The Immune Mechanisms of Metabolic-associated Fatty Liver Disease and Dietary Intervention Strategies

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Abstract. Metabolism-related fatty liver disease has become one of the most common chronic liver diseases globally, affecting about one-quarter of the adult population, with a prevalence of 29.2% in our country, showing a trend towards younger age groups. This disease is characterized not only by the accumulation of fat in the liver but also involves multidimensional pathological processes such as abnormal lipid metabolism, insulin resistance, and inflammatory immune responses. Among them, the abnormal activation of the immune system is the core driving force of disease progression, including disorders in the innate immune signaling pathways (such as Kupffer cell polarization dysfunction and excessive activation of the Nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 inflammasome) and imbalances in adaptive immunity (dysfunction of T cell subsets). At the same time, the gut microbiota regulates the hepatic immune microenvironment through metabolites and barrier functions, forming an "gut-liver" inflammatory loop.This study systematically reviews the immunopathological mechanisms of metabolic associated fatty liver disease, focusing on the interaction between innate and adaptive immunity, and integrates the latest clinical evidence to compare the immunomodulatory effects of dietary patterns such as the Mediterranean diet, intermittent fasting, and dietary fiber interventions. Based on patient BMI indices, genotypes, and gut microbiome characteristics, precise dietary intervention strategies are proposed. The research results provide theoretical support and practical guidance for the prevention and treatment of metabolic-associated fatty liver disease.

Keywords: Fatty liver diseases; immune mechanisms; gut microbiome-liver axis; dietary intervention; NOD-like receptor protein 3 inflammasome.

1. Introduction

Metabolic-associated fatty liver disease presents a significant global public health challenge, with the disease burden continuing to escalate alongside the increasing populations of obesity and metabolic disorders [1]. In China, the proportion of obese patients with fatty liver has reached 81.8%, far exceeding the global average. The disease is not merely a simple accumulation of fat in the liver, but a progressive pathological process: it develops from simple hepatic steatosis to non-alcoholic steatohepatitis, liver fibrosis, and may ultimately evolve into cirrhosis or even hepatocellular carcinoma [2]. At the same time, metabolic-associated fatty liver disease significantly increases the risk of type 2 diabetes and cardiovascular diseases, forming a vicious cycle of 'metabolic disorder - liver damage - multi-organ complications' [3].

In 2025, the Chinese Medical Association officially renamed non-alcoholic fatty liver disease to metabolic associated fatty liver disease, emphasizing the core role of metabolic disorders. The new diagnostic criteria require the simultaneous presence of liver fat degeneration and at least one metabolic risk factor (such as obesity, insulin resistance). This renaming reflects a deeper understanding of the nature of the disease—metabolic associated fatty liver disease is a systemic disease caused by metabolic abnormalities, with immune inflammation playing a key regulatory role [4]. Recent research has shown that disorders in the innate immune signaling pathways (such as Kupffer cell polarization imbalance and overactivation of Nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 inflammasome) directly lead to the imbalance of hepatic immune homeostasis, while the gut microbiota-liver axis further amplifies the immune-inflammatory response by modulating the hepatic immune microenvironment [5].

Currently, dietary intervention is recommended as the first-line strategy for the prevention and treatment of metabolism-related fatty liver disease due to its high safety and strong accessibility. However, the specific immune regulatory mechanisms by which different dietary patterns improve the disease have not been systematically elucidated. For example, how do polyunsaturated fatty acids in the Mediterranean diet affect liver immune cell function? Does a high-fiber diet indirectly modulate liver immunity through gut microbiota metabolites? The gaps in these key scientific questions have led to the current dietary interventions for metabolically related fatty liver disease being limited to 'empirical recommendations', making it impossible to develop personalized plans based on patients' immune status and characteristics of gut microbiota. Therefore, it is of significant scientific importance and clinical value to deeply explore the relationship between the immune mechanisms of metabolically related fatty liver disease and dietary interventions[6].

2. The Immune Pathogenesis of Metabolic-related Fatty Liver Disease

2.1. Abnormalities of the Innate Immune System

Innate immune activation is a key aspect of the early inflammatory initiation of metabolically associated fatty liver disease. Kupffer cells, as resident macrophages in the liver, polarize to the pro-inflammatory M1 type under lipid overload conditions, releasing pro-inflammatory factors such as interleukin-1β and tumor necrosis factor-α via the Toll-like receptor 4/Myeloid Differentiation Primary Response 88 (MyD88)/ Nuclear Factor Kappa-light-chain-enhancer of Activated B cells (NF-κB) pathway, while simultaneously inhibiting the anti-inflammatory function of M2 macrophages, disrupting the 'pro-inflammatory vs. anti-inflammatory' balance in the liver [7]. The research team at Beijing Chaoyang Hospital found that the mitochondrial function of double-negative T cells in the liver of patients with metabolic-associated fatty liver disease is impaired, further promoting macrophage activation and forming an inflammatory amplification loop [8]. Activation of the NOD-like receptor protein 3 inflammasome is a key molecular event linking steatosis and inflammation. Research from Guangzhou University of Traditional Chinese Medicine confirms that in a high-fat diet-induced model of metabolic-associated fatty liver disease, the reduced expression of zinc finger and Broad-Complex, Tramtrack, and Bric-à-brac (BTB) domain-containing protein 18 in the liver leads to insufficient activation of farnesoid X receptor, which relieves the inhibition of the NOD-like receptor protein 3 inflammasome by reducing the expression of clathrin C protein, triggering cysteine-aspartic protease 1-mediated hepatocyte pyroptosis and interleukin-1β release [9]. This study first reveals that the zinc finger structure and the BTB domain-containing protein 18/farnesoid X receptor/grid protein C axis affects the progression of metabolic-associated fatty liver disease by regulating the activity of NOD-like receptor protein 3, providing new targets for immune intervention [10].

2.2. Disorder of Adaptive Immune Response

Dysregulation of adaptive immunity plays an important role in the maintenance of chronic inflammation in metabolic-associated fatty liver disease. Clinical studies have found that patients with metabolic-associated fatty liver disease have an increased proportion of Th1 cells in the liver and peripheral blood, which secrete interferon-γ to promote macrophage activation; a decreased proportion of Th2 cells leads to a reduction in anti-inflammatory factors such as interleukin 4 and interleukin 13; the number of regulatory T cells is reduced and their function impaired, weakening the immunosuppressive effects mediated by interleukin 10 and transforming growth factor β, collectively exacerbating chronic inflammation in the liver [11]. These abnormalities in T cell subpopulations are significantly positively correlated with the degree of liver inflammation activity scoring, representing independent risk factors for disease progression [12].

2.3. Immune Regulation of the Gut Microbiome-liver Axis

The gut microbiota regulates the immune microenvironment of the liver through metabolites and barrier functions. The study by Zhang et al. confirmed that dysbiosis of the gut microbiota promotes the development of non-alcoholic fatty liver disease through the Toll-like Receptor 5 (TLR5) signaling pathway [13]. Meanwhile, the research by Zhou et al. indicated that dysfunction of the gut barrier leads to the translocation of endotoxins, which, upon reaching the liver via the portal vein, activates Kupffer cell Toll-like receptor 4 signaling, forming an 'intestinal-liver' inflammatory loop [14].

Short-chain fatty acids, as the main metabolic products of the gut microbiota, regulate hepatic immunity through multiple pathways: First, they activate G protein-coupled receptors 41/43 to promote the differentiation of regulatory T cells in the liver; Second, they inhibit the activity of histone deacetylases, reducing the expression of pro-inflammatory factors; Third, they enhance the transcription of chemokine ligand 11 through epigenetic regulation, recruiting natural killer cells to strengthen anti-tumor immunity [15]. The study by Liu et al. found that butyrate can remodel the enhancer region of chemokine ligand 11 through histone H3 lysine 27 acetylation/H3 lysine 9 acetylation modifications, significantly enhancing natural killer cell infiltration and cytotoxicity [16].

3. Immune Modulation Mechanisms of Dietary Intervention

3.1. Anti-inflammatory Effects of the Mediterranean Diet

The Mediterranean diet (rich in polyunsaturated fatty acids, polyphenols, and whole grains) regulates the immune status related to metabolic-associated fatty liver disease through multiple mechanisms. A randomized controlled trial presented at the 2024 American Association for the Study of Liver Diseases annual meeting showed that a 12-week intervention of the Mediterranean diet could reduce the degree of liver fat degeneration by 48.7 dB/m, liver stiffness by 1.3 kPa, and significantly lower the levels of inflammatory markers such as tumor necrosis factor α and interleukin 6 [17]. Its core mechanisms include: the conversion of Omega-3 fatty acids into resolution factors to inhibit the activation of the nuclear factor kappa B pathway; polyphenols such as oleuropein, clearing reactive oxygen species and inhibiting M1 polarization of Kupffer cells; and dietary fiber fermentation producing short-chain fatty acids that regulate the gut-liver immune axis [18].

It is worth noting that the study found the effects of the Mediterranean diet are not influenced by the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) genotype, suggesting it can serve as a broadly applicable basic intervention program. On the other hand, the genomic study by Gallagher et al. showed that carriers of the PNPLA3 risk allele, the intake of high-protein foods and fermented vegetables (such as pickles) can reduce the risk of metabolic-associated fatty liver disease through gene-diet interactions, providing a basis for personalized dietary adjustments [19].

3.2. Metabolic-immune Regulation of Intermittent Fasting

Intermittent fasting (especially 16/8 time-restricted eating) improves the immune metabolic state associated with metabolic-related fatty liver disease through metabolic conversion. A systematic review by Tinsley et al. indicates that time-restricted eating can lower liver enzyme levels and improve liver stiffness, with mechanisms related to the metabolic conversion from glucose to ketone bodies during fasting, reducing immune cell activation mediated by free fatty acids [20]. Clinical data show that the 16/8 intervention for 12 weeks can reduce liver fat content by 21%, significantly decrease inflammatory markers such as high-sensitivity C-reactive protein, and the effect is more pronounced in patients with metabolic-associated fatty liver disease combined with metabolic syndrome [21].

3.3. The Microbial Mediation Effect of High Dietary Fiber Diets

A high-fiber diet exerts immune regulatory effects by reshaping the structure of gut microbiota. A systematic review and meta-analysis by Mak et al. indicates that dietary fiber cannot be directly digested by the human body; after entering the colon, it is fermented by the microbiota to produce short-chain fatty acids, which influence liver immunity through the portal venous system: first, by promoting the expression of tight junction proteins in the intestinal barrier, reducing endotoxin translocation; second, by increasing the proportion of hepatic Foxp3 regulatory T cells, enhancing immunosuppressive functions; and third, by inhibiting the activation of hepatic stellate cells, slowing down the fibrosis process [22]. Research has confirmed that daily intake of more than 30g of dietary fiber can increase the abundance of bifidobacteria and lactobacilli in the intestines by 2-3 times and elevate the concentration of short-chain fatty acids in feces by 1.5-2 times, significantly improving liver function indicators in patients with metabolic-related fatty liver disease [23].

4. Personalized Dietary Intervention Strategies

Accurate dietary intervention based on patient characteristics can improve the prevention and treatment of metabolic-related fatty liver diseases. According to Body Mass Index (BMI) stratification, obese patients with BMI > 30 kg/m² are more suitable for low-carbohydrate diets, and the reduction in liver fat content in 12 weeks of intervention is 5%-8% higher than that of dietary fiber diets; patients with BMI < 30 kg/m² have better anti-inflammatory effects in Mediterranean diets [24].

The characteristics of intestinal flora are an important basis for personalized intervention: patients with low intestinal flora diversity and low short-chain fatty acid concentrations have increased by 30%-35% after dietary intervention of high dietary fiber, which is significantly higher than those with normal flora (15%-20%). While carriers of PNPLA3 I148M genotype can benefit from a high-protein diet and fermented vegetable intake, Korean studies have shown that intake of kimchi in such patients can reduce the risk of metabolic-related fatty liver disease ($p=0.012$) [25].

Disease stage also affects dietary choices: patients with simple steatosis respond well to all three dietary patterns; patients with non-alcoholic steatohepatitis combined with mild fibrosis, the Mediterranean diet combined with high dietary fiber can reduce Alanine Aminotransferase (ALT) by 20%-25%, and the inflammatory markers by 25%-30%, which is better than a single dietary pattern [26].

5. Conclusion

The immunopathological process of metabolic-related fatty liver disease involves multiple abnormalities of innate and adaptive immunity, and the intestinal flora-hepatic axis plays a key regulatory role through metabolites and barrier functions. Mediterranean diet, intermittent fasting, and high dietary fiber diet regulate liver immunity through differentiated mechanisms: Mediterranean diet strongly inhibits inflammatory signaling pathways, intermittent fasting improves metabolism-related inflammation, and high dietary fiber regulates immune cell function through flora metabolites. Personalized dietary strategies based on BMI, genotype, and intestinal flora characteristics can significantly improve intervention effectiveness.

Future research should focus on three aspects: First, analyze the "gene-flora-diet-immune" interaction mechanism through multiomics technology; second, develop the quantitative intervention effect of "diet immunomodulation index"; finally, explore the combined application of diet and new drugs (such as farneside X receptor agonists and NOD-like receptor protein 3 inhibitors). With the deepening of the concept of precision nutrition, the prevention and treatment of metabolic-related fatty liver disease will move from "broad-spectrum dietary advice" to a new stage of "personalized immune regulation".

However, this study still has limitations: the long-term effects of some dietary interventions still need to be verified in large-scale clinical trials, and the cost-benefit analysis of individualized programs needs to be improved. It is recommended that follow-up research strengthen multi-center cooperation, establish a standardized evaluation system, and promote the transformation of research results into clinical practice.

Authors Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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