

Macrophage stimulating protein (MSP) in the metabolic syndrome

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Valorization

Social and clinical relevance

Metabolic syndrome (MetS) has become a worldwide health threat. Today, approximately one quarter of the adult world population has MetS. Despite the availability of a number of treatment options that ameliorate specific aspects of MetS, their overall curative effect is unsatisfactory. Moreover, public prevention programs largely failed their targets. Consequently, the prevalence of MetS is still increasing and the burden on healthcare systems and treatment cost is rising dramatically.

Clinical and epidemiologic studies have tightly associated the MetS with non-alcoholic fatty liver disease (NAFLD) – a disease consisting of a variety of steatosis-induced liver pathologies [1]. Non-alcoholic steatohepatitis (NASH) represents the stage that is composed of steatosis and hepatic inflammation, and could lead to irreversible liver damage and sets the stage for further liver injury, like cirrhosis and liver cancer [2]. Currently, the accurately-defined prevalence of NASH remains largely unknown due to the limitation of histological diagnosis. A recent report estimates that around 25% of the global population is suffering from NAFLD, and the prevalence of NASH among biopsied NAFLD patients has increased to around 60% [3]. Thus, NASH has become a major public-health challenge worldwide. In addition, type 2 diabetes mellitus (T2DM), another metabolic disorder which is tightly linked to MetS is investigated in this thesis as well. T2DM affects a large part of the world population and poses a long-term burden to the societies. However, despite a number of attempts in drug development, there is still no effective treatment for NASH. Similarly, the overall curative effects of T2DM are lacking satisfaction and need to be improved.

In this thesis, we proposed macrophage stimulating protein (MSP) as a novel target in the therapeutic strategies of NASH. The novel findings obtained in this thesis show the diversity of the treatment outcome of MSP. Hence, future studies are needed to clarify its therapeutic potential in NASH. Moreover, several clues about the influence factors, e.g. gender and lipid profile, that may impact its therapeutic effects are given by this thesis. These findings suggest that before using MSP as a therapy option, probable factors should be evaluated and some selecting criteria could be made for clinical indications and contraindications. In light of those discoveries, our findings hold significance in optimizing MSP as a clinical target in NASH. In Chapter 5, we determined an inverse association between plasma MSP and glucose. This finding may benefit the accuracy of the prognosis in T2DM, and provides a new hidden therapeutic connection with hyperglycemia. In addition, the newly discovered correlation of low density lipoprotein cholesterol with MSP levels also adds to the motivation of exploring MSP for

therapeutic use in dyslipidemia. Furthermore, the novel links between MSP with glucose and cholesterol could possibly lead to identification of a new biomarker for T2DM and its complications. Considering the high occurrence of T2DM and the diabetes dyslipidemia [4,5], our findings holds significant promise to its clinical application related to T2DM. As such, our studies could positively affect the economic burden related to NASH and T2DM.

Novelty of the concept

Within this thesis, we investigated a novel protein - MSP- as a key factor and a potential treatment target in the MetS. Currently, the investigation about MSP is mainly limited to the fields of cancer and inflammation, while the other aspects of this protein are still largely unknown. Hence, this presented work provides novel insights in a more comprehensive view of the functions of MSP. Moreover, while most studies focus on the separate role of MSP in inflammation or lipid/glucose regulation, the current thesis investigates its systemic therapeutic effects in NASH models. We therefore provide the innovative views regarding to the treatment potential of MSP in NASH. In addition, while the investigations about MSP were confined in different cellular or animal models, this current work explores the associations of MSP with the metabolic profile in human population, and uncovers the novel links between MSP with glucose and cholesterol. This innovative study thus provides more direct evidence about the clinical potential of MSP.

Future perspectives & Potential application

Findings from this thesis showed that the treatment effect of MSP in NASH is discrepant, and it may be affected by several factors like hormones and lipids. Based on the current findings, several future perspectives regarding to the application of MSP could be given: Firstly, the longer-term treatment effects of MSP in NASH will be worthwhile to explore. Secondly, in view of the potential influence of sexual hormones to the action of MSP, gender difference should be considered when utilizing MSP in clinical practice. Furthermore, multiple factors that may affect the effects of MSP should be further investigated and clarified. Before using MSP as a therapy option, the influence factors are suggested to be evaluated and the selecting criteria could be made for clinical indications and contraindications. For instance, menopausal status might be used as an instruction of dose usage, or considered as selecting criteria. In addition, patients with hypercholesterolemia need carefully evaluation before receiving MSP supplement.

Additionally, regarding to its inverse association with glucose, MSP may be considered as a negative regulator of plasma glucose. Further studies focusing on treatment effects of MSP in T2DM models is worthwhile, and the effect of MSP in particular hepatic glucose

metabolism should be closely investigated. As an endogenous factor which is constitutively generated in the body, MSP has great advantages to be implemented in clinical application compared to synthetic drugs by virtue of its safe and stable nature. Therefore, the supplement of recombinant MSP may serve as a promising treatment option for T2DM patients.

Taken together, in light of the discoveries described in this thesis, our findings hold significance in optimizing MSP as a clinical target in NASH, and could provide proof-of-principle for MSP supplements as an anti-diabetic strategy.

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