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The Role of Stress-Related Inflammatory Mediators in Hepatocyte Injury in Fatty Liver Disease and Current Research Status

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Abstract: Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease globally, with its incidence rising annually. It can progress to cirrhosis and even hepatocellular carcinoma, posing a serious threat to human health. Stress can participate in the pathological process of NAFLD by activating inflammatory responses and regulating levels of inflammatory mediators, with hepatocyte injury being a core component of NAFLD progression. This paper focuses on three key stress-related inflammatory mediators: tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), elucidating their core mechanisms in the pathway related to stress signal, followed by inflammatory activation and hepatocyte injury respectively, and reviewing current research. Research indicates that certain inflammatory mediators can damage hepatocytes by directly inducing apoptosis or indirectly regulating metabolic disorders and fibrosis progression. However, questions regarding causal relationships, target specificity for intervention, and quantification of psychological stress remain unresolved. This paper aims to provide theoretical support for NAFLD intervention strategies targeting inflammatory mediators, clarifying future research directions to advance clinical translation.

Keywords: Hepatocyte injury; Inflammatory cytokines; Fatty liver disease; Non-alcoholic fatty liver disease; Stress

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1. Introduction

With rising global obesity rates and lifestyle changes, NAFLD has become the world's most prevalent chronic liver disorder, affecting over 25% of the global population. In China, the prevalence of NAFLD among adults exceeds 20%. NAFLD is not a benign disease; approximately 20%–30% of patients may progress to non-alcoholic steatohepatitis (NASH), which can further develop into cirrhosis, hepatocellular carcinoma, or even necessitate liver transplantation [1]. Hepatocyte injury serves as the core initiating event in NAFLD's pathological progression, involving a cascade of changes including steatosis, inflammatory infiltration, apoptosis, and fibrosis. Inflammatory

response acts as the pivotal link connecting these stages [2].

"Stress," a pervasive physiological and psychological state in modern society, plays a significant role in the development of NAFLD. Here, "stress" carries dual connotations, where physiological stress primarily encompasses metabolic disorders, oxidative stress, and gut microbiota dysbiosis; psychological stress mainly manifests as chronic anxiety, prolonged mental tension, and sleep disorders.

These two forms do not act independently but through a common pathway: activating systemic inflammatory responses, inducing abnormal expression of inflammatory mediators, and thereby exacerbating hepatocyte injury [3]. Currently, inflammatory mediators such as TNF-α, IL-6, and CRP have been confirmed to be closely associated with the severity of liver damage in NAFLD patients. However, the specific activation mechanisms of these mediators under stress, their damaging effects on hepatocytes, and their interactions still require systematic clarification.

Therefore, this paper adopts the core logic of "stress-inflammatory factors-hepatocyte injury" to review the sources, classification, and mechanisms of action of three key inflammatory factors (TNF-α, IL-6, CRP) in hepatocyte injury. It also summarizes the current research landscape to provide references for selecting diagnostic biomarkers and developing therapeutic targets for NAFLD.

2. Stress-related inflammatory factors and hepatocyte injury

2.1. Classification and sources of stress-related inflammatory factors

Stress-related inflammatory factors are small-molecule proteins or peptides secreted by immune cells and parenchymal cells in response to stress stimuli, functioning to regulate inflammatory responses. Based on their functions and origins, they can be categorized into two main types:

(1) Pro-inflammatory cytokines that are centered on TNF-α and IL-6 are primarily secreted by Kupffer cells (hepatic macrophages), hepatocytes, and hepatic stellate cells within the liver. Kupffer cells, as the primary immune cells in the liver, can rapidly activate and release TNF-α and IL-6 in response to physiological stressors (e.g., hepatic steatosis induced by high-fat diets, accumulation of oxidative stress products) or psychological stressors (e.g., elevated cortisol levels). Additionally, damaged hepatocytes can directly secrete the aforementioned factors, further amplifying the local inflammatory response [4];

(2) Acute phase reactants represented by CRP are primarily synthesized by hepatic parenchymal cells under the induction of proinflammatory factors like IL-6. CRP itself does not directly initiate inflammation but serves as a sensitive marker reflecting systemic and local hepatic inflammatory severity, with its levels positively correlated with stress intensity and inflammatory response severity.

Regarding activation mechanisms, stress primarily induces inflammatory factor production through two pathways:

(1) The physiological stress pathway, such as high-fat diets causing lipid droplet accumulation in hepatocytes, triggering endoplasmic reticulum stress and oxidative stress, activating the nuclear factor-κB (NF-κB) signaling pathway, and subsequently promoting TNF-α and IL-6 gene transcription and protein secretion;

(2) The psychological stress pathway, where chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, elevating cortisol levels. Excess cortisol suppresses the anti-inflammatory function of immune cells, disrupting the "pro-inflammatory-anti-inflammatory" balance. This leads to abnormal increases in pro-inflammatory factors like TNF-α and IL-6 while inducing hepatocyte synthesis of CRP [5].

2.2. Mechanisms of core inflammatory factors in hepatocyte injury

2.2.1. Mechanism of TNF-α

TNF-α is the earliest pro-inflammatory factor activated under stress. Its hepatocyte damage occurs primarily through two pathways: "direct apoptosis induction" and "indirect pathological regulation":

In the activation pathway, physiological stressors (such as lipotoxicity induced by high-fat diets or oxidative stress products from alcohol metabolism) directly stimulate Toll-like receptor 4 (TLR4) on Kupffer cell surfaces, activating the NF-κB pathway and prompting Kupffer cells to secrete large amounts of TNF-α. Elevated cortisol levels induced by psychological stress enhance Kupffer cell activation, further increasing TNF-α release.

On the other hand, TNF-α exacerbates liver injury through indirect effects, whereby it activates hepatic stellate cells, promoting collagen fiber synthesis and deposition, thereby accelerating liver fibrosis progression. Concurrently, TNF-α inhibits hepatic lipase activity within hepatocytes, reducing lipolysis and causing massive lipid droplet accumulation within hepatocytes, thereby worsening steatosis. Clinical studies confirmed that TNF-α expression levels in liver tissue from NAFLD patients positively correlate with hepatocyte apoptosis rates and the stage of liver fibrosis.

2.2.2. Mechanism of action of IL-6

IL-6 serves as a pivotal link between stress, inflammation, and metabolic disorders, with its hepatocellular damage centered on "inflammatory amplification" and "metabolic imbalance."

The activation pathway of IL-6 exhibits duality, where under physiological stress, endoplasmic reticulum stress triggered by hepatic lipid accumulation directly induces IL-6 secretion from hepatocytes; Kupffer cells stimulated by TNF-α can further release IL-6, forming an inflammatory cascade reaction. Elevated cortisol levels induced by psychological stress promote IL-6 gene expression by activating signal transducer and activator of transcription 3 (STAT 3) within hepatocytes [6].

Its pathogenic mechanisms are outlined below:

(1) IL-6 binds to its receptor (IL-6R) on hepatocyte surfaces, activating the Janus kinase (JAK)-STAT3 signaling pathway. This promotes STAT3 phosphorylation and nuclear translocation, where it regulates the expression of acute-phase proteins like CRP and serum amyloid A, thereby amplifying local hepatic inflammation;

(2) IL-6 reduces hepatic insulin sensitivity by inhibiting the phosphorylation of insulin receptor substrate 1 (IRS-1) in the insulin signaling pathway. This leads to abnormal hepatic glucose and lipid metabolism, decreased glucose uptake, impaired glycogen synthesis, and increased fatty acid synthesis, thereby exacerbating steatosis.

Additionally, IL-6 promotes the proliferation and activation of hepatic stellate cells, accelerating the progression of liver fibrosis. Animal studies demonstrated that in IL-6 knockout mice, hepatic steatosis and inflammation induced by a high-fat diet are significantly milder compared to wild-type mice.

2.2.3. Mechanism of action of CRP

As an acute-phase reactant protein, CRP does not directly initiate inflammation but exacerbates hepatocyte damage through "inflammatory amplification" and "cytotoxic" effects.

CRP activation depends on IL-6 induction. Elevated IL-6 under stress binds to IL-6R on hepatocyte surfaces, activating the acute-phase response pathway within hepatocytes and promoting CRP synthesis and secretion.

CRP itself lacks direct pro-inflammatory activity but binds to CRP receptors on hepatocyte surfaces to activate the complement system. This releases complement fragments (e.g., C3a, C5a), recruiting inflammatory cells like neutrophils to infiltrate the liver and amplify local inflammation. Concurrently, CRP induces reactive oxygen species (ROS) production in hepatocytes, triggering oxidative stress that impairs mitochondrial function and disrupts cellular energy metabolism, thereby exacerbating hepatocyte damage [7].

Clinical studies indicate that serum CRP levels in NAFLD patients are significantly higher than in healthy individuals. Moreover, CRP levels correlate positively with liver function markers (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and the degree of liver fibrosis, making it a potential biomarker for assessing NAFLD disease progression.

2.3. Synergistic interactions among inflammatory cytokines

TNF-α, IL-6, and CRP do not act independently but form an inflammatory cascade through "mutual regulation and synergistic amplification," collectively exacerbating hepatocyte injury [8].

TNF-α serves as the initiator of the inflammatory cascade. It directly promotes IL-6 gene transcription and secretion by activating the NF-κB pathway, while simultaneously upregulating IL-6R expression on hepatocyte surfaces to enhance IL-6's effects. IL-6 also acts as an intermediate regulator, where it further promotes TNF-α release while inducing CRP synthesis in hepatocytes, creating a positive feedback loop (TNF-α-IL-6-CRP). Additionally, CRP activates the complement system to recruit inflammatory cells, which in turn stimulate Kupffer cells to secrete TNF-α and IL-6, amplifying the inflammatory response.

This synergistic interaction ultimately produces a "compounding effect" of hepatocyte damage: TNF-α-driven apoptosis, IL-6-regulated metabolic dysfunction and fibrosis, and CRP-amplified inflammation collectively led to hepatic steatosis, increased apoptosis, and advanced fibrosis. This accelerates the progression of NAFLD from simple steatosis to NASH and cirrhosis.

3. Current research status

Regarding the relationship between stress-related inflammatory factors and hepatic cell damage in fatty liver disease, multiple cross-sectional studies and meta-analyses have demonstrated that serum levels of TNF-α, IL-6, and CRP in NAFLD patients are significantly higher than in healthy individuals. These levels correlate closely with the severity of liver damage as serum inflammatory factor levels are markedly elevated in NASH patients compared to those with simple fatty liver disease, and cirrhosis patients exhibit even higher levels than NASH patients. Concurrently, serum TNF-α, IL-6, and CRP levels positively correlate with liver function markers (ALT, AST) and fibrosis staging (e.g., FIB-4 score, transient elastography values), positioning them as potential biomarkers for assessing NAFLD progression [9–12].

Mechanistic evidence from animal studies confirms that gene knockout or pharmacological inhibition of TNF-α and IL-6 expression significantly attenuates hepatic steatosis, inflammatory infiltration, and apoptosis in mice induced by high-fat diet or stress. *In vitro* cell experiments also indicate that adding TNF-α and IL-6 to hepatocyte culture systems induces hepatic steatosis and apoptosis, while adding corresponding neutralizing antibodies reverses such damage. Furthermore, clinical studies reveal that reducing stress levels in NAFLD patients through lifestyle interventions significantly lowers serum TNF-α, IL-6, and CRP levels while improving hepatic cell injury [13].

Despite these advances, several controversies and unresolved issues persist:

(1) The causal relationship remains debated. Most existing studies are cross-sectional, confirming elevated inflammatory factor levels in NAFLD patients but failing to clarify whether "elevated inflammatory factors are the cause or consequence of NAFLD" [14]. Some scholars propose that hepatic steatosis itself induces cellular stress, which in turn triggers inflammatory cytokine secretion, establishing a vicious cycle of "steatosis → elevated cytokines → further damage" rather than cytokines directly initiating NAFLD. Confirming this causal relationship requires additional prospective cohort studies and interventional trials (e.g., evaluating whether early cytokine suppression prevents NAFLD development);

(2) The issue of intervention target specificity, as inhibitors targeting TNF-α (e.g., etanercept, adalimumab) demonstrate significant efficacy in autoimmune diseases like rheumatoid arthritis. However, in clinical studies of NAFLD, their improvement in hepatic cell injury is limited, and they may induce side effects such as infections and abnormal liver function [15-18]. This may stem from TNF-α's multifaceted physiological roles, where systemic inhibition disrupts the "pro-inflammatory-anti-inflammatory" balance. Additionally, synergistic interactions among inflammatory mediators exist; single-target inhibition of TNF-α may trigger compensatory increases in other factors like IL-6, negating therapeutic effects. Thus, enhancing the specificity of inflammatory mediator interventions while avoiding systemic side effects remains a key research challenge;

(3) The quantification of psychological stress poses challenges because there is no unified assessment standard for the impact of psychological stress on inflammatory factors. Existing studies predominantly employ self-reported stress scales (e.g., the Perceived Stress Scale, PSS) or cortisol level measurements. However, stress scales exhibit significant subjectivity, while cortisol levels are susceptible to circadian rhythms and testing timing, leading to poor reproducibility across studies [19].

Furthermore, the synergistic mechanisms linking psychological and physiological stress to inflammatory factors remain unclear. Establishing more precise stress assessment systems is essential to quantify stress's impact on inflammatory factors and hepatocyte damage [20].

4. Conclusion

Stress-related inflammatory factors (TNF-α, IL-6, CRP) serve as the core bridge connecting "stress" to "fatty liver hepatocyte damage." Both physiological and psychological stress activate signaling pathways such as NF-κB and JAK-STAT3, inducing abnormal expression of these inflammatory factors. This leads to exacerbated hepatocyte injury through direct induction of apoptosis and indirect regulation of metabolic disorders and fibrosis progression. Simultaneously, synergistic interactions among inflammatory factors amplify the inflammatory response, accelerating NAFLD progression. Current research confirms that TNF-α, IL-6, and CRP serve as potential biomarkers for assessing NAFLD progression, and their targeted intervention offers new therapeutic directions.

However, three core challenges remain:

(1) Prospective studies are needed to establish the causal relationship between inflammatory cytokines and NAFLD;

(2) Developing liver-specific inhibitors for these cytokines is essential to enhance intervention efficacy while reducing side effects;

(3) Establishing a precise stress assessment system to quantify the impact of psychological stress on

inflammatory factors and hepatocyte damage.

Future efforts should integrate multi-omics technologies (e.g., genomics, metabolomics) with clinical translational research to deeply explore the regulatory network linking stress, inflammatory factors, and hepatocyte damage, thereby providing a more robust theoretical foundation for the precise diagnosis and treatment of NAFLD.

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