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Opinion Article

Signaling Pathways Involved in Non-Alcoholic Steatohepatitis

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DESCRIPTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a metabolic disorder characterized by excessive fat accumulation in hepatocytes, occurring in individuals without significant alcohol consumption. It encompasses a spectrum ranging from simple steatosis to Non-Alcoholic Steatohepatitis (NASH), fibrosis, cirrhosis and in some cases, hepatocellular carcinoma. The increasing prevalence of obesity, type 2 diabetes and metabolic syndrome has made NAFLD a major public health concern worldwide. Its complex pathogenesis involves interactions among dietary factors, adipose tissue dysfunction, hepatic lipid metabolism, insulin resistance, inflammatory pathways and the gut-liver axis. Among the molecular mechanisms implicated in NAFLD, Free Fatty Acid (FFA) receptors have gained attention due to their regulatory roles in metabolism, inflammation and energy homeostasis.

In the liver, FFARs regulate lipid metabolism, glucose homeostasis and inflammatory signaling. Activation of FFAR1 and FFAR4 by long-chain fatty acids influences insulin sensitivity, promotes beta-oxidation and modulates the synthesis of lipids within hepatocytes. FFAR4, in particular, has been shown to exert anti-inflammatory effects through inhibition of pro-inflammatory cytokine production and suppression of macrophage activation. Conversely, dysregulation of these receptors can contribute to lipid accumulation, oxidative stress and low-grade inflammation, which are key features of NAFLD progression.

The regulation of FFAR expression and activity is bidirectional. Not only do FFARs influence hepatic lipid and glucose metabolism, but the metabolic state of hepatocytes and systemic factors modulate FFAR expression. For instance, insulin resistance and hyperlipidemia observed in NAFLD can alter receptor expression levels and downstream signaling pathways. Similarly, chronic low-grade inflammation and oxidative stress can impair receptor function, creating a feedback loop that perpetuates metabolic derangements. This bidirectional interaction underscores the dynamic relationship between FFARs and the liver's metabolic environment.

FFAR1 has also been studied in the context of liver disease. Activation of FFAR1 enhances insulin secretion from pancreatic beta cells and improves systemic glucose handling. Improved glycemic control reduces hepatic de novo lipogenesis and diminishes fatty acid flux to the liver, indirectly protecting against steatosis. However, chronic exposure to high levels of circulating free fatty acids can lead to receptor desensitization, reducing the effectiveness of FFAR1 signaling and contributing to metabolic stress. This phenomenon illustrates the bidirectional nature of FFAR regulation, where receptor function is influenced by the metabolic environment it regulates.

The interaction between FFARs and inflammatory pathways is significant in NAFLD progression. FFAR4 activation suppresses the nuclear factor-kappa B pathway and reduces macrophage-mediated inflammatory responses within the liver. In addition, FFAR-mediated signaling influences adipokine secretion from adipose tissue, which affects systemic inflammation and hepatic immune cell recruitment. In NAFLD, dysregulated FFAR signaling exacerbates cytokine release, promotes hepatic stellate cell activation and contributes to fibrotic remodeling. This highlights the importance of maintaining balanced receptor function for metabolic and immunological homeostasis.

Therapeutic strategies targeting FFARs are emerging as potential approaches for NAFLD management. FFAR agonists can restore receptor signaling, improve insulin sensitivity, reduce hepatic triglyceride accumulation and suppress inflammation. Experimental administration of FFAR4 agonists in obese and diabetic animal models demonstrates reduced hepatic steatosis, improved glucose tolerance, and lower inflammatory markers. Similarly, modulation of gut microbiota to enhance short-chain fatty acid production activates FFAR2 and FFAR3, improving metabolic and immunological outcomes. These strategies highlight the potential of FFAR-focused interventions in managing metabolic liver disorders.

Despite the potential benefits, challenges remain in targeting FFARs for NAFLD treatment. Receptor expression and function vary among individuals based on genetic factors, diet, microbiota

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composition and disease stage. Chronic metabolic stress may induce receptor desensitization or downregulation, reducing the efficacy of therapeutic interventions. Moreover, FFARs are expressed in multiple tissues and systemic activation may produce unintended effects on other organs, including the pancreas, intestine and adipose tissue. Careful consideration of tissue-specific effects, dosing and duration is necessary to optimize therapeutic outcomes.

In conclusion, free fatty acid receptors are integral regulators of hepatic metabolism, inflammation and systemic energy balance. Their bidirectional relationship with non-alcoholic fatty liver disease highlights a dynamic interplay where receptor activity influences disease progression and the metabolic and inflammatory state of the liver affects receptor function. Long-chain fatty acid receptors FFAR1 and FFAR4 modulate lipid metabolism, insulin sensitivity and inflammatory responses, whereas short-chain fatty acid receptors FFAR2 and FFAR3 mediate gut-liver interactions and energy homeostasis. Dysregulation of these receptors contributes to lipid accumulation, oxidative stress, inflammation and fibrosis. Therapeutic strategies that restore or enhance FFAR function, combined with lifestyle modifications, hold potential for mitigating disease progression, improving metabolic control and reducing liver injury. Continued investigation into the mechanisms regulating FFAR activity, their interactions with metabolic networks and their influence on liver pathology will deepen understanding of NAFLD and guide development of effective interventions.