis C virus and reported that GDF15 is a new biomarker to stratify the risk of liver carcinogenesis (2).

## Background & Results

In many cancers, including liver cancers, the cancer cells themselves interact with stromal cells such as immune cells, fibroblasts, and vascular endothelial cells surrounding the cancer cells to form the tumor microenvironment promoting cancer development. However, it was not known how hepatic stellate cells (HSCs), which play a central role in fibrosis in the liver, interact with cancer cells in the liver tumor microenvironment.

We found that autophagy of HSCs is promoted by liver cancer cells in the liver tumor microenvironment, and that GDF15 is secreted from HSCs via autophagy promotion, thereby promoting the proliferation of liver cancer cells (Fig.1). We found that the deletion of GDF15 in HSCs in xenograft mouse models or liver carcinogenesis mouse model suppressed liver cancer progression, and that GDF15 would be a new therapeutic target for liver cancer (Fig.2). We found that HSCs expressing GDF15 are present in the human liver cancers and revealed that liver cancer patients with high serum GDF15 have a poor prognosis (3).

Hepatitis C patients, on the other hand, can now be eliminated with oral medication, and elimination of the virus suppress the progression to liver cancer. However, some hepatitis C patients progresses to liver cancer even after the virus is eliminated. Interestingly, we found that high serum GDF15 is a risk factor for liver carcinogenesis after viral elimination, independent of high serum AFP and high FIB-4 index, an index of liver stiffness (Fig.3). We reported that GDF15 can be used as a new predictive biomarker for liver carcinogenesis (3).

## Significance of the research and Future perspective

For patients with liver cancer, the development of new therapeutic methods or drugs targeting the cancer microenvironment is expected. For patients with chronic liver disease, it is expected to establish a new biomarker to narrow down patients at high risk of liver carcinogenesis.

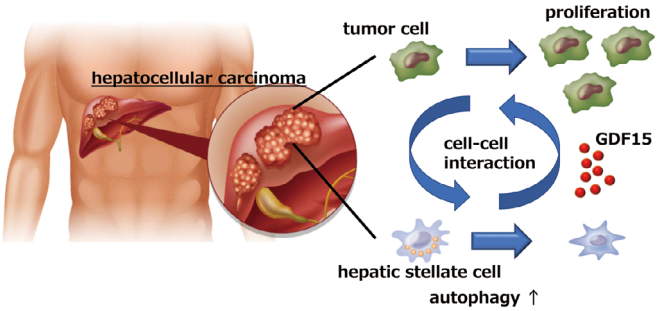


Fig.1 The interaction between tumor cells and stellate cells in tumor microenvironment

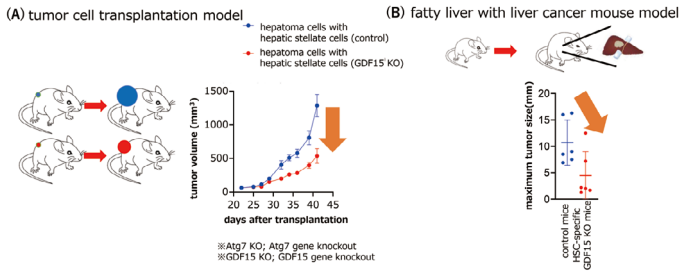


Fig.2 The liver tumor growth was attenuated by GDF15 knockout in hepatic stellate cells.

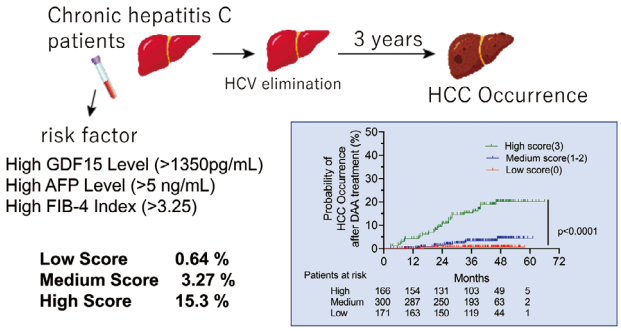


Fig.3 Serum GDF15 is a predictive factor for HCC occurrence after HCV elimination

**Patent** Japanese Patent Application No. 2021-12187, Japanese Patent Application No. 2022-106996

**Treatise**
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