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代谢相关脂肪性肝病与心血管疾病共病机制研究进展

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[摘要]　代谢相关脂肪性肝病(MAFLD)与动脉粥样硬化、高血压病、心力衰竭(简称心衰)及心房颤动(简称房颤)等疾病密切相关,可通过多种病理机制促进心血管疾病(CVD)的发展,包括糖脂代谢功能障碍、慢性低度炎症、肾素-血管紧张素与交感神经系统亢进、促进氧化应激与血栓形成及肠道菌群紊乱等。本文就 MAFLD 与 CVD 共病机制最新研究进展进行综述。

[关键词]　代谢相关脂肪性肝病;　胰岛素抵抗;　慢性低度炎症;　脂代谢异常;　氧化应激;　肾素-血管紧张素系统;　肠道菌群紊乱

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代谢相关脂肪性肝病(MAFLD)全球患病率已超过 25%,成为最常见的慢性肝病[1-2]。MAFLD 患者心血管疾病(CVD)发病率与心血管死亡风险显著升高,成为 MAFLD 患者的首要死因。美国国家健康和营养调查(NHANES)结果显示,即使调整人口学、疾病史及代谢因素,罹患 MAFLD 仍可导致 CVD 发病风险增加 23%[3]。两项前瞻性队列研究报道,MAFLD 患者心血管死亡风险是健康对照的 2~3 倍[4-5]。MAFLD 可通过多种机制促进 CVD 发生与进展,包括糖脂代谢异常、免疫与系统炎症、神经内分泌稳态失衡、血栓形成激活及肾素-血管紧张素系统(RAS)亢进等[6]。同时,MAFLD 与 CVD 之间存在许多共同危险因素,协同性促进 CVD 的发病与进展[7-8]。本文就 MAFLD 与 CVD 之间共病机制研究进展予以综述。

一、胰岛素抵抗(IR)与内皮细胞功能障碍

MAFLD 患者肝脏脂肪含量与空腹血糖及 IR 指数呈正相关[9-10]。当出现 IR 时,脂肪组织中胰岛素对甘油三酯(TG)分解抑制作用减弱,大量游离脂肪酸(FFAs)释放入血液并进入肝脏;肝脏则表现为胰岛素抑制糖异生作用减弱、促进糖原合成能力降低,葡萄糖利用障碍引起血糖升高,后者负反馈刺激胰岛 β 细胞分泌更多胰岛素,造成外周高胰岛素血症。胰岛素可促进固醇调节元件结合蛋白 1c(SREBP-1c)和碳水化合物反应元件结合蛋白(ChREBP)调控的脂质从头合成,并抑制极低密度脂蛋白(VLDL)所介导的 TG 分泌出肝脏,加之血清 FFAs 大

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量流入肝脏,导致肝内 TG 合成增加和脂质蓄积,引起肝细胞“脂毒性”,促进 MAFLD 发生与进展[11]。

IR 可导致血管内皮细胞功能障碍,参与动脉粥样硬化发生与进展。胰岛素作用于血管内皮细胞,激活磷脂酰肌醇 3 激酶/蛋白激酶 B 信号通路,上调内皮一氧化氮(NO)合酶表达,促进 NO 的生成与释放,后者以旁分泌形式作用于血管平滑肌细胞,发挥舒张血管的作用[12]。当内皮细胞内发生 IR 时,NO 生成减少而缩血管物质内皮素 1 生成增加,引起内皮细胞功能障碍与血管壁僵硬度增加,促进高血压发生与进展[13]。同时,NO 能够抑制内皮细胞表面黏附分子表达、血小板聚集,抑制炎症因子产生与平滑肌细胞增殖[12]。IR 发生时,内皮细胞表面黏附分子 ICAM-1 与 VCAM-1 表达升高,有利于循环中单核-巨噬细胞黏附并向内膜下趋化浸润。巨噬细胞随即吞噬和摄取氧化低密度脂蛋白(ox-LDL)转变为泡沫细胞,分泌大量炎症因子,促使动脉粥样斑块形成[13]。

二、慢性低度炎症与动脉粥样硬化

MAFLD 患者血浆高敏 C 反应蛋白、IL-6 等炎症因子水平显著升高,且在非酒精性脂肪性肝炎(NASH)患者中进一步增高[14]。肝脏脂肪变性与氧化应激可诱导炎症标志物的分泌,如 IL-6、肿瘤坏死因子、胎球蛋白 A(Fetuin-A)、C 反应蛋白与纤维蛋白原等。Fetuin-A 是肝细胞分泌的一种蛋白,能够抑制胰岛素受体酪氨酸激酶的活性,同时也是细胞膜 Toll 样受体 4 的内源性配体,介导脂质诱导的 IR 发生[15]。Fetuin-A 可诱导体内慢性低度炎症产生,与内皮功能障碍、颈动脉粥样硬化密切相关,并可增加心肌梗死、缺血性卒中和 2 型糖尿病(T2DM)的发病风险[16-17]。C 反应蛋白能增加内皮细胞黏附分子与纤溶酶原激活物抑制剂-1 表达,抑制 NO 合成,促进巨噬细胞吞噬摄取 ox-LDL,加剧血管炎症反应和动脉粥样硬化[18]。此外,相比正常人群,MAFLD 患者体内脂联素水平降低。脂联素能激活 AMP 活化蛋白激酶与过氧化物酶体增殖物激活受体 α(PPARα)通路,增强肝脏和骨骼肌中脂肪酸氧化。脂联素还可抑制肥胖和脂多糖诱导的内毒素血症小鼠巨噬细胞 MyD88/核因子(NF)-κB 炎症通路激活,发挥抗炎和抗氧化的作用[19]。MAFLD 患者体内长期慢性低度炎症状态,无疑将促进高血压、动脉粥样硬化等 CVD 的发生与进展。

三、脂代谢紊乱与血脂异常

MAFLD 患者中普遍存在致动脉粥样硬化性血脂异常,表现为血浆 TG、ox-LDL 水平增加,高密度脂蛋白胆固醇(HDL-C)水平降低[20]。血浆中高胰岛素水平激活肝脏 SREBP-1c,启动下游基因乙酰辅酶羧化酶(ACC)与脂肪酸合成酶转录表达,促进肝脏脂质从头合成[21]。同时,中间产物丙二酰辅酶 A 生成增多,可抑制肉碱脂酰转移酶的活性,导致脂肪酸氧化分解降低和线粒体功能障碍,加剧肝细胞内脂质蓄积[21-22]。肝脏中 TG 增加会导致富含 TG 的脂蛋白 VLDL 组装和分泌增加,引起血浆中 TG 和致动脉粥样硬化脂蛋白水平升高[23]。此外,肝细胞内胆固醇水平增加还会抑制 SREBP2 通路,后者可增加 LDLR 和 PCSK9 转录和表达,最终导致肝细胞膜上 LDLR 表达的降低,肝脏摄取 LDL-C 减少[20]。此外,MAFLD 患者体内血管生成素样蛋白(ANGPTL3/8)水平升高可抑制脂蛋白脂酶的活性,促进肝细胞内 TG 蓄积[24]。ANGPTL8 还可抑制脂肪 TG 脂酶表达,减少细胞内 TG 水解、促进脂质蓄积[25]。线粒体内脂质氧化分解能量受限,促使 FFAs 重新酯化生成 TG,加重脂质与脂蛋白代谢异常,进而促进动脉粥样硬化。

四、氧化应激损伤与脂质过氧化

在 MAFLD 发生过程中,肝脏内 FFAs 过度蓄积与氧化分解,超出肝细胞正常代偿能力,引起内质网应激、线粒体功能障碍等,ROS 大量产生,导致氧化应激损伤与脂质过氧化,诱导脂肪变性与肝细胞死亡[26]。MAFLD 患者外周血与肝脏中谷胱甘肽、超氧化物歧化酶与过氧化氢酶水平降低,丙二醛水平升高[27],提示存在脂质过氧化与抗氧化能力过度耗竭。活检结果证实,MAFLD 患者肝细胞内脂质过氧化标志物 4-羟基壬烯醛表达增加,而在接受维生素 E 干预治疗后表达下降[28]。此外,NASH 患者中线粒体质量虽然增加,但呼吸效率降低 30% ~40%,并伴有线粒体解偶联和电子传递链泄漏[29],导致 NASH 患者肝内过氧化氢、脂质过氧化产物增多,DNA 氧化损伤加重,同时伴有抗氧化应激能力降低与炎症反应升高[29]。动物实验也证实类似结果,高脂饮食诱导的 MAFLD 大鼠中肝脏转氨酶、胰岛素与 IR 指数升高,伴有丙二醛与血管内皮生长因子(VEGF)水平升高。而在予锌-硒补充干预后,能够降低血浆丙二醛与 VEGF 水平及 TG/HDL-C 比值,从而降低 CVD 风险[30]。

五、RAS 过度激活

RAS 过度激活与 IR、机体炎症、氧化应激等密切相关,是高血压与心力衰竭(简称心衰)发生的重要病理机制。血管紧张素Ⅱ(Ang Ⅱ)作为 RAS 主要活性物质,能够刺激血管平滑肌收缩、促进醛固酮分泌增加,保钠排钾导致液体潴留,引起动脉血压升高与心脏负荷增加,心室重构和心衰风险增加。MAFLD 患者体内蓄积的内脏脂肪中肾素、血管紧张素原等 RAS 成分产生增多,是全身系统 RAS 亢进的重要来源[31]。Ang Ⅱ能够干扰胰岛素受体及其下游信号通路,促进 IR 发生[32]。同时,Ang Ⅱ还可影响血浆 FFAs 与 TG 的利用、抑制肝脏脂肪酸氧化、促进肝脏 VLDL 分泌及脂质的从头生成,影响肝内 TG 蓄积,参与 MAFLD 致病过程[33]。动物实验结果表明,肾素、血管紧张素转换酶(ACE)敲除小鼠及肝脏特异性血管紧张素Ⅱ受体(AT_1R)敲除小鼠的肝脂肪变性显著减轻[33]。临床研究证实,合并高血压病的 MAFLD 患者使用 ACE 或 AT_1R 抑制剂,能够减轻肝脂肪变性与转氨酶升高,改善 IR,延缓纤维化进展,尤其是在合并肥胖或 T2DM 的高危人群中[34]。

六、肠道菌群紊乱

肠道菌群紊乱与 MAFLD 和动脉粥样硬化、心衰、房颤等密切相关。肝脏与肠道在解剖学与功能上均存在着密切联系,门静脉收集来自肠道富含营养物质的血液,回流入肝脏并负责供应其 70% 的血流[35]。同时,肝脏也接收了大量来自肠道的病原体、短链脂肪酸、次级胆汁酸、胆碱、内源性乙醇及各种外毒

素或细菌内毒素[36]。正常情况下，肝细胞能够迅速清除这些病原体与毒素，避免其进入外周循环。而 MAFLD 患者出现明显肠道微生物失调、菌群易位，并伴有肠上皮通透性增加[37-38]，导致肠道来源的病原体或微生物相关模式分子及内毒素等大量进入肝脏，诱发肝内免疫炎症。肝实质细胞与固有免疫细胞激活后产生大量 DAMPs、炎症趋化因子、急性期蛋白等释放入血，加剧全身系统慢性炎症反应[39]。三甲胺 N-氧化物（TMAO）是目前已知与动脉粥样硬化关系最为密切的肠道代谢产物[40]。MAFLD 患者中肠道菌群发生紊乱，分解代谢红肉中的肉碱和胆碱，产生三甲胺增多，进入肝脏氧化生成 TMAO 并分泌入血，可促进心衰与动脉粥样硬化疾病进展[40]。

七、总结与展望

越来越多证据表明，MAFLD 可能是 CVD 的独立危险因素，与动脉粥样硬化、高血压病、心衰及房颤等发生密切相关。MAFLD 可通过多种病理机制促进 CVD 的发展，包括 IR、糖脂代谢紊乱、免疫炎症、RAS 与交感神经系统激活、氧化应激与血栓形成及肠道菌群紊乱等。同时，MAFLD 与肥胖、T2DM 及 IR 等密不可分，与 CVD 之间存在许多共同危险因素与致病机制。目前，包括法尼醇受体激动剂、PPARα/γ 双重激动剂、ACC 抑制剂等新型 MAFLD 治疗药物相关临床试验正在开展。此外，胰高血糖素样肽 1 受体激动剂、钠-葡萄糖共转运蛋白 2 抑制剂等新型降糖药物及传统噻唑烷二酮类、双胍类降糖药物与他汀类降脂药物等也被证实具有良好的改善 MAFLD 效果。

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