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Short commentary Open Access

Diagnostic and Therapeutic Values of Apoptosis Inhibitor of Macrophage in Nash-Associated Hepatocellular Carcinoma

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Abstract

The number of patients in Non-alcoholic Steatohepatitis (NASH) and its associated Hepato Cellular Carcinoma (HCC) is increasing rapidly along with the change of lifestyle. So far, however, no diagnostic tools specifically use for NASH-associated HCC have not been established yet. Recently, we have reported circulating levels of activated Apoptosis Inhibitor of Macrophage (AIM, also called CD5L) can be a sensitive and specific biomarker to diagnose NASH-associated HCC in human. In addition, we demonstrated that AIM facilitated the diminishment of HCC tumors in mice. In this report, we discuss about the benefits of application of AIM as future diagnostic and therapeutic tools against NASH-associated HCC.

Keywords: Non-alcoholic steatohepatitis; HCC tumor; Tissue macrophages

Introduction

Creating a bridge between basic research and clinical medicine is a critical challenge. Research on AIM and NASH-associated HCC is now succeeding in bridging between basic research and clinical medicine.

AIM is a circulating protein produced by tissue macrophages such as Kupffer cells and peritoneal macrophages [1]. Production of AIM is regulated by a nuclear receptor called liver X- receptor/retinoid X-receptor [2]. In the blood, AIM is inactivated when it associates with the IgM pentamer [3]. AIM is almost 40 kDa and can pass through the glomerulus. Association with IgM prevents excretion of AIM in urine and enables AIM to circulate stably in the blood. The level of AIM in the blood is 4.99 ± 1.8 μg/ml and 6.06 ± 2.1 μg/ml in healthy men and women, respectively [4]. However, in patients with specific diseases, such as obesity [5], acute kidney disease [6], and NASH-associated HCC [7], AIM dissociates from IgM and is activated, contributing to the recovery of each disease.

Role of AIM in NASH-associated HCC

In a healthy state, AIM is incorporated into hepatocytes via CD36 and associates with fatty acid synthase directly, causing downregulation of lipid-droplet coating proteins such as fat-specific protein 27 and perilipin [8]. As a result, lipid storage in hepatocytes is decreased. However, in patients with NASH-associated diseases, some hepatocytes undergo malignant transformation into HCC and AIM is not endocytosed into hepatocytes but attached on the cell surface. This phenotypic change in AIM helps to distinguish HCC cells from normal hepatocytes. Surprisingly, AIM on the cell surface inactivates multiple regulators of complement activation, causing necrotic cell death of only HCC cells. A previous study showed that most AIM-/- mice fed a high-fat diet for a year developed multiple HCC tumors, but the wild-type mice did not develop any tumors; thus, AIM prevents HCC tumor development [9]. This role of AIM in NASH-associated HCC was revealed through basic research.

To assess the clinical aspects of AIM in NASH-associated HCC, we investigated patients with non-alcoholic fatty liver disease and measured the level of activated AIM in the serum by using ELISA. Significantly elevated levels of activated AIM imply that AIM dissociates from IgM in NASH-associated HCC patients specifically. Few markers are sensitive to NASH-associated HCC. Therefore, we analyzed the possibility of activated AIM as a biomarker for the detection of NASH-associated HCC. When the cut-off value of activated AIM was set at 1.6 g/ml, sensitivity was 88.5% and specificity was 86.4%; these results are better than those for the conventional HCC markers des-γ-carboxy prothrombin and α-fetoprotein [7].

Future Perspectives and Conclusion

AIM has two roles in NASH-associated HCC: elimination of HCC cells by activating complement cascades and as a diagnostic marker for NASH-associated HCC. Both roles are performed by activated AIM. The mechanism underlying the release of AIM from IgM and its activation is still not known. However, the binding scheme has been revealed, and small molecules with release activity were determined. These findings may contribute to understanding the activation mechanism. In addition, we will determine AIM activation in HCC caused by non-NASH reasons, as well as other types of cancer.

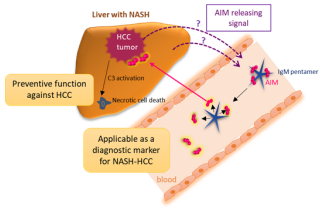

Figure 1: Diagnostic and therapeutic values of AIM

Under heathy state, AIM associates with IgM pentamer, and functionally inactivated. In NASH-HCC patients, a large amount of AIM dissociates from IgM pentamer, which is promoted by unknown releasing signal probably derived from HCC tumor or NASH-bearing liver tissue (Figure 1). IgM-free AIM accumulate at HCC cell surface, thereby activating complemental cascade to induce necrotic death in HCC cells. On the other hand, IgM-free AIM are applicable as a sensitive diagnostic marker for NASH-HCC.

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