ARTICLE IN PRESS

+ MODEL

Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine xx (2017) 1–4

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Perspective

Potential role of thymosin beta 4 in the treatment of nonalcoholic fatty liver disease

Yong Jiang [a,b], Tao Han [b,*], Zhi-Guang Zhang [a], Man Li [a], Feng-Xiang Qi [a], Ying Zhang [a], Ying-Lan Ji [a]

[a] *Department of Gastroenterology, The Second Hospital of Tianjin Medical University, Tianjin 300211, China*

[b] *Department of Hepatology and Gastroenterology, Tianjin Third Central Hospital of Tianjin Medical University, Tianjin 300070, China*

Received 29 December 2016

Abstract

As a result of increased prevalence of obesity worldwide, non-alcoholic fatty liver disease (NAFLD) has become one of the most common causes of chronic liver disease. Although most NAFLD cases remain benign, some progress to end-stage liver diseases such as cirrhosis and hepatocellular carcinoma. Therefore, treatment should be considered for NAFLD patients who are likely to progress to nonalcoholic steatohepatitis (NASH) or fibrosis. Thymosin beta 4 (Tβ4), a G-actin sequestering peptide, regulates actin polymerization in mammalian cells. In addition, studies have reported anti-inflammatory, insulin-sensitizing, and anti-fibrotic effects of Tβ4. However, no research has been done to investigate the effects of Tβ4 on NAFLD. Based on the findings above mentioned, we hypothesize that Tβ4 may represent an effective treatment for NAFLD.

Keywords: Thymosin beta 4; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Hypothesis

Introduction

Thymosin beta 4 (Tβ4) is a G-actin sequestering peptide that regulates actin polymerization in living cells. Through this biological function, it plays roles in many cellular processes, such as promoting angiogenesis and cell migration, accelerating collagen deposition, promoting wound healing, and inhibiting fibrosis.[1] Thus, under normal physiological conditions and pathological statuses, it plays a role in regulating the signals of many cytokines. Non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver disease in western countries,[2] and is considered the hepatic component of insulin resistance or obesity.[3] Liver fibrosis, the main characteristic of chronic liver diseases including some NAFLD, is strongly associated with the activation of hepatic stellate cells (HSCs), which are responsible for extracellular matrix production.[4] Although its precise role has not been established, Tβ4 influences HSC activation, suggesting that

* Corresponding author.
E-mail address: hantaomd@126.com (T. Han).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2017.06.003

Please cite this article in press as: Jiang Y et al., Potential role of thymosin beta 4 in the treatment of nonalcoholic fatty liver disease, Chronic Diseases and Translational Medicine (2017), http://dx.doi.org/10.1016/j.cdtm.2017.06.003

Tβ4 is a potential therapeutic target for treating liver disease.[5,6] Here, we outline the evidence suggesting that Tβ4 may be an effective treatment for NAFLD.

NAFLD

The global obesity epidemic has increased the prevalence of NAFLD, which is estimated to affect one billion patients worldwide.[2] Cases of NAFLD can range from benign nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), and the latter can lead to fibrosis, cirrhosis, and more severe diseases such as liver failure and hepatocellular carcinoma. Increasing amounts of epidemiological data indicate a close association between NAFLD and the gut microbiota.[7] Interactions between immune cells and the gram-negative bacteria cell wall endotoxin lipopolysaccharide (LPS) directly activate NF-κB signaling in Kupffer cells, causing the transcription of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6.[8] Increased plasma endotoxin levels have been reported in NAFLD.[9] Probiotics can result in a significant reduction in endotoxin levels and in histological liver steatosis in mice and patients suffering from nonalcoholic steatohepatitis (NASH),[10] suggesting that proper regulation of the intestinal environment is important to prevent NAFLD progression. Bashiardes et al[11] reported several microbiome-associated mechanisms contributing to NAFLD and NASH, including dysbiosis-induced deregulation of gut endothelial barrier function, which facilitates systemic bacterial translocation, and intestinal and hepatic inflammation. Furthermore, increases in microbiome-modulated metabolites such as LPSs, short chain fatty acids (SCFAs), bile acids, and ethanol can affect liver pathology through multiple direct and indirect mechanisms. Zhu et al[12] suggested that the altered NAFLD microbiome may produce increased SCFAs and alcohol, and contain more LPS-producing gram-negative species, thereby directly and indirectly participating in NAFLD development. Taken together, these findings indicate that gut microbiome plays an important role in the progression of NAFLD.

Inflammation is a key process in NAFLD pathogenesis.[13] The development of NAFLD is accompanied by obesity as well as metabolic disruptions that cause excessive hepatic lipid accumulation.[13] Liver steatosis then increases the vulnerability of the liver to oxidative stresses or proinflammatory insult, resulting in NAFLD. Thus, measures that suppress oxidative stress and inflammation could prevent the development of NAFLD. The involvement of inflammation in NAFLD implicates that the NF-κB pathway has been activated, and increased NF-κB activation has been reported in patients with NAFLD.[14]

NAFLD is closely related with insulin resistance.[3,15] Approximately 50% of NASH patients have complications such as diabetes mellitus, cardiovascular disease, and hyperlipidemia.[16] Therefore, improving insulin resistance might reduce the incidence of NAFLD and NASH.[17]

Many NASH patients develop fibrosis. Great progress has been made in understanding the pathophysiology of liver fibrosis, and several forms of therapy have evolved in attempts to prevent the disease. Most therapies target the molecular mechanisms involved in the activation of HSCs and the increased production of type I collagen.[18] However, the mechanisms behind NAFLD development are poorly understood, and available treatments are far from satisfactory.

Tβ4: possible mechanisms in the treatment of NAFLD

Tβ4 is a beta thymosin, a G-actin sequestering peptide involved in many critical biological processes including apoptosis, angiogenesis, cell migration, and fibrosis.[1] Badamchian et al[19] reported that a median lethal dose of LPS in rats led to a significant reduction of blood Tβ4, and administration of Tβ4 immediately following the dose of LPS in mice significantly reduced mortality rates ($P = 0.024$) and lowered the levels of inflammatory cytokines in blood. Significant decreases in blood Tβ4 levels were also reported in septic shock patients and in human subjects given low doses of endotoxin. Therefore, the authors suggested that Tβ4 has clinical utility in the treatment of septic shock and syndromes associated with endotoxemia. Zhao et al[20] reported that Tβ4 improved the 72-h survival rate of mice in septic shock, and reduced levels of inflammatory cytokines (TNF-α and IL-1β). Santra et al[21] deduced that Tβ4-mediated upregulation of microRNA-146a promotes oligodendrocyte differentiation and suppression of the toll-like receptor (TLR) proinflammatory pathways, including the TLR-4 pathway. These studies suggest that Tβ4 is negatively correlated with endotoxemia, and could suppress proinflammatory TLR signaling and reduce inflammatory cytokines. According to the gut-liver axis theory, the effects of Tβ4 could play an important role in the treatment of NAFLD.

Sosne et al[22] reported that Tβ4 treatment significantly reduced the level of nuclear NF-κB, and

Please cite this article in press as: Jiang Y et al., Potential role of thymosin beta 4 in the treatment of nonalcoholic fatty liver disease, Chronic Diseases and Translational Medicine (2017), http://dx.doi.org/10.1016/j.cdtm.2017.06.003