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Research progress on the mechanism of non-alcoholic fatty liver disease caused by hepatic insulin resistance

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Abstract: Non-alcoholic fatty liver disease (NAFLD) refers to a clinicopathological syndrome characterized by macrovesicular steatosis and lipidaccumulation of hepatocytes, except for alchol and other specific factors associated with liver damage. In terms of etiology, NAFLD is highly correlated with hepatic insulin resistance (IR). In terms of etiology, NAFLD is highly correlated with hepatic insulin resistance (IR). Elucidation of the pathogenesis of hepatic IR is expected to provide theoretical support for drug research in NAFLD. Therefore, this article reviews the research progress on the mechanism of NAFLD. Elucidation of the pathogenesis of hepatic IR is expected to provide theoretical support for drug research in NAFLD.

Keywords: Non-alcoholic fatty liver disease; Hepatic insulin resistance; Molecular mechanism; Lipid metabolism; Inflammatory response

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Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver disease, and its prevalence continues to rise globally to about 25%[1]. In China, changes in the prevalence of NAFLD parallel the epidemiological trends of obesity, type 2 diabetes mellitus and metabolic syndrome. NAFLD is closely related to the high prevalence of diabetes mellitus, atherosclerotic cardiovascular disease, and colorectal tumors, and it has now become an invisible killer that affects human health. There is no wonder drug for the treatment of NAFLD at home and abroad. Therefore, it has become an urgent problem to clarify NAFLD's mechanism of action and effectively prevent disease progression. Numerous clinical studies have shown that insulin resistance (IR) plays a key role in the development of NAFLD, while fat storage is a characteristic of NAFLD[2]. This paper will further explore the relationship between NAFLD and IR, elucidate its specific molecular mechanism, and provide more theoretical support for NAFLD drug development.

1 Relationship between NAFLD and IR

The pathophysiologic mechanisms underlying the development of NAFLD are mainly related to hepatocellular steatosis, which is mainly due to impaired regulation of hepatic lipid metabolism, in which hepatic IR and increased free fatty acid (FFA) play an important role [3]. Under normal conditions, insulin exerts physiological functions in the liver including promoting glycogen synthesis, inhibiting gluconeogenesis, promoting lipid synthesis and inhibiting lipid breakdown. When the sensitivity of target organs to insulin decreases

(when IR occurs), the body will produce more insulin compensatorily to meet the body's glucose metabolism demand, resulting in high levels of insulin in the blood. In the IR state, the insulin receptor signaling pathway is impaired, gluconeogenesis is no longer inhibited, but hepatic lipid deposition can continue to increase, which induces the development of NAFLD. It has been found that in patients with NAFLD, IR elevates the rate of FFA release from adipose tissue[4], and elevated FFA not only stimulates insulin secretion, but also causes abnormalities in hepatic lipid metabolism and exacerbates hepatocellular steatosis.

The hepatic *de novo* lipogenesis (DNL) pathway is one of the important factors causing the development of NAFLD, and studies have shown that insulin can promote hepatic DNL[5]. Therefore, excess insulin in the body relatively promotes hepatic DNL during IR, increasing hepatic steatosis. Insulin also stimulates adipose tissue to secrete adipokines and inflammatory cytokines, which ultimately leads to dysregulation of adipose tissue catabolism[6-7]. In turn, fat accumulation in the liver increases lipotoxicity, leading to increased oxidative stress, which severely impairs mitochondrial function in the liver and causes fatty acid accumulation, and the presence of this positive feedback loop allows for the continued progression of NAFLD.

2 Molecular mechanisms associated with NAFLD and IR

Insulin binds to the insulin receptor substrate (IRS) and signals downstream of the IRS, such as phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and other pathways. IR can be induced by any abnormal part of protein signaling pathways. The mechanism of NAFLD-induced IR is complex, and it is related to the oxidative stress in adipose tissues and the dysfunctions of the mitochondria, inflammation, intestinal microbiota dysregulation, and other factors, and the related molecular mechanisms will be discussed one by one.

2.1 Liver IR and lipid metabolism

Lipid-induced hepatic IR is mainly activated by the ceramide or diacylglycerol-protein kinase C (PKC) pathway to inhibit the phosphorylation of IRS1 and further inhibit the PI3K/AKT pathway. This pathway reduces the activation of glycogen synthase and inhibits glycogen synthesis, and reduces the inactivation of forkhead box O1 (FoxO1) to increase hepatic gluconeogenesis, the produced glucose is released into the blood through glucose transporter protein 2 (GLUT-2) channels, resulting in a significant decrease in hepatic sensitivity to insulin[8]. In addition, of the many lipid molecules associated with NAFLD, diacylglycerol has been identified as the key molecule causing hepatic IR[9]. Geradshulman's team at Yale University revealed the specific molecular mechanism involved. In NAFLD, the accumulated cell membrane sn-1,2-diacylglycerol (DAG) in the liver activates the PKC protein, which is anchored to the T1,160 site of the phosphorylated insulin receptor on the cell membrane. Phosphorylation of this site inhibits the activation of the insulin receptor, leading to a decrease in the downstream insulin signalling pathway, resulting in hepatic IR[10]. Zhao's team found that WD repeat domain protein 6 (WDR6) was up-regulated in the livers of mice with IR, and its expression level was positively correlated with hepatic lipid content; through combined transcriptomics and other multi-omics analyses, it was found that WDR6 promotes the phosphorylation of serine/threonine protein phosphatase 1, which enhances fatty acid synthetase transcription, leading to increased fatty acid synthesis and increased hepatic lipid triacylglycerol production. This study suggests that WDR6 is an effective target for the treatment of hepatic steatosis[11].

2.2 Hepatic IR and mitochondrial dysfunction

Mitochondria are organelles that maintain the energy required for cellular activity and coordinate energy metabolism through substrate oxidation, the tricarboxylic acid cycle, oxidative phosphorylation for the synthesis of adenosine triphosphate (ATP), and the generation of reactive oxygen species (ROS). A variety of mitochondria-related factors are involved in the development of NAFLD, including reduced β-oxidation, damage and depletion of the electron transport chain (ETC), excessive ROS production, oxidative stress-mediated cellular damage, and alterations in mitochondrial ultrastructure, which can induce IR[12]. Jin et al.[13] found that the tumor necrosis factor (TNF)-α / Myc interaction zinc-finger protein (Miz) 1-positive feedback loop is a key component in promoting non-alcoholic steatohepatitis (NASH) progression by an essential molecular mechanism, which mainly exacerbates mitochondrial damage by inhibiting mitochondrial autophagy in hepatocytes, leading to NAFLD progression. Mitochondrial autophagy is the selective removal of dysfunctional or loss-of-function mitochondria by autophagosomes, which is regulated by Parkin protein and phosphatase and tensin homolog (PTEN)-induced putative kinase (PINK) 1. Studies have shown that in human NASH, Miz1 levels are reduced in hepatocytes. Miz1 binds to peroxiredoxin 6 (PRDX6) and remains in the cytoplasm, preventing PRDX6 from interacting with mitochondrial Parkin at the Cys431 locus and inhibiting Parkin-mediated mitochondrial autophagy. Meanwhile, decreased mitochondrial autophagy led to increased ROS and activation of nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain containing 3 (NLRP3) inflammasome, both of which increased the secretion of pro-inflammatory factors, which in turn activated the release of TNF-α and interleukin (IL)-1β from macrophages. TNF-α induced the degradation of Miz1 via E3 ubiquitination, which led to a further decrease in hepatocyte mitochondrial autophagy. Thus, it generates a positive feedback loop that drives NAFLD progression. It has also been

proposed that receptor-interacting protein kinase (RIPK) 3 is involved in impairing mitochondrial function during NAFLD[14]. Its deletion ameliorates mitochondrial dysfunction in response to fatty acid overload in hepatocytes, which may be related to the upregulation of the peroxisome proliferator-activated receptor γ (PPARγ). Still, the specific pathway remains to be explored. Mitochondrial function and structure changes exacerbate hepatic fat accumulation, which triggers inflammation and fibrosis. Fat accumulation promotes the onset and progression of NAFLD.

2.3 Hepatic IR and the inflammatory response

Chronic inflammation is a hallmark of metabolic diseases, and in NAFLD, elevated pro-inflammatory cytokines induce IR[15]. This in turn disrupts the metabolic balance of the liver. Kupffer cells are macrophages located in the hepatic sinusoids, which produce IL-6 and TNF-α when inflammation occurs in the liver. Inflammatory factors, fatty acids, and other factors activate the inhibitory kappa B kinase β (IKKβ), which phosphorylates IRS proteins at the inhibitory serine site to induce IR. Nuclear factor-κB (NF-κB) also affects insulin signaling by transcriptionally inducing tyrosine phosphatase protein 1B (PTP1B) and suppressor of cytokine signaling 3 (SOCS3)[8]. In addition, inflammatory vesicles are closely associated with the development of metabolic diseases, as they activate caspase-1/11 to release IL-1 and IL-18 from cells, allowing inflammatory responses to occur[15]. It has been shown that in high-fat-induced metabolic syndrome, IL-18 inhibits lipid formation and ameliorates IR. In the presence of ROS, oxidized mitochondrial DNA (ox-mtDNA) and thioredoxin-interacting protein (TXNIP) activate the NLRP3 inflammasome[16], resulting in reduced phosphorylation of the AKT-Ser307 site and inhibition of IRS/AKT signaling pathway. Inhibition and impaired insulin-stimulated glucose uptake by hepatocytes, leading to hepatic IR. This role of NLRP3 has been demonstrated in rodents fed a high-fat diet, which reduces hepatic steatosis by inhibiting the NLRP3 inflammasome pathway[17]. Inflammatory vesicle dysfunction leads to an excessive hepatic inflammatory response, allowing NAFLD to progress to hepatic fibrosis.

2.4 Liver IR and imbalance of gut microbiota

The production of the gut microbiome and its metabolites promotes IR in the liver and is involved in the pathogenesis of NAFLD. An imbalance in the gut microbiota is defined as a bacterial translocation and an increase in intestinal permeability, leading to an increase in fatty acid absorption. This increased intestinal permeability allows bacterial migration across the intestinal epithelial barrier, along with the release of toxic bacterial products, bile acids, lipopolysaccharides (LPS), and proinflammatory cytokines, which are now thought to migrate mainly through the portal vein and activate Toll-like receptors (TLRs) on Kupffer cells, which further activate NF-κB, resulting in an inflammatory cascade that promotes development of NAFLD[18]. The gut microbiota of NAFLD patients is enriched in ethanol-producing bacteria, such as Escherichia coli, which produces ethanol under anaerobic conditions. Some studies have compared the microbiota of NAFLD patients with those of healthy controls, with the former producing more ethanol, which can stimulate the NF-κB signaling pathway by impairing the intestinal barrier function, leading to increased levels of LPS. LPS plays an important role in mediating chronic low-grade inflammation by activating the ERS GRP78-IRE1α-ASK1 signaling pathway, which promotes the persistence of metabolic syndrome[19].

Intestinal microbiota can also alter bile acid metabolism. Bound bile acids in human body are degraded by intestinal microbiota and converted to secondary bile acids. Secondary bile acids bind to the farnesoid X receptor (FXR) and can stimulate insulin secretion and increase its sensitivity. At the same time, secondary bile acids activate the Takeda G protein-coupled receptor 5 (TGR5)[20], and TGR5 stimulates the release of glucagon-like peptide-1(GLP-1) from the gut. Therefore, selective modulation of FXR in the gut may be an effective therapeutic strategy for the treatment of NAFLD.

2.5 Hepatic IR and oxidative stress

The interaction between oxidative stress and hepatic IR accelerates hepatocellular injury and inflammatory response, ultimately leading to liver fibrosis. It has been documented that detoxification pathways are weakened in the liver of NAFLD patients, leading to increased ROS production[21]. ROS activate inflammatory signaling pathways, such as NF-κB, c-Jun N-terminal kinase (JNK), and PKC pathways, which stimulate the secretion of pro-inflammatory factors by the Kupffer cells to accelerate the progression of NAFLD. In addition, FFA can also activate inflammatory signaling, impair mitochondrial function, and increase ROS production, leading to serine phosphorylation of IRS proteins and causing IR. It has been reported that the NF-κB/Orai1 pathway affects ROS production and further enhances endoplasmic Reticulum stress (ERS)[22] during NAFLD pathology and facilitates NAFLD development. Koliaki *et al.*[23] found that NASH patients had additional increased mitochondrial ROS production and damage of oxidative function compared to patients with simple steatosis, revealing the important role of oxidative stress in NAFLD.

Currently, iron death as a form of non-apoptotic cell death has been found in about 1/3 of patients with iron overload in NAFLD, as evidenced by elevated serum ferritin concentrations[24-25]. Therefore, iron-induced organ damage may play a role in the progression of NAFLD. In IR, excess FFA leads to upregulation of mitochondrial citric acid cycle activity, resulting in increased production of ROS and lipid peroxidation,

which leads to hepatocyte injury. Due to the pro-oxidant capacity of iron, iron and iron overload are important factors in ROS production and the development of NAFLD and NASH[26]. Increased iron accumulation and exacerbated steatohepatitis were found in mice[27]. Similarly, another model of mice fed with dietary iron showed elevated levels of lipid peroxidation derivatives and exhibited more severe histologic manifestations of NASH[28]. However, previous studies have shown no clinical studies linking IR, iron metabolism, oxidative stress, and NAFLD to NASH.

2.6 Hepatic IR and endocrine hormones

Growth hormone is produced in a pulsatile manner by the anterior pituitary gland. It stimulates the production of insulin-like growth factor 1 (IGF-1) via JAK2 and signal transducer and activator of transcription (STAT) 5. The relationship between IGF-1 and IR is well established. Growth hormone deficiency promotes intrahepatic fat accumulation. Studies have shown that serum IGF-1 and growth hormone levels are low in NAFLD patients and correlate with disease severity[29]. Thyroid hormone (TH) acts on thyroid hormone receptor (TR) α to stimulate hepatic lipogenesis, and plays a greater role in fatty acid β-oxidation when it acts on TR β. TH induces hepatic steatosis, and there is a strong correlation between NAFLD and thyroid dysfunction[30], but the relationship between the two and IR has been poorly studied. There is increasing evidence that androgens are important mediators in regulating hepatic fat content, and their physiological levels can prevent fatty liver disease, IR and related metabolic syndromes, etc. In male 5α reductase type 1 and androgen receptor knockout mice fed a high-fat diet, the experimental group developed IR and impaired glucose tolerance earlier than the control group, and also developed hepatic steatosis [31]. Higher levels of androgen deficiency due to testicular resection were observed in males. In addition, higher levels of triacylglycerols were observed in male mice with androgen deficiency due to orchiectomy[32]. The importance of endocrine hormones in NAFLD should not be ignored. However, there are still few studies and the specific molecular mechanisms need to be supported by a large amount of experimental data.

2.7 Other Mechanisms

The process by which the autophagic system selectively recognizes and degrades intracellular lipids is known as lipophagy. Impaired autophagy has been shown to be associated with susceptibility to NAFLD in experimental and clinical studies[33]. Furthermore, it has been shown that hepatic autophagy is inhibited in obesity-induced IR mice due to reduced expression of autophagy-related genes or proteolytic cleavage of essential autophagy proteins by calpain. In addition, animals with targeted deletion of autophagy in specific tissues exhibited IR[34]. These findings suggest that autophagy dysregulation plays an important role in the progression of IR and NAFLD. ERS has been observed to be associated with IR in patients with NAFLD, and ERS is involved in the development of IR with an increase in unfolded protein response (UPR)[36]. Five gene variants have been found to be strongly associated with NAFLD susceptibility and progression[37], namely transmembrane 6 superfamily member 2 (TM6SF2), glucokinase regulator gene (GCKR), membrane-bound O-acyltransferase 7 (MBOAT7), and hydroxysteroid 17β dehydrogenase 13 (HSD17β13). All of these gene variants are associated with insulin sensitivity and IR. In addition, the role of some non-coding RNAs in NAFLD has also attracted attention[36].

3 Conclusion

NAFLD has become the most common chronic liver disease in the world, and there is no specific drug in the clinic. IR plays a key role in the progression of NAFLD. The molecular mechanism of IR in NAFLD is very complex. Among all the mechanisms by which hepatic IR leads to NAFLD, FFA-induced lipotoxicity and activation of inflammatory response are the two most important factors. Therefore, drugs that improve lipid metabolism and produce anti-inflammatory effects hold great promise in the prevention and treatment of NAFLD by hepatic IR, but more experimental data are still needed to support them.

Conflict of interest All authors declare no conflict of interest

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· 学术前沿 ·

肝脏胰岛素抵抗引起非酒精性脂肪性肝病相关机制研究进展

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摘要：非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）指除外酒精和其他明确损肝因素所致的肝细胞弥漫性大泡性脂肪变性和脂肪贮积为特征的临床病理综合征。在病因学上，NAFLD 与肝脏胰岛素抵抗（insulin resistance，IR）具有高度的相关性，阐明肝脏 IR 发病机制有望为 NAFLD 药物研究提供理论支持。因此，本文就肝脏 IR 引起 NAFLD 相关机制的研究进展做一综述。

关键词：非酒精性脂肪性肝病；肝脏胰岛素抵抗；分子机制；脂质代谢；炎症反应

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Research progress on the mechanism of non-alcoholic fatty liver disease caused by hepatic insulin resistance

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Abstract: Non-alcoholic fatty liver disease (NAFLD) refers to a clinicopathological syndrome characterized by macrovesicular steatosis and lipid accumulation of hepatocytes, except for alcohol and other specific factors associated with liver damage. In terms of etiology, NAFLD is highly correlated with hepatic insulin resistance (IR). Elucidation of the pathogenesis of hepatic IR is expected to provide theoretical support for drug research in NAFLD. Therefore, this article reviews the research progress on the mechanism of NAFLD caused by hepatic IR.

Keywords: Non-alcoholic fatty liver disease; Hepatic insulin resistance; Molecular mechanism; Lipid metabolism; Inflammatory response

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非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)是肝脏疾病最常见的病因之一,其患病率在全球范围内持续上升,约为 25%[1]。在中国,NAFLD 患病率变化与肥胖、2 型糖尿病和代谢综合征的流行趋势相平行。NAFLD 与糖尿病、动脉硬化性心血管疾病及结直肠肿瘤等的高发密切相关,目前已经成为影响人类健康的隐形杀手,但国内外还没有针对 NAFLD 治疗的特效药物。因此明确其作用机制,有效阻止疾病进展成为了亟待解决的问题。大量临床研究表明胰岛素抵抗(insulin resistance, IR)是 NAFLD 发生的关键环节,而脂肪贮积则是 NAFLD 发生的特征表现[2]。本文将进一步探索 NAFLD 与 IR 之间的关系,阐明其具体分子机制,为 NAFLD 药物研发提供更加有利的理论支持。

1　NAFLD 与 IR 之间的关系

NAFLD 发生的病理生理机制主要与肝细胞脂肪变性有关,这种脂肪变性主要是由于肝脏脂质代谢调节受损,其中,肝脏 IR 和游离脂肪酸(free fatty acid, FFA)的增加发挥着重要作用[3]。正常情况下,胰岛素在肝脏中发挥的生理功能包括促进糖原合成、抑制糖异生、促进脂肪合成并抑制其分解。当靶器官对胰岛素敏感性降低,即出现 IR 时,机体会代偿性产生更多的胰岛素来满足人体糖代谢需求,导致血液中胰岛素维持在较高水平。在 IR 状态下,胰岛素受体信号通路传导受损,糖异生不再被抑制,但肝脏脂质沉积却能继续增加,进而诱发 NAFLD 的产生。有研究发现,在 NAFLD 患者中,IR 可提升脂肪组织释放 FFA 的速度[4],而 FFA 的升高不仅可以刺激胰岛素分泌,并且会使肝脏脂肪代谢异常,加重肝细胞脂肪变性。

肝脏脂质从头合成途径(*de novo* lipogenesis, DNL)是引起 NAFLD 发生的重要因素之一,研究显示胰岛素可以促进肝脏 DNL[5]。因此在 IR 期间,体内过多的胰岛素会相对促进肝脏 DNL,使得肝脏脂肪变性增加。胰岛素还可刺激脂肪组织分泌脂肪因子和炎性细胞因子,最终导致脂肪组织分解失调[6-7]。而肝脏中的脂肪堆积会增加脂毒性,导致氧化应激增加,严重损害肝脏中线粒体功能,造成脂肪酸堆积,这种正反馈环的存在使得 NAFLD 持续进展。

2　NAFLD 与 IR 相关分子机制

胰岛素通过与胰岛素受体底物(IRS)结合,经过 IRS 下游信号途径,如磷脂酰肌醇-3-激酶(PI3K)、丝裂原激活蛋白激酶(MAPK)等途径逐级信号传导,通路的任一环节出现异常均能引起 IR。NAFLD 诱发 IR 的机制较为复杂,与脂肪组织氧化应激,线粒体功能紊乱、炎症、肠道菌群失调等因素有关,现就相关分子机制进行逐一探讨。

2.1　肝脏 IR 与脂代谢　脂质诱导的肝脏 IR 主要是通过激活神经酰胺或二酰甘油-蛋白激酶 C(PKC)通路来抑制 IRS1 的磷酸化,进一步抑制 PI3K/AKT 途径,该途径一方面可以使糖原合成酶的激活减少,抑制糖原合成,另一方面还可以减少叉头框转录因子(FoxO1)的失活来增加肝脏糖异生,生成的葡萄糖通过葡萄糖转运蛋白 2(GLUT-2)通道释放入血,使得肝脏对胰岛素的敏感性显著降低[8]。此外,有研究指出,长期以来,在众多与非酒精性脂肪肝相关的脂质分子中,二酰甘油被认为是引起肝脏 IR 的关键分子[9]。耶鲁大学 Geradshulman 团队揭示了此过程中的具体分子机理,在 NAFLD,肝脏中积累的细胞膜 sn-1,2-二酰甘油激活 PKC 蛋白,激活的 PKC 蛋白锚定在细胞膜上磷酸化胰岛素受体的 T1160 位点;该位点被磷酸化后,抑制了胰岛素受体的激活,从而阻止下游胰岛素信号通路的传导,导致肝脏 IR[10]。赵家军团队发现 WD 重复域蛋白 6(WDR6)在 IR 小鼠的肝脏中上调,其表达水平与肝脏脂质含量呈正相关;通过转录组学等多组学联合分析,发现 WDR6 可促进丝氨酸/苏氨酸蛋白磷酸酶 1 的磷酸化,后者通过增强脂肪酸合成酶转录导致脂肪酸合成三酰甘油增加,肝脏脂质沉积,该研究表明 WDR6 是治疗肝脏脂肪变性的有效靶点[11]。

2.2　肝脏 IR 与线粒体功能紊乱　线粒体是维持细胞活动所需能量的细胞器,它通过底物氧化、三羧酸循环、氧化磷酸化合成三磷酸腺苷和形成活性氧(ROS)来协调能量代谢。多种线粒体相关因素参与了 NAFLD 的发生发展,包括 β 氧化减少、电子传递链(ETC)受损和耗竭、ROS 产生过多、氧化应激介导的细胞损伤以及线粒体超微结构的改变,这些因素均可诱导 IR[12]。Jin 等[13]发现肿瘤坏死因子-α(TNF-α)/锌指蛋白 1(Miz1)正反馈环是促进非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)进展的重要分子机制,主要是通过抑制肝细胞线粒体自噬来加重线粒体损伤,从而导致 NAFLD 进展。线粒体

自噬是自噬体选择性清除功能失调或失去功能的线粒体,其受 Parkin 蛋白和蛋白酪氨酸磷酸酶基因(PTEN)诱导的蛋白激酶(PINK1)调控。研究显示在人类 NASH 中,Miz1 含量在肝细胞中减少,Miz1 与过氧还原蛋白 6(PRDX6)结合并停留在胞质中,阻止了 PRDX6 在 Cys431 位点与线粒体 Parkin 相互作用,抑制 Parkin 介导的线粒体自噬。同时,线粒体自噬减少使得 ROS 增加和核苷酸结合寡聚化结构域样受体蛋白 3(NLRP3)炎症小体的激活,两者增加促炎因子的分泌,进而激活巨噬细胞释放 TNF-α 和白细胞介素(IL)-1β。TNF-α 可通过 E3 泛素化诱导 Miz1 的降解,从而导致肝细胞线粒体自噬进一步减少,因此它产生了一个正反馈循环,推动 NAFLD 进展。另有学者提出受体相互作用蛋白激酶(RIPK3)参与了 NAFLD 过程中线粒体功能的损害[14],可能与过氧化物酶体增殖剂活化受体 γ(PPARγ)的上调有关,但具体通路有待探索。线粒体功能和结构的变化加剧了肝脏的脂肪堆积,引发了炎症和纤维化,促进 NAFLD 的发生和发展。

2.3　肝脏 IR 与炎症反应　慢性炎症是代谢性疾病的特征,在 NAFLD 中,促炎细胞因子的升高可诱导 IR,进而打破肝脏的代谢平衡[15]。Kupffer 细胞是位于肝窦内的巨噬细胞,肝脏发生炎症时产生 IL-6 和 TNF-α。炎症因子、脂肪酸等可以激活核因子-κB 激酶亚单位 β(IKKβ),IKKβ 会在丝氨酸抑制位点磷酸化 IRS 蛋白以诱导 IR。核因子-κB(NF-κB)还通过转录诱导酪氨酸磷酸酶蛋白 1B(PTP1B)和细胞因子信号传导抑制剂 3(SOCS3)来影响胰岛素信号传导[8]。此外,已有研究发现炎症小体与代谢性疾病的发生发展关系密切,其可以活化 Caspase-1/11 使得 IL-1 和 IL-18 从细胞当中释放出来,炎症反应得以发生[15]。已有研究表明在高脂诱导的代谢综合征中,IL-18 抑制脂质形成,同时可以改善 IR。在 ROS 情况下,氧化线粒体 DNA(ox-mtDNA)与硫氧还蛋白相互作用蛋白(TXNIP)可激活炎症小体 NLRP3[16],使得 AKT-Ser307 位点磷酸化减少,IRS/AKT 信号途径受抑制,胰岛素刺激肝细胞对葡萄糖的摄取受损,从而导致肝脏 IR。NLRP3 的这种作用已在高脂饮食喂养的啮齿动物中得到证实,这些啮齿动物通过抑制 NLRP3 炎症小体通路减少肝脏脂肪变性[17]。炎症小体功能障碍导致肝脏炎症反应过度,使 NAFLD 逐渐进展为肝纤维化。

2.4　肝脏 IR 与肠道菌群失衡　肠道微生物组及其代谢产物的产生可促进肝脏中的 IR,参与 NAFLD 的发病机制。肠道菌群失衡是指菌群易位,肠道渗透性增加,导致脂肪酸吸收增加。这种肠道渗透性的增加使细菌通过肠道上皮屏障发生迁移,同时释放有毒细菌产物、胆汁酸、脂多糖(LPS)和促炎细胞因子,目前认为这些产物主要通过门静脉转移,激活 Kupffer 细胞上的 Toll 样受体(TLR),进一步激活 NF-κB,导致炎症级联反应,从而促进 NAFLD 的发展[18]。NAFLD 患者的肠道菌群中富含可以产生乙醇的细菌,如:大肠杆菌,其在无氧条件下产生乙醇,有研究将 NAFLD 患者与健康人群的微生物群相比,前者可产生更多的乙醇,而乙醇可通过损害肠道屏障功能来刺激 NF-κB 信号途径,导致 LPS 浓度升高。LPS 可通过激活 ERS GRP78-IRE1α-ASK1 信号通路在介导慢性低度炎症中发挥重要作用,促进代谢综合征的持续存在[19]。

肠道菌群还可以改变胆汁酸代谢,人体内的结合胆汁酸被肠道菌群分解转换为继发性胆汁酸,继发性胆汁酸与法尼样 X 受体(FXR)结合,可促进胰岛素分泌并增加其敏感性。同时,继发性胆汁酸可激活 G 蛋白胆汁酸偶联受体 5(TGR5)[20],TGR5 可刺激肠道释放胰岛素样生长因子-1(GLP-1)。因此,在肠道中选择性调节 FXR 为治疗 NAFLD 可提供有效的治疗策略。

2.5　肝脏 IR 与氧化应激　氧化应激和肝脏 IR 之间的相互作用会加速肝细胞损伤和炎症反应,并最终导致肝纤维化。有文献记载,NAFLD 患者肝脏中的解毒途径减弱,导致 ROS 的产生增加[21]。ROS 激活炎症信号通路,如 NF-κB、c-Jun 氨基末端激酶(JNK)、PKC 通路,刺激 Kupffer 细胞分泌促炎因子加速 NAFLD 的进展。此外,FFA 也可激活炎症信号传导,损伤线粒体功能,增加 ROS 产生,导致 IRS 蛋白的丝氨酸磷酸化并引起 IR。有学者指出在 NAFLD 病理过程中 NF-κB/Orai1 通路影响 ROS 的产生并进一步增强内质网应激(ERS)[22],促进 NAFLD 的发展。Koliaki 等[23]发现,与单纯脂肪变性患者相比,NASH 患者表现出额外的线粒体 ROS 生成增加和氧化功能下降,揭示了氧化应激反应在 NAFLD 中的重要作用。

当前,铁死亡作为非凋亡性细胞死亡的一种形式,在 NAFLD 中,发现约 1/3 的患者存在铁过量,表现为血清铁蛋白浓度升高[24-25]。因此,铁诱导的器官损伤可能在 NAFLD 疾病进展中起作用。在 IR 中,过量的 FFA 会导致线粒体柠檬酸循环活性上调,导致 ROS 和脂质过氧化的产生增加,从而导致肝细胞损伤。由于铁的促氧化能力,铁和铁过载被认为是 ROS 产生以及 NAFLD 和 NASH 发展的重要因素[26]。

在小鼠中发现更多的铁积累和加重的脂肪性肝炎[27]。同样,另一种膳食铁喂养小鼠的模型显示脂质过氧化衍生物水平升高,表现出更严重的 NASH 组织学表现[28]。然而,既往研究显示,还没有临床研究将 IR、体内铁代谢、氧化应激以及 NAFLD 和 NASH 联系起来。

2.6　肝脏 IR 与内分泌激素　生长激素由垂体前叶以脉冲方式产生,并通过 JAK2 和信号传导及转录激活蛋白(STAT5)刺激胰岛素样生长因子 1(IGF-1)的生成。IGF-1 与 IR 关系已明确。生长激素缺乏会促进肝内脂肪堆积,研究表明 NAFLD 患者的血清 IGF-1 和生长激素水平低,且与疾病严重程度相关[29]。甲状腺激素(TH)作用于甲状腺激素受体 α 可刺激肝脏脂肪生成,作用于甲状腺激素受体 β 时在脂肪酸 β 氧化中发挥更大的作用。TH 可诱导肝脏脂肪变性,NAFLD 与甲状腺功能失调之间存在密切相关性[30],但两者与 IR 的关系研究甚少。越来越多的证据表明雄激素是调节肝脏脂肪含量的重要介质,其生理水平可以预防脂肪肝疾病、IR 及相关代谢综合征等,将雄性 5α 还原酶 1 型和雄激素受体敲除的高脂饮食小鼠与对照组相比,实验组更早出现 IR 和糖耐量受损,还会出现肝脏脂肪变性[31],另外在睾丸切除导致雄激素缺乏的雄性小鼠中观察到更高的三酰甘油含量[32]。内分泌激素在 NAFLD 中的重要性不容忽视,但目前相关的研究还很少,具体的分子机制还需要大量的实验数据支撑。

2.7　其他机制　自噬系统选择性识别并降解细胞内脂质的过程称为脂质吞噬。在实验和临床研究中,自噬受损已被证明与易患 NAFLD 相关[33]。此外,已经表明,由于自噬相关基因的表达减少或钙蛋白酶对必需自噬蛋白的蛋白水解裂解,肥胖诱导的 IR 小鼠的肝自噬受到抑制。此外,在特定组织中靶向缺失自噬的动物表现出 IR[34]。这些研究结果表明,自噬失调在 IR 和 NAFLD 的进展中起着重要作用。另外,在 NAFLD 患者中可观察到 ERS 与 IR 相关,ERS 随着未折叠蛋白(UPR)的增加而参与 IR 的发展[35]。目前已发现有五种基因变体与 NAFLD 的易感性和进展密切相关[36],即跨膜 6 超家族成员 2(TM6SF2)、葡萄糖激酶调节因子(GCKR)、膜结合蛋白 O-酰转移酶 7(MBOAT7)、羟基类固醇 17β 脱氢酶 13(HSD17β13)。这些基因变体都与胰岛素敏感性和 IR 有关。此外,一些非编码 RNA 在 NAFLD 中的作用也引起关注[37]。

3　结　语

NAFLD 已经成为全球最常见的慢性肝病,目前在临床上没有特效药。IR 在 NAFLD 的进展中起着关键作用,IR 在 NAFLD 中的分子机制非常复杂,在肝脏 IR 导致 NAFLD 的所有机制中,FFA 诱导的脂毒性及炎症反应的激活是两个最重要的因素。因此,药物改善脂质代谢并产生抗炎作用,在肝脏 IR 预防和治疗 NAFLD 方面具有广阔前景,但仍需要更多的实验数据支撑。

利益冲突　所有作者均声明不存在利益冲突

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