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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*

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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).

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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

decreased NF-κB activity and p65 subunit phosphorylation in TNF-α-stimulated corneal epithelial cells. The authors concluded that Tβ4 exerts its anti-inflammatory effects via NF-κB-related signaling pathways. Consistently, Gupta et al[23] found that Tβ4 could improve cardiac function by suppressing NF-κB activity. Qiu et al[24] observed that Tβ4 directly inhibited the nuclear translocation of p65, suppressing TNF-α-mediated NF-κB activation. These results indicate that Tβ4 could exert its anti-inflammatory effects through inhibition of the NF-κB pathway. Liang et al[25] detected Tβ4 expression in the sera and tissues of patients with chronic hepatitis B combined with NAFLD, and observed that the Tβ4 level was negatively correlated with inflammation and fibrosis scores, and Tβ4 expression in both serum and liver tissue was negatively correlated with TNF-α expression. Moreover, Tβ4 played a defensive role in the development of liver disease by inhibiting oxidative stress and proinflammatory factors.

Zhu et al[26] evaluated the effects of Tβ4 on hyperglycemia and insulin sensitivity in a type 2 diabetes mellitus mouse model, and reported that Tβ4 improved glucose intolerance and ameliorated insulin resistance. Another study reported that Tβ4 could reduce mean fasting and 2-hour blood glucose levels during oral glucose tolerance testing.[27] These studies suggest that Tβ4 treatment may improve insulin sensitivity and/or glucose tolerance in NAFLD.

Furthermore, more than one quarter of NASH patients develop fibrosis,[4] and Tβ4 has been reported to have anti-fibrotic effects in mice.[5,6] Reyes-Gordillo et al[28] reported that Tβ4 treatment prevented the proliferation and migration of cultured human HSCs by inhibiting platelet derived growth factor (PDGF) -ββ-dependent phosphorylation of Akt. Xiao et al[29] noted that Tβ4 expression was significantly decreased in fibrotic liver. This decrease in Tβ4 expression can increase the proliferation and migration of LX-2 cells (a kind of human HSC line) through activation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. In addition, activation of HSCs through the enhanced expression of α-smooth muscle actin (α-SMA) and vimentin was also associated with Tβ4 depletion. Tβ4 participated in liver fibrosis by inhibiting the migration, proliferation, and activation of HSCs, suggesting that Tβ4 may be an effective treatment for liver fibrosis. Kim et al[30] also suggested that decreased Tβ4 expression is associated with chronic liver disease, and affects liver fibrosis by regulating the proliferation and activation of HSCs. These studies indicate that Tβ4 may have an anti-fibrotic effect in patients with liver fibrosis.

When the concentration of serum Tβ4 was compared between patients with NAFLD and healthy controls, serum Tβ4 levels in patients with NAFLD were significantly lower. After treatment and subsequent improvement in liver function, the concentration of Tβ4 increased.[31] Tian et al[32] observed 83 cases of NAFLD and 80 healthy patients, and found that Tβ4 level can effectively be used as a biomarker of liver function, as increased Tβ4 level indicated improved liver function, and decreased Tβ4 level indicated severe liver damage. These studies indicate that Tβ4 expression is related to liver function in NAFLD patients. However, no research has been performed to investigate the effects of Tβ4 on the treatment of NAFLD.

Conclusions

Our hypothesis is that Tβ4 could represent a promising and effective treatment for NAFLD. Our viewpoint is based on evidence that Tβ4 is negatively correlated with endotoxemia, suppresses proinflammatory TLR and NF-κB signaling, and reduces inflammatory cytokine levels, with anti-inflammatory and insulin-sensitizing effects. Furthermore, Tβ4 could inhibit the migration, proliferation, and activation of HSCs, which is a critical event in the fibrogenic cascade. Importantly, Tβ4 treatment has been safely used in patients or animals to treat traumatic brain injury,[22] corneal epithelial defects,[33] lung inflammation,[34] and fibrosis.[35] Therefore, Tβ4 should be safe in clinical applications.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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