【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Elucidation of the mechanism required for AIM activation, and its therapeutic application to NASH-induced hepatocellular carcinoma

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Research Project Number : 16H06389 Researcher Number : 30396270
Research Area : Gastroenterology
Keyword : NASH-HCC, AIM, Fatty liver, Obesity

【Purpose and Background of the Research】

Non-alcoholic steatohepatitis (NASH) is a manifestation of metabolic syndrome in the liver, and is a potent risk factor for the development of hepatocellular carcinoma (HCC). The number of patients of NASH as well as NASH-HCC is increasing recently. Previously, we showed that the circulating protein AIM exhibits strong anti-HCC effect brought about by complement activation. Alongside the therapeutic use of recombinant AIM protein, we here aim to develop the system that activates blood AIM through its dissociation from IgM pentamer, and to apply it for the therapy of NASH-HCC. We will also establish a system to evaluate IgM-free AIM levels in serum, and use it for early diagnosis and prognosis prediction of NASH-HCC.

【Research Methods】

(1) Exploration of mechanism for AIM activation: In healthy states, AIM associates with IgM-pentamer, which stabilizes but inactivates AIM. However, AIM converts to active form via dissociating from IgM under various disease states including acute kidney injury (AKI). First, we will investigate the "physiological activator(s)" which are induced during AKI and dissociate AIM from IgM. In addition, we will search "chemical (artificial) activators" such as specific peptides or small compounds, which interact with the binding site of AIM responsible to binding with IgM, and lead to AIM-IgM dissociation (Figure 1).

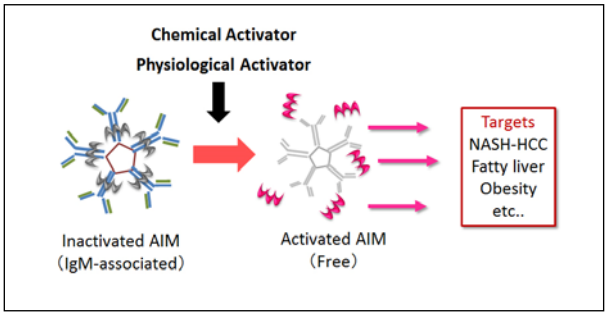

Figure 1 Activation of endogenous AIM

(2) Application of AIM activators for NASH-HCC therapy: Physiological and Chemical activators obtained in (1), will be tested for their anti-HCC effect using animal disease models towards the future drug development for human disease.

(3) Global analysis of serum IgM-free AIM (= active AIM) levels in patients: Blood samples from patients with liver diseases including simple steatosis, NASH, and NASH-HCC, will be analyzed for total and active AIM levels to investigate their relations with disease progression. Through this study, we would like to achieve early diagnosis of NASH-HCC by AIM levels.

【Expected Research Achievements and Scientific Significance】

We have demonstrated marked therapeutic effects of AIM administration against NASH-HCC. However, the large scale production of functional AIM protein possesses some technical difficulties due to its complicated structure caused by its many cysteine residues, and thus, demands a high cost. This problem will be overcome by activating endogenous AIM, which are present abundantly in blood. Our study will be the basis for the development of novel therapeutic and diagnostic tools for NASH-HCC.

【Publications Relevant to the Project】

・Arai S, Kitada K, et al, Apoptosis inhibitor of macrophage protein enhances intraluminal debris clearance and ameliorates acute kidney injury in mice. Nat Med 22:183-193, 2016
・Maehara N, Arai S, et al, Circulating AIM prevents obesity-associated hepatocellular carcinoma through complement activation. Cell Rep. 9:61-74, 2014

【Term of Project】 FY2016-2020

【Budget Allocation】 133,800 Thousand Yen

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