

· 综述 ·

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短链脂肪酸对肝纤维化的保护作用及其机制在胰腺纤维化中的类推应用

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摘要: 短链脂肪酸(SCFA)是膳食纤维经肠道微生物发酵产生的主要代谢产物。研究表明,SCFA不仅在能量代谢中发挥作用,更可作为重要信号分子,在缓解肝及胰腺纤维化进程中展现出显著潜力。其核心机制主要涉及:通过激活G蛋白偶联受体和抑制组蛋白去乙酰化酶活性,调控多种关键信号通路,从而抑制肝星状细胞(HSC)和胰腺星状细胞(PSC)的活化与增殖,干预纤维化形成的核心环节。同时,SCFA能有效减轻组织炎症反应、改善肠道屏障功能、调节肠道菌群平衡,间接阻止“肠-肝/胰轴”介导的纤维化进程。相较于SCFA在肝纤维化中的研究,其在胰腺纤维化中的研究较少。考虑到HSC及PSC高度同源,已在肝纤维化相关研究中证实的转录因子及蛋白在PSC中同样表达,提示其可能同样影响PSC活化。本综述系统梳理了近年SCFA在缓解肝纤维化及胰腺纤维化中的研究进展,旨在为胰腺纤维化的机制探索与干预策略提供新的思路。

关键词: 肝纤维化; 脂肪酸类; 肝星状细胞**基金项目:** 甘肃省科技重大专项计划项目(24ZDFA005); 甘肃省卫生行业优秀青年人才和骨干人才项目(GSWSQN2023-01)

Protective effect of short-chain fatty acids against liver fibrosis and analogical application of its mechanism to pancreatic fibrosis

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Abstract: Short-chain fatty acids (SCFA) are the main metabolic products generated by the fermentation of dietary fiber by gut microbiota. Studies have shown that SCFA not only play a role in energy metabolism, but also act as important signaling molecules, exhibiting a significant potential in alleviating liver and pancreatic fibrosis. The core mechanism of SCFA mainly involves the regulation of various key signaling pathways by activating G protein-coupled receptors and inhibiting the activity of histone deacetylase, thereby suppressing the activation and proliferation of hepatic stellate cell (HSC) and pancreatic stellate cell (PSC),

which is a key link in fibrosis formation. In addition, SCFA can effectively alleviate tissue inflammation response, improve intestinal barrier function, and regulate gut microbiota balance, thus indirectly preventing the process of fibrosis mediated by the “gut-liver/pancreas axis”. Compared with the research on SCFA in liver fibrosis, studies on their role in pancreatic fibrosis are limited. Given that HSC and PSC are highly homologous, the transcription factors and proteins that have been confirmed in liver fibrosis-related studies are also similarly expressed in PSC, suggesting that they may also influence the activation of PSC. This article systematically summarizes the recent advances in the research on SCFA in alleviating liver and pancreatic fibrosis, in order to provide new perspectives for exploring the mechanism of pancreatic fibrosis and developing related interventional strategies.

Key words: Liver Fibrosis; Fatty Acids; Hepatic Stellate Cells

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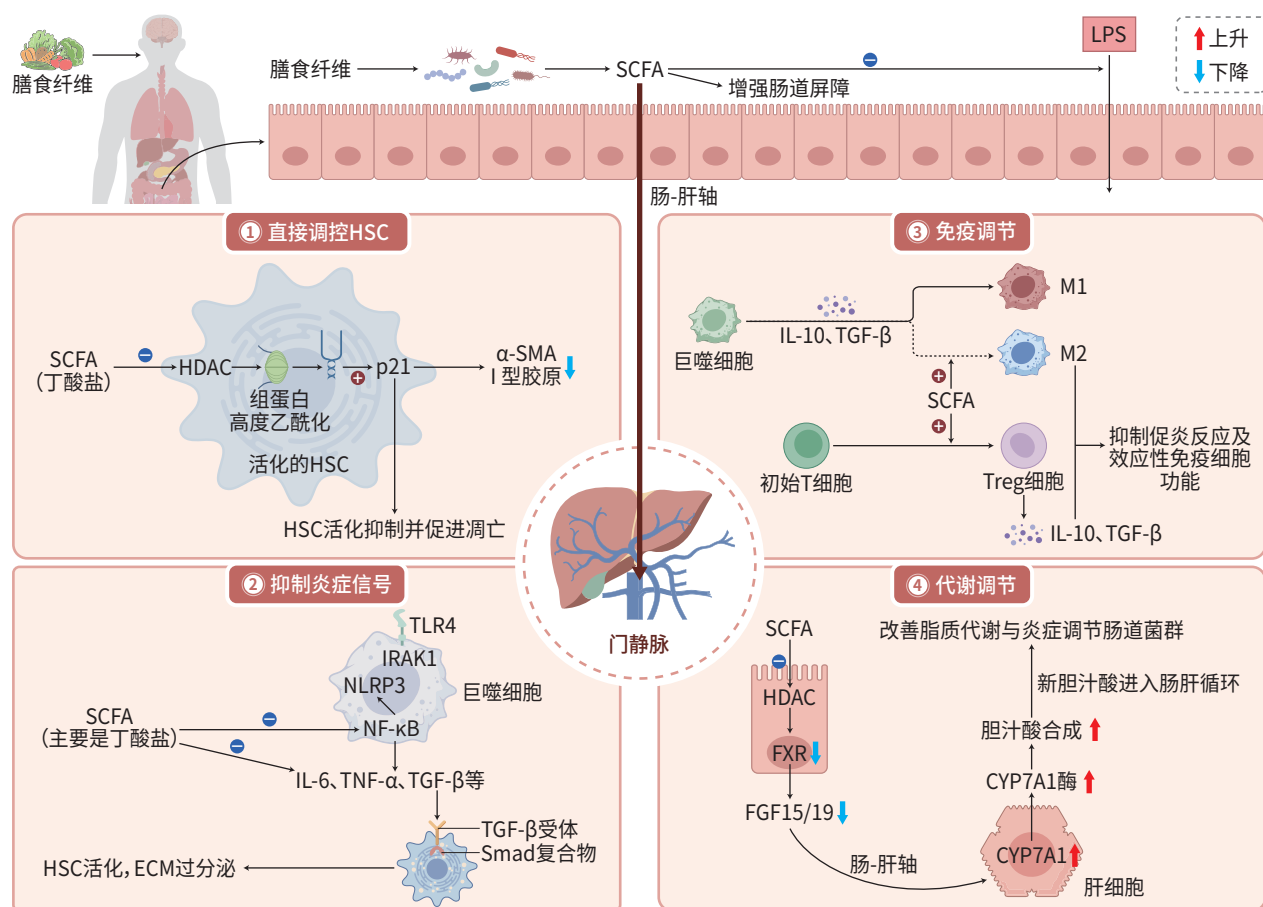
肝纤维化与胰腺纤维化是多种慢性肝病(如病毒性肝炎、酒精性肝病、非酒精性脂肪性肝炎)和慢性胰腺炎(如酒精性、梗阻性)共同的核心病理过程。其本质是肝脏或胰腺在长期反复组织损伤与修复过程中,细胞外基质(extracellular matrix, ECM)过度沉积与降解不足所致的瘢痕样改变^[1-2]。若纤维化持续进展,将最终导致肝硬化和肝衰竭,或胰腺内分泌与外分泌功能不全,甚至显著增加肝癌和胰腺癌的发生风险,严重威胁人类健康。目前,临床上除针对病因治疗和晚期器官移植外,尚缺乏能够有效逆转纤维化的特异性药物。因此,探寻干预纤维化发生发展的新靶点与新策略,已成为当前研究的热点与难点。

与此同时,人类与肠道菌群的相互作用,在全身健康与疾病中发挥核心作用。“肠-X轴”概念的兴起,揭示了肠道菌群失调及其代谢产物紊乱是远端器官疾病的重要驱动因素^[3]。在菌群产生的代谢物中,短链脂肪酸(short chain fatty acid, SCFA)是目前研究最为深入的类别之一。SCFA主要由膳食纤维经肠道细菌发酵产生,包括乙酸、丙酸和丁酸等。SCFA通过多种机制发挥广泛生理效应,其作为组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂调控基因转录,不仅通过G蛋白偶联受体(G protein-coupled receptor, GPCR)发挥作用,还可调节细胞能量代谢和氧化应激^[4-5]。基于这些机制,SCFA在维持肠道屏障完整性、调节免疫平衡方面具有重要作用。本文将聚焦于SCFA在肝纤维化中的保护作用,梳理其相关分子机制,并关注与肝星状细胞(hepatic stellate cell, HSC)高度同源的胰腺星状细胞(pancreatic stellate cell, PSC),强调二者在纤维化过程中的关联性,进而探讨将HSC相关的研究模式延伸至胰腺纤维化的可行性,以期为其进一步研究提供参考。

1 SCFA在缓解肝纤维化中的作用机制

1.1 表观遗传调控 SCFA(特别是丁酸和丙酸)是内源性I类和IIa类HDAC的有效抑制剂,这是其发挥抗纤维化作用的核心机制之一^[6]。SCFA通过抑制HDAC活性,导致组蛋白高度乙酰化,染色质结构变得松弛,从而激活特定基因的转录^[7]。在纤维化环境中,这种表观遗传重编程主要产生两方面效应。首先,SCFA能激活一系列保护性基因的转录。在HSC中,丁酸通过抑制HDAC,显著上调细胞周期蛋白依赖性激酶抑制剂p21的表达,诱导细胞周期G1期停滞,从而抑制HSC的增殖,这是抗肝纤维化的关键步骤^[8]。同时,SCFA通过HDAC抑制激活核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)抗氧化通路,增强抗氧化反应元件驱动基因的转录,从而减轻氧化应激对组织的损伤^[9]。其次,SCFA能抑制促纤维化基因的表达^[10]。其中,转化生长因子 β 1(transforming growth factor- β , TGF- β 1)是最强效的促纤维化因子,下调其信号通路是抗纤维化治疗的重要目标^[11]。丁酸通过抑制HDAC活性,干扰母系抗十五表态蛋白同源物(mothers against decapentaplegic homolog, Smad)蛋白与DNA的结合能力,并促进抑制性Smad7的表达,从而负向调控TGF- β 1/Smad信号通路,最终下调平滑肌肌动蛋白 α (smooth muscle actin α , α -SMA)和I型胶原等关键促纤维化基因的表达(图1)。此外,SCFA通过作用于核因子 κ B(nuclear factor kappa-B, NF- κ B)信号轴,抑制中性粒细胞趋化因子及巨噬细胞炎症小体激活,并调节辅助性T细胞亚群分化格局,重塑局部免疫微环境,从免疫调节层面间接抑制纤维化进程。

1.2 通过GPCR介导的信号转导 SCFA通过激活特定的GPCR发挥其广泛的生理功能^[12],这是其抗纤维化作



注:SCFA,短链脂肪酸;LPS,脂多糖; α -SMA,平滑肌动蛋白 α ;HSC,肝星状细胞;HDAC,组蛋白去乙酰化酶;IL-6,白细胞介素6;IL-10,白细胞介素10;TNF- α ,肿瘤坏死因子 α ;TGF- β ,转化生长因子 β ;Treg细胞,调节性T细胞;TLR4,Toll样受体4;Smad,母系抗十五表态蛋白同源物;IRAK1,白细胞介素1受体相关激酶1;ECM,细胞外基质;FXR,法尼醇X受体;FGF15/19,成纤维生长因子15/19;CYP7A1,细胞色素P450家族7A亚家族A成员1;NLRP3,核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3;NF- κ B,核因子 κ B。

图1 肠道菌群代谢产物SCFA在缓解肝纤维化中的机制

Figure 1 Mechanism of intestinal microbiota metabolite SCFA in alleviating liver fibrosis

用的另一核心机制。SCFA 主要与 GPR41、GPR43 和 GPR109A 3 种受体结合,但不同 SCFA 对这些受体的亲和力存在差异。乙酸和丙酸主要激活 GPR41 和 GPR43;而丁酸是 GPR109A 的高亲和力配体,同时也能激活 GPR43^[13-14]。这些受体在不同器官和细胞类型中的差异性表达,决定了 SCFA 信号通路的多样性和组织特异性。SCFA 与 GPCR 结合后,主要通过 Gi/o 和 Gq 蛋白亚型介导下游信号传导^[15]。激活 GPR43(Gq 耦合)可刺激磷脂酶 C 活化,产生肌醇三磷酸和二酰基甘油,导致细胞内钙离子动员和蛋白激酶 C 激活。相反,GPR41 和 GPR43 与 Gi/o 蛋白耦合时,则会抑制腺苷酸环化酶,降低细胞内环磷酸腺苷水平,进而调控蛋白激酶 A 活性^[16]。上述第二信使系统的变化共同调节着关键转录因子的活性。其中,最关键的抗纤维化通路之一是抑制

NF- κ B 信号。降低的环磷酸腺苷水平或激活的蛋白激酶 C 均可通过复杂交叉对话抑制巨噬细胞 NF- κ B 的活化,从而显著减少肿瘤坏死因子 α 、白细胞介素(interleukin, IL)6 等促炎细胞因子的产生^[17]。此外,GPR43 的激活还能通过抑制巨噬细胞核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3(nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3, NLRP3)炎症小体来减轻炎症反应^[18]。在肾脏纤维化模型中,GPR43 缺陷小鼠表现出更严重的病理损伤,而 SCFA 通过 NLRP3 显著减轻了炎症和纤维化程度,证明了其核心作用^[19]。GPR109A 的激活则与促进抗炎 M2 型巨噬细胞极化和诱导调节性 T 细胞(regulatory T cell, Treg 细胞)分化密切相关,共同构建抑制纤维化的微环境^[20]。

1.3 免疫调节与炎症抑制 SCFA通过多靶点调节先天性和适应性免疫系统,有效抑制慢性炎症这一纤维化核心驱动力。其核心机制是促进Treg细胞的分化与功能:SCFA通过抑制HDAC,增强叉头框蛋白P3基因位点的组蛋白乙酰化水平,不仅促进Treg细胞分化,更增强其功能稳定性与免疫抑制能力,从而有效抑制过度活化的效应T细胞反应^[21]。此外,SCFA通过激活GPCR和抑制HDAC,协同促使巨噬细胞从促炎、促纤维化的M1表型向抗炎、促修复的M2表型转化,并抑制炎症因子释放^[22]。SCFA还可抑制中性粒细胞衰老、促炎细胞因子分泌和中性粒细胞胞外陷阱的形成,从而减轻组织炎症损伤^[23]。

1.4 维持/修复上皮屏障功能 SCFA是维持肠道屏障完整性的关键物质,主要通过“肠-肝轴”间接发挥抗纤维化作用。丁酸是结肠上皮细胞的首选能量源,结肠上皮细胞通过多种途径代谢SCFA,包括 β 氧化和柠檬酸循环,产生三磷酸腺苷,这是细胞的主要能量货币。短链脂肪酸对这些细胞的能量需求做出了重大贡献,为维持细胞正常功能提供能量支持^[24]。此外,SCFA通过激活腺苷一磷酸活化的蛋白质激酶、GPCR等信号通路,显著上调紧密连接蛋白的表达和正确装配,有效降低肠道通透性,巩固物理屏障^[25]。坚固的肠道屏障可有效防止肠道内脂多糖(lipopolysaccharide, LPS)等病原相关分子模式易位入血。LPS进入循环后可通过激活巨噬细胞Toll样受体4信号通路,强力驱动肝脏等远端器官的炎症与纤维化进展^[26]。SCFA通过修复肠漏,阻断系统性炎症驱动源,对肝纤维化产生重要的间接保护作用。

1.5 代谢重编程及氧化应激调控 SCFA在肝脏代谢重编程中扮演着关键角色,丁酸虽大部分被结肠细胞利用,但其部分入血后可通过激活GPCR及抑制HDAC,上调胰高血糖素样肽-1分泌,进而改善肝脏糖脂代谢紊乱,减少炎症信号和氧化损伤,从代谢层面间接阻遏纤维化的启动与发展^[27]。SCFA还能激活法尼醇X受体/成纤维生长因子15/胆固醇7 α -羟化酶基因通路,减少胆汁酸合成并改善胆汁酸代谢,影响肝脏脂质代谢和炎症反应,为肝纤维化的治疗提供了新的靶点^[28]。

2 SCFA在肝纤维化中作用机制的迁移应用

2.1 SCFA在胰腺纤维化中作用机制的现状 & 局限性 近年多项研究报道,慢性胰腺炎患者普遍存在肠道微生物多样性降低、产SCFA菌群丰度减少的特征性改变,同时伴有粪便和血清中SCFA水平显著下降,且其下降程

度与疾病严重程度呈负相关^[29]。SCFA在胰腺纤维化中的作用机制主要涉及通过“肠-胰腺轴”调节免疫炎症反应、抑制PSC活化以及减轻氧化应激。SCFA作为HDAC抑制剂,可通过表观遗传调控方式下调促纤维化基因的表达;同时,通过激活GPCR,抑制NF- κ B等炎症信号通路,减少肿瘤坏死因子 α 、IL-1 β 、IL-6等炎症细胞因子的释放,从而缓解胰腺慢性炎症及其引发的纤维化进程^[30]。研究表明,丁酸钠可显著改善L-精氨酸诱导的大鼠胰腺炎及相关纤维化,其作用与抑制炎症反应和硝化应激密切相关^[31]。此外,肠道菌群失调及SCFA产生减少被认为是慢性胰腺炎发生与发展的重要诱因,恢复SCFA水平或补充益生菌能够增强肠道屏障功能、减少细菌移位,并间接抑制胰腺纤维化^[30,32]。然而,目前尚缺乏针对不同SCFA组分的对比研究,也缺乏SCFA受体在胰腺组织中的具体表达和功能研究。因此,基于“肠-胰腺轴”理论和合理的机制推测,SCFA在胰腺纤维化防治中展现出巨大潜力,但仍需要更多高质量的基础研究来验证其直接效应并深入探索分子机制,并结合目前SCFA在其他组织器官中纤维化研究的成熟方法,验证其在胰腺纤维化中的作用机制,为临床转化提供坚实的理论基础。

2.2 迁移基础: PSC与HSC高度同源 HSC与PSC在胚胎起源、细胞表型、功能及激活机制上均表现出高度同源性。二者均来源于中胚层,在正常生理状态下处于静息期,以胞内富含维生素A脂滴为特征,主要功能是储存脂肪和维持器官基质微环境的稳定。当受到慢性损伤(如酒精、毒性物质等)刺激时,两者会经历极为相似的激活过程,表现为脂滴丢失,细胞增殖并转化为肌成纤维细胞样表型,高表达 α -SMA,并异常分泌以I型和III型胶原为主的ECM,最终导致器官纤维化及功能衰竭。

近年来的研究表明,PSC与HSC在分子调控机制上的同源性得到进一步证实。两者在激活过程中均依赖多种共同的信号通路,如TGF- β 、PDGF和Wnt信号通路,这些通路通过调控下游转录因子(如Smad、 β -catenin等)促进其向肌成纤维细胞转化^[33-34]。此外,表观遗传调控如DNA甲基化、组蛋白修饰及非编码RNA(如microRNA-29、microRNA-200家族)也参与维持静息状态或推动激活进程^[35]。研究还发现,二者与局部免疫微环境的相互作用在纤维化中发挥关键调控作用,通过分泌细胞因子及趋化因子形成正反馈环路,加速纤维化进程^[36-38]。利用谱系追踪及单细胞测序技术,研究表明,PSC和HSC

在激活过程中存在细胞亚群异质性及可塑性,部分细胞甚至可能逆转至静息状态^[39-40]。这为开发针对纤维化疾病的靶向治疗提供了新思路,例如通过干预关键信号节点或调控表观遗传状态以抑制其活化。

将HSC相关研究模式迁移到PSC的研究已有成功实践。例如,维生素D在肝纤维化中的作用研究较多,基于二者的高度同源性,将研究模式迁移至胰腺纤维化,证实了维生素D在胰腺纤维化中发挥重要作用^[41]。同样,补体因子5(complement component 5, C5)在肝纤维化中发挥关键作用,但尚未在慢性胰腺炎的背景下开展相关研究,基于PSC与HSC具有相似的激活剂谱,有研究已证实C5的表达可促进胰腺纤维化^[42]。因此,凭借HSC与PSC的高度同源性,将肝纤维化的研究范式系统性地应用于胰腺领域,能够有效避免重复探索,实现知识和技术的高效转化,为攻克目前缺乏有效治疗手段的胰腺纤维化及相关疾病提供方向。

3 小结与展望

SCFA在肝纤维化和胰腺纤维化中均表现出多通路的抗纤维化作用。在肝纤维化中,SCFA通过抑制HDAC调控表观遗传,诱导HSC周期停滞并抑制TGF- β 1/Smad信号通路;同时通过激活GPCR调节免疫炎症反应,促进Treg细胞分化和巨噬细胞M2极化;此外,还通过“肠-肝轴”维持肠道屏障功能,以减少LPS易位。在胰腺纤维化中,尽管SCFA的直接研究较少,但现有研究已证实可通过类似机制抑制PSC活化,并通过“肠-胰腺轴”调节免疫微环境,从而缓解慢性炎症和纤维化进程。

基于HSC与PSC在细胞起源、表型特征和激活机制上的高度同源性,且相关研究已证实将肝纤维化中成熟的SCFA研究模式系统性地迁移至胰腺领域具有显著可行性。未来可积极检索与肝纤维化相关,但并未在胰腺纤维化中证实作用的转录因子及蛋白等,重点探索SCFA对PSC的直接作用机制和受体特异性表达,将有助于突破当前胰腺纤维化研究的瓶颈,为开发新的治疗策略提供理论依据。

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