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靶向肝星状细胞治疗肝纤维化及天然产物调控作用的研究进展

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[摘要]肝纤维化(liver fibrosis,LF)是多种慢性肝病的共同病理阶段,可逐步发展为肝硬化甚至肝癌,目前临床上仍缺乏有效的治疗药物。肝星状细胞(hepatic stellate cells,HSCs)是LF的核心效应细胞,HSCs活化后会分泌大量细胞外基质在肝内沉积,最终驱动LF发展。因此靶向HSCs的治疗成为逆转LF的关键,其中抑制HSCs活化、促进活化HSCs程序性死亡是较为成熟的传统方向,而近年来,诱导活化态HSCs失活已成为新颖且具前景的研究热点。本文将简要回顾前2种传统策略的研究现状,重点阐述诱导活化态HSCs失活的分子机制,并系统总结天然产物在上述3种调控方式中的作用机制与研究进展,以期为深入阐明LF发病机制、挖掘天然产物治疗LF的潜在靶点提供新视角。

[关键词]肝纤维化;肝星状细胞;分子机制;天然产物
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Research progress on targeted hepatic stellate cells treatment for liver fibrosis and the regulatory role of natural product

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View from specialist: It is creative, and of certain scientific and educational value.

[Abstract] Liver fibrosis (LF), a common pathological stage observed in various chronic liver diseases, can progress to cirrhosis and even hepatocellular carcinoma. Currently, effective clinical therapeutic agents for LF remain limited. Hepatic stellate cells (HSCs) are recognized as the primary effector cells in LF. When activated, HSCs secrete large amounts of extracellular matrix, resulting in excessive deposition within the liver and ultimately contributing to the progression of LF. Therefore, targeting HSCs is crucial for reversing LF. While traditional approaches focus on inhibiting HSCs activation and promoting programmed cell death of activated HSCs, inducing the quiescence of activated HSCs has emerged as a novel and promising research area in recent years. This article briefly reviews the current status of the first two traditional strategies, elucidates the molecular mechanisms involved in the inactivation of activated HSCs, and systematically summarizes the mechanisms of action and research progress of natural products in these three regulatory approaches. The aim is to provide new perspectives for enhancing the understanding of LF pathogenesis and identifying potential therapeutic targets of natural products for LF treatment.

[Key words] Liver fibrosis; Hepatic stellate cells; Molecular mechanism; Natural product

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肝纤维化(liver fibrosis, LF)是一种由慢性肝损伤引起的病理修复反应。在全球范围内,每年约有200万人因LF进展为肝硬化、肝功能衰竭及肝细胞癌而死亡[1,2]。其核心特征是肝星状细胞(hepatic stellate cells, HSCs)活化后导致细胞外基质(extracellular matrix, ECM)过度沉积形成纤维瘢痕,涉及炎症环境失衡、氧化应激等环节[3]。近年来,以HSCs为靶点的治疗策略是LF研究领域的重点方向。本文将围绕HSCs与LF重点综述2方面内容:一是明确活化态肝星状细胞(activate hepatic stellate cells, aHSCs)作为LF核心效应细胞的关键地位;二是系统梳理当前靶向HSCs的3类干预策略,即抑制HSCs活化、促进aHSCs程序性死亡、诱导aHSCs失活,并分别总结各类策略下天然产物的作用机制与研究进展,为天然产物靶向HSCs逆转LF研究提供参考。

1 aHSCs是LF的核心驱动细胞

静息态肝星状细胞(quiescent hepatic stellate cells, qHSCs)呈星状分布于窦周间隙,主要储存视黄醇酯形式的维生素A及维持肝窦血流稳态[4]。肝脏持续受到病毒感染、酒精摄入等损伤刺激时,qHSCs迅速活化,形态上细胞体积增大3~5倍,伪足伸展且脂滴消失,转变为分泌大量胶原的肌成纤维细胞样表型;功能上,α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)表达量激增10倍以上,Ⅰ型胶原蛋白(type Ⅰ collagen, Col Ⅰ)分泌量达静息态的20倍,成为ECM的主要来源[5],并自分泌转化生长因子-β(transforming growth factor-beta, TGF-β)以维持自身活化。这种由aHSCs的功能异常与ECM沉积导致的结构破坏,共同推动慢性肝病向不可逆的肝硬化进展,故靶向aHSCs成为抗LF的关键策略。

2 HSCs活化的触发因素与天然产物干预机制

2.1 肝脏炎症

当肝脏受到酒精、病毒等因素损伤时,中性粒细胞作为炎症反应的早期应答细胞会迅速被招募至受损部位,通过吞噬作用清除凋亡的肝细胞(hepatocytes, HCs)[6,7]。但其具有强烈的促炎特性,会分泌大量炎性物质形成促炎微环境,诱导HSCs活化并表达α-SMA[7,8],使其分化为aHSCs合成ECM在窦周间隙大量沉积,同时分泌金属蛋白酶组织抑制剂1抑制ECM降解,双重推动纤维化过程[9]。此外,aHSCs自分泌TNF-α等促炎细胞因子和趋化因子CXCL1,募集更多免疫细胞加剧炎症,炎症与aHSCs互相驱动,最终导致ECM过度沉积,破坏肝小叶结构并形成疤痕,进一步加重LF[10-12]。

炎症小体是连接肝脏炎症与HSC活化的关键复合物,在LF中作用显著,其中NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor pyrin domain-containing protein 3, NLRP3)炎症小体的促纤维化作用已被广泛证实[13]:在脂多糖(lipopolysaccharide, LPS)刺激下,巨噬细胞表面的toll样受体首先激活NF-κB信号通路,启动NLRP3/半胱氨酸天冬氨酸蛋白酶1(cysteine aspartate-specific protease 1, Caspase1)/pro-IL-1β/pro-IL-18的转录。随后,受损HCs释放损伤相关分子模式(damage-associated molecular patterns, DAMPs)与免疫细胞表面的嘌呤能受体P2X7(P2RX7)结合,激活NLRP3炎症小体促使Caspase1成熟,后者通过切割pro-IL-1β、pro-IL-18生成促炎因子IL-1β和IL-18,加剧肝脏炎症并直接激活HSCs,加速肝损伤与LF进展[14]。

2.2 氧化应激

持续性肝损伤使HCs与非实质细胞抗氧化失衡,引发活性氧(reactive oxygen species, ROS)大量释放及肝脏局部炎症反应[15,16]。过量ROS与炎症因子协同激活HSCs推动LF进展,故抗氧化、清除自由基是逆转LF的重要机制[17]。核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)抗氧化通路是细胞响应氧化应激的起点,生理状态下Nrf2与Kelch样ECH相关蛋白1(kelch-like ECH-associated protein 1, Keap1)结合后被泛素化降解,慢性肝损伤中ROS刺激使二者解离,Nrf2核转位结合抗氧化反应原件,促进抗氧化基因转录以清除ROS,维持HSCs静息表型[18]。

细胞氧化应激可触发有丝分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)/细胞外信号调节激酶(extracellular regulated protein kinases, ERK)通路磷酸化。qHSCs被TGF-β、血小板源性生长因子(platelet-derived growth factor, PDGF)及ROS刺激激活该通路,p-ERK入核诱导NOS生成NO,NO与ROS反应加剧氧化应激;同时p-ERK激活NOX,催化O_2^-转化为H_2O_2,最终促进HSCs增殖、胶原合成并增强TGF-β的促纤维化作用[19]。此外,肝损伤氧化应激时,ROS会抑制HSCs中SIN3转录调控蛋白(SIN3 transcriptional regulator A, SIN3A)/p38 MAPK轴活性,解除SIN3A对miR-144的转录抑制,致miR-144异常上调并进而激活HSCs,虽然SIN3A调节p38 MAPK的具体机制还不清楚,但特异性抑制HSCs中miR-144为LF

的治疗提供一种新的治疗策略[20]。

值得注意的是,Nrf2抗氧化通路与MAPK/ERK促活化通路在HSCs氧化应激与活化进程中存在潜在交互[21]。Nrf2可能通过调控抗氧化酶减少ROS,间接抑制MAPK/ERK激活;MAPK/ERK通路激活后产生的ROS抑制Nrf2核转位、削弱其抗氧化功能[22]。二者互作的具体分子机制及对HSCs活化表型转换的精准调控仍需深入研究。

2.3 旁分泌生长因子

2.3.1 肝细胞源性生长因子 HCs分泌的生长因子除了促进细胞生长,还能直接作用于HSCs在LF中发挥复杂作用。研究表明,HCs高表达神经损伤诱导蛋白2(nerve injury-induced protein 2, Ninjurin2)通过胰岛素样生长因子1受体(insulin-like growth factor 1 receptor, IGF1R)/早期生长反应因子1(early growth response 1, EGR1)通路促进PDGF-BB分泌,后者作为强促有丝分裂原结合HSCs表面PDGFβ受体(PDGF receptor beta, PDGFR-β),激活大鼠肉瘤(rat sarcoma, Ras)/ERK和磷脂酰肌醇-3激酶(phosphati-dylinositol-kinase, PI3K)/蛋白激酶B(protein kinase B,AKT)信号,诱导HSCs增殖与迁移[23]。此外,肝细胞源性血管内皮生长因子A(vascular endothelial growth factor A, VEGFA)能够与HSCs表面VEGR受体2(VEGF receptor 2, VEGFR2)结合,将HSCs活化为成纤维表型[24]。

2.3.2 非肝细胞源性生长因子 非肝细胞来源的生长因子可靶向HCs间接调控HSCs。aHSCs分泌的成纤维细胞生长因子7(fibroblast growth factor 7, FGF7)具有高度细胞靶向特异性,与结合HCs表面FGF受体2b(FGF receptor 2b, FGFR2b)后迅速激活AKT/ERK通路促进HCs存活,并抑制其分泌CCL2/CXCL8和TGF-β,削弱HSCs活化信号以缓解LF[25]。此外,FGF9同样由aHSCs分泌,与HCs表面FGFR1/2/3结合后,一方面抑制HCs内脂肪酸合成关键基因如ChREBP、Fasn、PPARγ的表达,减少甘油三酯堆积以降低脂毒性;另一方面,通过ERK1/ERK2/糖原合成酶激酶3β(glycogen synthase kinase 3 beta, GSK-3β)通路激活HCs内β-连环蛋白,该蛋白部分通过HCs分泌的细胞外囊泡释放至肝窦间隙,作为旁分泌信号与HSCs表面的低密度脂蛋白受体相关蛋白5/6(low-density lipoprotein receptor-related protein 5/6, LRP5/6)受体结合,抑制COL1A1、ACTA2基因表达,减缓LF进展[26]。

综上,肝脏炎症、氧化应激与旁分泌生长因子共同驱动并加剧HSCs活化,见图1、2,基于以上病理机制梳理了通过调控不同通路而发挥抑制HSCs活化作用的代表性天然产物,见表1。

3 aHSCs程序性死亡的调控机制及天然产物干预机制

3.1 凋亡(apoptosis)

细胞凋亡是维持组织平衡与正常功能的细胞程序性死亡,通过诱导aHSCs凋亡是预防LF进展的有效策略[36, 37]。目前已有大量研究证实天然产物中的化合物能够通过诱导aHSCs凋亡缓解LF,其作用机制主要涉及细胞凋亡的内源性(线粒体途径)、外源性(死亡受体途径)及信号通路等核心环节。柚皮素通过调节转化生长因子β激活激酶1(transforming growth factor-β-activated kinase 1, TAK1)/MAPK/叉头框蛋白O3A(forkhead box protein O3A, FOXO3A)轴诱导aHSCs凋亡,从而抑制代谢相关脂肪性肝病纤维化[37];银杏双黄酮通过信号转导与转录激活因子1(signal transducer and activator of transcription 1, STAT1)介导aHSCs凋亡发挥抗纤维化活性,并通过IL-6/STAT3信号通路促进aHSCs凋亡和HCs增殖[38];戈米辛D靶向PDGFRβ并调控PDGF-BB/PDGFRβ信号通路,抑制下游MAPK/p-ERK信号以促进aHSCs凋亡,缓解LF[39];姜黄素则通过激活PI3K/Akt/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路抑制LX-2过度自噬和促进凋亡[40];连翘苷元和五味子乙素通过调节BCL-2相关X蛋白(BCL-2-associated X protein, Bax)/B细胞淋巴瘤2蛋白(B-cell lymphoma 2 protein, Bcl-2)诱导小鼠HSCs和LX-2凋亡发挥抗LF作用[41,42]。

3.2 自噬(autophagy)

自噬是细胞清除代谢产物和损伤细胞器的一种自我保护机制[43]。在自噬过程中,待降解的细胞质或细胞器被膜状结构包裹形成自噬体,与溶酶体融合后形成自噬溶酶体,通过溶酶体降解维持细胞稳态[44]。龙血素B和能够通过激活HSCs自噬来抑制HSCs活化和增殖[45]。白藜芦醇通过激活沉默信息调节因子1(silent information regulator 1, SIRT1)和c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)通路诱导HSCs自噬来抑制HSCs活化减轻LF[46]。然而,多项研究表明,抑制HSCs自噬同样能够缓解LF。人参皂苷2/3均通过抑制硫代乙酰胺处理的小鼠和LPS刺激的HSC-T6细胞中的自噬,发挥抗纤维化作用[47, 48];姜黄素通过抑制自噬减

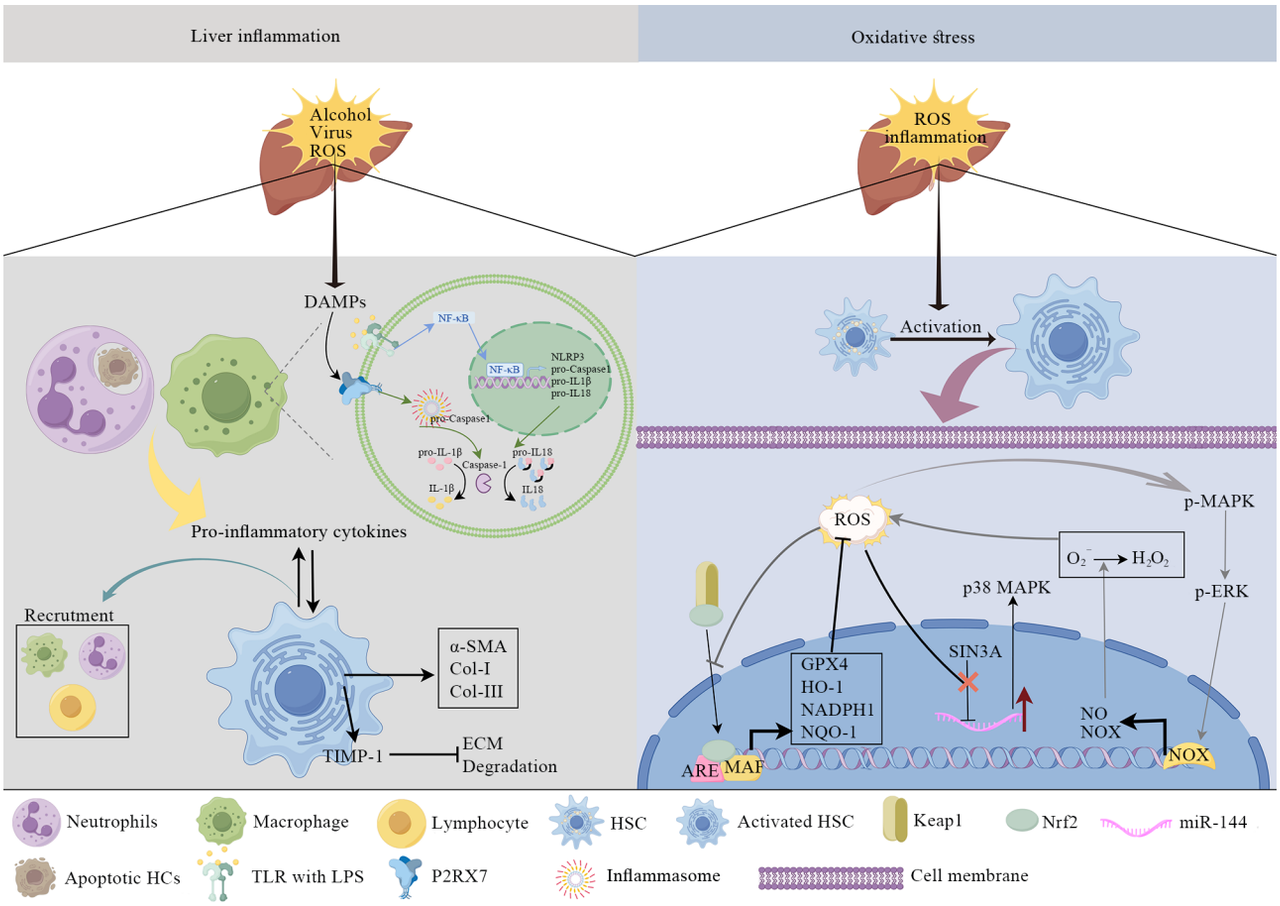


图1　炎症和氧化应激诱导肝星状细胞活化机制

Fig 1　Mechanisms of inflammation and oxidative stress-induced hepatocyte activation

缓LF[40]；消退素D1通过AKT/mTOR通路抑制自噬来抑制LF进展[49]。有研究表明在LF过程中，aHSCs激活mTOR通路能够抑制自噬并激活Rho相关蛋白激酶1来释放细胞外囊泡加重LF[50]，这与消退素D1[49]中发现抑制自噬能够抑制LF的结果相反。由此可见，自噬在HSCs中具有双重作用，诱导或抑制HSCs自噬都可能进一步影响LF的进展。

3.3　铁死亡(ferroptosis)

铁死亡是铁依赖性细胞死亡，细胞内脂质过氧化产物蓄积超过抗氧化系统清除能力，最终导致细胞膜结构破坏与细胞死亡[51]。诱导aHSCs铁死亡是逆转LF的方法，但多数铁死亡诱导剂缺乏细胞特异性，在作用于aHSCs同时易触发肝脏中其他驻留细胞，引发肝实质损伤、炎症微环境紊乱等[52, 53]。相比之下，天然产物凭借“多成分、多靶点、低毒性”的优势，在诱导aHSCs铁死亡、缓解LF进展方面表现突出[54]。例如，人参皂苷Rb1经肌球蛋白样BCL2结合蛋白(coiled-Coil, myosin-like BCL2-interacting protein, BECN1)/溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)轴[55]、人参皂苷RK1激活脂酰辅酶合成酶4(Acyl-CoA synthetase 4, ACSL4)/溶血磷脂酰胆碱酰基转移酶3(lysophosphatidylcholine acyltransferase 3, LPCAT3)/5-脂氧合酶(5-lipoxygenase, ALOX5)通路[56]、人参皂苷Rg3经miR-6945-3p/DNA甲基转移酶3B(DNMT3B)/ACSL4[57]、人参皂苷Rh2经干扰素调节因子1(interferon regulatory factor 1, IRF1)/SLC7A11[58]、异甘草素经谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)/转铁蛋白受体(transferrin receptor, TfR)/二价金属转运体1(divalent metal transporter 1, DMT1)[59]、万寿菊苷通过泛素化降解GPX4[60]，均能诱导aHSCs铁死亡，有效减少aHSCs数量、缓解LF进展，进一步完善铁死亡的通路调控网络，为诱导aHSCs铁死亡缓解LF的机制研究提供重要支撑。

4　aHSCs向失活表型转变的机制及天然产物干预机制

早期研究表明，CCl_4诱导的LF模型中约40%～50%的aHSCs在纤维化消退时不发生凋亡，而是下调α-SMA、Col Ⅰ，重新积累视黄醇酯脂滴，

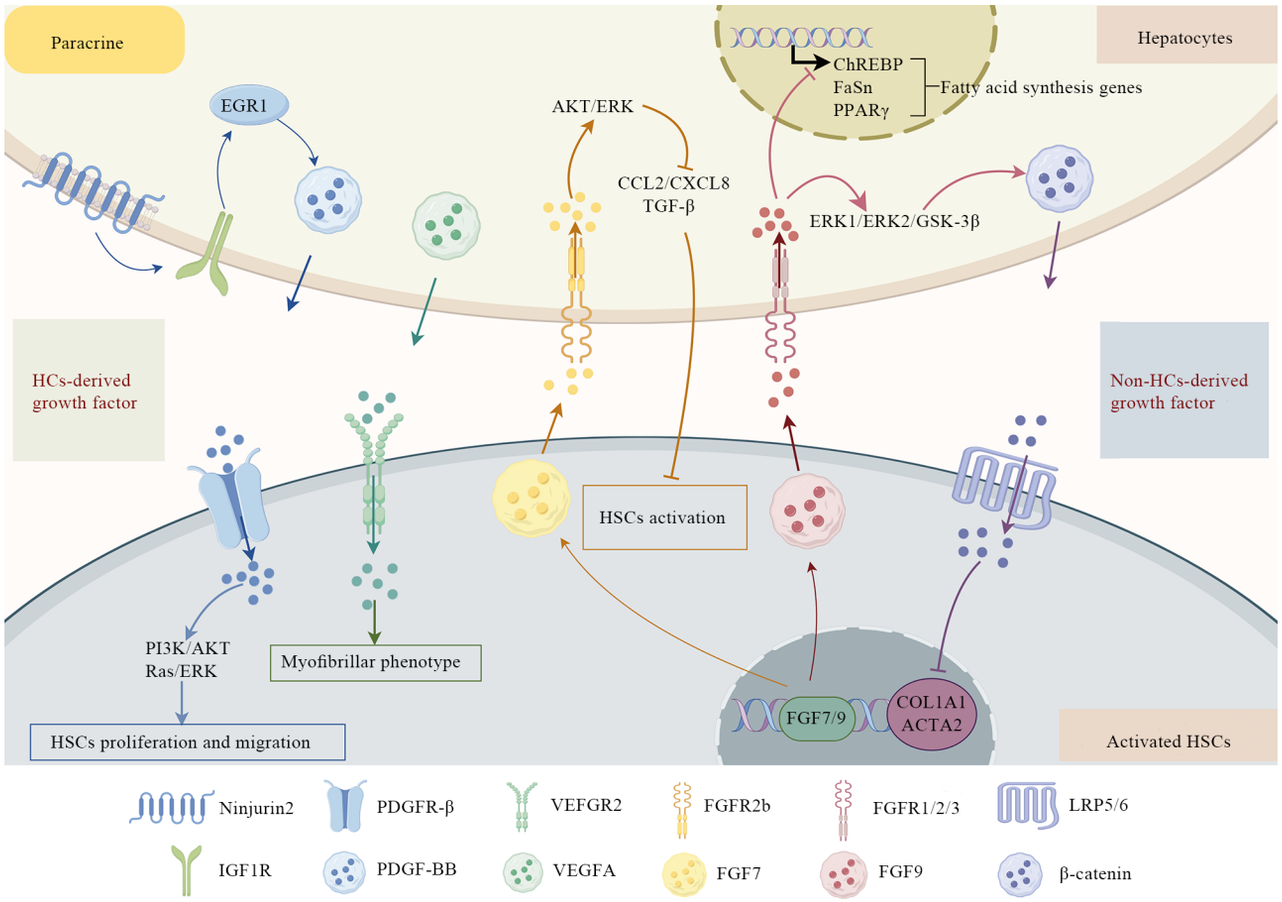


图2　旁分泌信号诱导肝星状细胞活化机制

Fig 2　Mechanism of hepatic stellate cell activation induced by paracrine

上调Adfp表达，呈现类似qHSC的静息样表型（q-like HSC），首次揭示aHSCs表型的逆转潜力，并明确视黄醇脂滴及PAT家族蛋白是q-like HSC核心特征，但未能区分该静息样细胞与qHSCs的本质差异[61-63]。为厘清这一细胞身份，Kisseleva等[64]分别追踪CCl_4和酒精诱导的LF模型，证实37%～56% aHSCs在纤维化过程中转化为兼具部分静息特征的iHSCs，首次明确aHSCs逆转后的细胞身份并非qHSCs，而是一种独立的失活态表型，明确提出aHSCs可逆转至iHSCs的创新性观点。

4.1　aHSCs向iHSCs逆转的核心机制

aHSCs逆转为iHSCs需通过“抑制糖酵解”与“脂滴重构”2大关键过程协同实现。在抑制糖酵解方面，Hedgehog（Hh）信号通路可调控HSCs的有氧糖酵解过程，通过抑制Hh信号通路及下游HIF-1α的表达[65]，能够进一步抑制糖酵解、减少乳酸积累，最终推动aHSCs向iHSCs转化。其中，2-脱氧葡萄糖可直接抑制糖酵解关键酶HK2的活性；乳酸脱氢酶抑制剂FX11则能阻断aHSCs内丙酮酸向乳酸的转化[66]。此外，最新研究发现，借助VA-PEG-PCL胶束将喜树碱靶向递送至aHSCs，可有效抑制丙酮酸激视黄酸酶PKM2及糖酵解相关基因（*Hk2*、*Pfkp*、*MPK*、*Glut1*）的表达[67]。上述2种调控方式均能通过抑制糖酵解通路，明显降低aHSCs的乳酸生成量（降幅达65%～70%），同时有效削弱aHSCs的活化表型。

在脂滴重构方面，阻断TGF-β1诱导的aHSCs自噬可恢复脂滴合成与积累[68]。研究发现，脂滴储存的视黄酸能够结合RARβ/RXRα，进而抑制CoL1A2等纤维化基因并维持静息标志物GFAP、PPARγ的表达，从而推动aHSCs向iHSCs转变[65, 69]。此外，视黄醇、棕榈酸和油酸协同作用时，可以下调ACTA2、COL1A1及LOX的表达，将aHSCs转化为iHSCs表型[70]。

4.2　aHSCs逆转为iHSCs的核心调控因子

过氧化物酶体增殖物激活受体γ（peroxisome proliferator-activated receptor gamma，PPARγ）和GATA结合蛋白4/6（GATA binding protein 4/6，GATA4/6）是该表型转化的核心调控因子[63]。PPARγ是PPAR核受体家族的关键亚型，已被证实

表1 天然产物抑制肝星状细胞活化防治肝纤维化的作用机制

Tab 1 The mechanism of natural products in preventing and treating liver fibrosis by inhibiting hepatic stellate cell activation fibrosis

靶向	天然产物	中药来源	通路	机制	文献
炎症	灵芝多糖(*Ganoderma* lucidum polysaccharide)	灵芝 (*Ganoderma lucidum*)	TLR4/NF-κB；TFG-β/Smad	抑制TGF-β/Smad2/3磷酸化、上调Smad7、抑制TLR4/NF-κB、下调整合素α6/α8(ITGA6/8),从而抑制TNF-α、IL-1β、IL-6等促炎因子诱导的HSC-T6活化	[27]
	棕矢车菊素(Jaceosidin)	魁蒿(*Artemisia princeps* Pamp)	VGLL3/HMGB1/TLR4	抑制VGLL3/HMGB1/TLR4信号通路,从而抑制NLRP3炎性小体激活,降低aHSCs中α-SMA表达	[28]
	龙胆苦苷(Gentiopicroside)	龙胆(*Gentiana scabra*)	TLR4;NLRP3	抑制TLR4和NLRP3通路减少HCs焦亡及炎症反应,抑制HSCs活化	[29]
	茯苓三萜(*Poria* triterpenoids)	茯苓(*Poria cocos* Wolf)	Caspase-1/NLRP3	靶向Caspase-1抑制巨噬细胞中NLRP3炎性小体激活	[30]
氧化应激	芹菜素(Apigenin)	-	PKM2/HIF-1α	调控EGFR-MEK1/2-ERK1/2通路抑制PKM2/HIF-1α,改善肝脏氧化应激指标(下调MDA、CAT,升高GSH、SOD、GSH-PX及T-AOC),从而抑制HSCs活化。	[31]
	补骨脂乙素(Isobavachalcone)	补骨脂(*Psoralea corylifolia* Linn);明日叶(*Angelica keiskei*)	Nrf2/HO-1	激活Nrf2/HO-1并抑制NF-κB信号减轻氧化应激和肝脏炎症反应来抑制HSCs活化	[17]
	红景天苷(Salidroside)	红景天(*Rhodiola rosea* L.)	PI3K/AKT/GSK-3β	激活PI3K/AKT/GSK-3β信号通路,改善胆汁淤积引起的肝脏炎症和氧化应激,进而抑制HSCs活化缓解LF	[32]
旁分泌生长因子	Antrodin C	牛樟芝(*Antrodia camphorata*)	TGF-β1/Smad2/AKT/ERK/P38;PDGF-BB/AKT/ERK	负调节TGF-β1诱导的Smad2、AKT、ERK、P38磷酸化及PDGF-BB诱导的AKT、ERK磷酸化来抑制HSCs活化、迁移和ECM产生	[33]
	丹酚酸B(Salvianolic acid B)	丹参(*Salvia miltiorrhiza* Bunge)	PDGF-B/PDGFRβ	靶向HSCs中PDGFRβ,阻止PDGF-B与PDGFRβ结合,从而抑制aHSCs活化并减轻炎症反应	[34,35]
	紫甘薯花青素(purple sweet potato anthocyanins)	紫薯(*Ipomoea batatas* (L.) Lam)			

是维持HSCs静息表型的核心分子,能通过负向调控胶原相关基因如COL1A1的转录,抑制胶原合成与沉积[71]。视黄醇结合蛋白7(retinol-binding protein 7, *RBP7*)属于脂肪酸结合蛋白(fatty acid-binding proteins, FABP)家族,主要参与HSCs内视黄醇的转运与代谢过程,是PPARγ的靶基因[72]。研究表明,PPARγ能够直接结合*RBP7*基因的启动子区域,上调*RBP7*的表达,进而影响HSCs的脂代谢及表型状态,将aHSCs逆转至iHSCs[73]。GATA4/6是锌指转录因子家族成员,GATA4直接抑制aHSCs中内皮PAS结构域蛋白1基因的转录,诱导aHSCs失活,促进LF的消退。通过体外敲低GATA6,会使HSCs增殖能力增强、活化程度升高,且失去qHSCs特异性表型,表明GATA6会促进aHSCs逆转为iHSCs[74,75]。靶向HSCs失活的调控机制见图3。

总之,qHSCs储存富含视黄醇酯的脂滴,其稳态依赖ADPP、TIP47、LRAT、CRBP-Ⅰ等PAT家族蛋白调控[61]。aHSCs向iHSCs转化的标志分子涵盖:Adfp、Adipor1、CREBP、PPAR-γ、SREBP1C[64,76]、TCF21[74]、LHX2、LRAT[77]、GCLc[78]、GFAP[79]、HSP90aa1、HSPA/B1[64,74]及ETS1[63]等。其中,iHSCs的存活稳态与GATA4、PPARγ、FOX-1等转录因子上调及AP1、CTCF1等下调相关[63]。值得注意的是,尽管PPARγ、GATA4/6[63,70]等少数转录因子已被证实参与调控,但驱动aHSCs失活的完整分子网络仍有待深入解析。有关aHSCs向iHSCs表型转变的具体调控见图4。

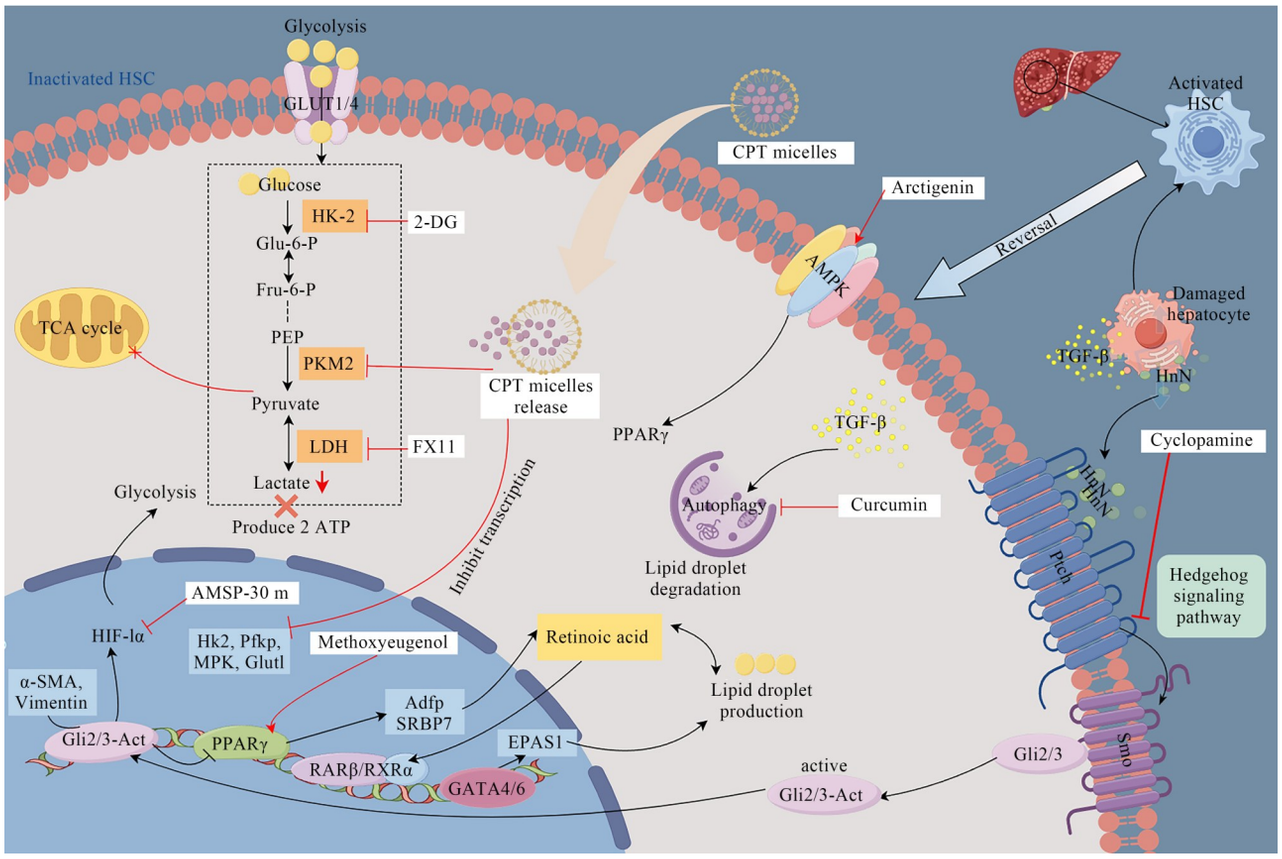


图3　肝星状细胞失活的调控机制

Fig 3　Regulatory mechanisms of hepatic stellate cell inactivation

目前,研究中已发现多种天然产物能够诱导aHSCs失活,具体靶点与机制汇总于表2,其中黄芪甲苷与阿魏酸的联合作用可能缺乏对iHSCs关键转录因子的验证。

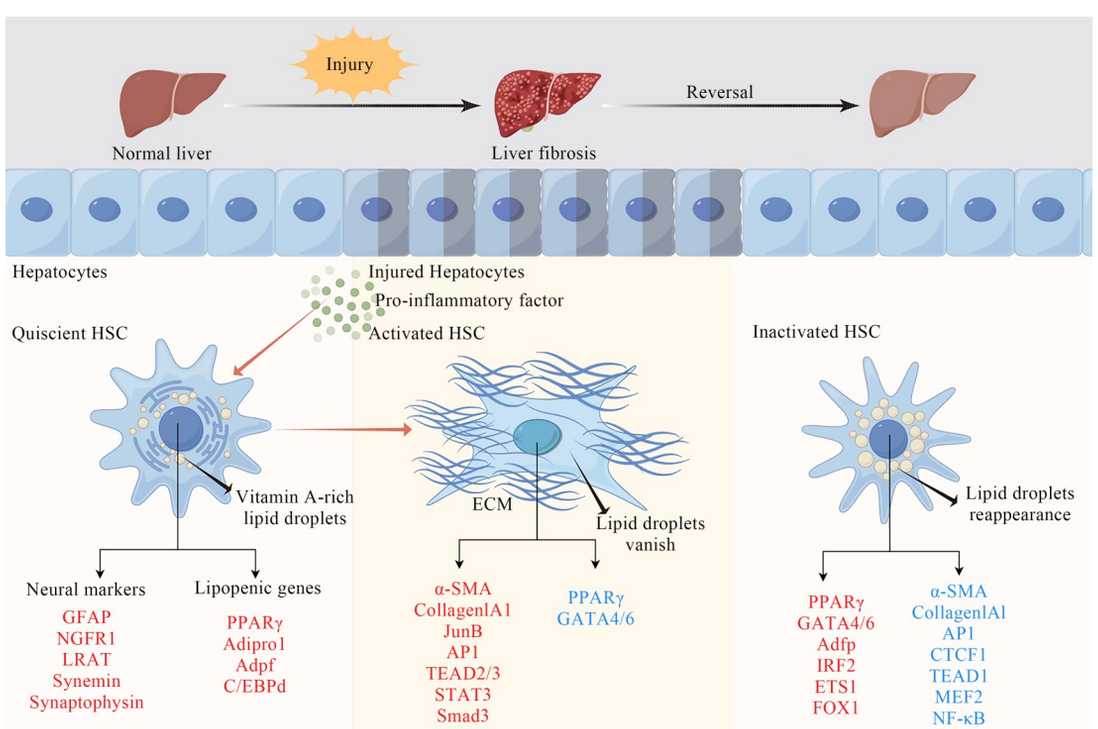


图4　肝星状细胞不同表型的核心基因

Fig 4　Core genes of different phenotypes in hepatic stellate cells

表2 天然产物诱导肝星状细胞失活发挥抗肝纤维化的作用机制

Tab 2 The mechanism of natural products exerting anti-liver fibrosis effects by inducing hepatic stellate cell inactivation

天然产物	中药来源	靶点/通路	作用机制	文献
牛蒡子苷元(Arctigenin)	牛蒡子(*Arctii Fructus*)	AMPK/PPARγ	激活AMPK,上调PPARγ、GFAP,增加脂滴	[80]
甲基丁香酚(Methoxyeugenol)	肉豆蔻(*Myristica fragrans* Houtt.)	PPARγ	激活PPARγ,脂滴增加、收缩能力丧失、成纤维细胞标记物的增殖率和基因表达下降为特征的静止表型	[81]
独一味总多酚苷(total polyphenol glycosides of *Lamiophlomis rotata*)	独一味(*Lamiophlomis rotata* (Benth.) Kudo)	RAGE/RAS/MAPK/NF-κB	竞争性结合RAGE受体,抑制下游RAS/MAPK/NF-kB通路,下调促纤维化转录因子AP1、CTCF;上调静息相关转录因子EST1、PPARγ	[82]
覆盆子酮(Raspberry Ketone)	覆盆子(*Rubus idaeus* L.)	FXR/PGC-1α	激活FXR/PGC-1α通路,逆转aHSCs以减轻LF	[83]
黄芪甲苷Ⅳ(Astragaloside Ⅳ)	黄芪(*Astragalus membranaceus*); 当归(*Angelica sinensis*)	Nrf2	Astragaloside IV诱导Nrf2核内蓄积,负调控GSK-3β以合成抗氧化酶,清除ROS; Ferulic Acid抑制TGF-β1及其受体的表达,进而下调Smad3/4,二者协同诱导aHSCs失活	[84]
阿魏酸(Ferulic Acid)		TGF-β/Smad3/4		
虾青素(Astaxanthin)	-	LRAT、NOX2	上调LRAT mRNA促进脂滴产生;下调NOX2减少ROS蓄积	[76]
原花青素A2(Proanthocyanidin A2)	-	PPAR-γ/Smad	激活PPAR-γ/Smad通路,促使aHSCs逆转为iHSCs	[85]

5 总结与展望

当前已明确3类逆转LF核心治疗策略:减少原发病引起的组织损伤;调控HSCs的状态;抑制ECM沉积并促进其降解[86]。尽管控制原发病是治疗LF的根本措施,但LF呈动态性病理进程,难以通过去除致病因素得到完全逆转[87]。因此HSCs成为逆转LF的突破口。其中,抑制qHSCs活化和诱导aHSCs死亡仍是主流研究方向[86],而诱导aHSCs失活以逆转LF并重建肝脏稳态被认为是更具潜力的新策略,Ilha等[88]发现吲哚-3-丙酸可重塑线粒体动力学,诱导aHSCs失活,降低纤维化标志物;Bouguéon等[89]通过多尺度模型进一步证实,iHSCs可减少ECM来源并降低炎症风险,Xu等[90]通过智能微针阵列整合无细胞与铂基纳米催化疗法实现活化态肝星状细胞失活,有效抑制纤维化进展。

尽管前景广阔,但诱导aHSCs失活的研究仍面临诸多瓶颈。一是虽然iHSCs低表达COL1A1、ACTA等活化标志物,可重新表达PPARγ等静息标志物并恢复维生素A储存,但相较于qHSCs,其对纤维化刺激更敏感,易加速病情复发[79]。而针对iHSCs易被激活的特征仅停留在现象描述,缺乏可干预的分子靶点,难以解决“复发性损伤中iHSCs易被激活”的问题[62];其次,现有研究仅证实aHSCs可转化为iHSCs,却未明确iHSCs究竟是逆转aHSCs终产物,还是向qHSCs转化的中间形态[91]。对此,未来可建立动态追踪模型,结合单细胞测序与谱系追踪技术解析iHSCs的分子特征,验证iHSCs是否具备向qHSCs进一步转化的潜力;同时挖掘iHSCs再激活的关键信号通路或分子靶点。

当前研究聚焦纳米颗粒靶向载体的开发,以提升对aHSCs的靶向性与干预效率[92,93]。Zhang等[94]开发的ROS敏感性双靶向纳米颗粒,释放药物抑制活化通路的同时诱导失活;Xia等[95]构建的多功能仿生纳米系统TM-ATRA/NPs明显提升天然产物对aHSCs的靶向递送效率,可精准靶向aHSCs并诱导其向iHSCs转化,进一步说明靶向递送技术能为天然产物高效作用于aHSCs抗LF的应用价值。

本综述创新在于系统梳理调控HSCs的机制并整合相关天然产物的研究进展,重点阐述HSCs失活的核心机制与调控因子,分析失活表型的可行性及未来研究方向,为逆转LF提供新视角。

作者贡献度说明:

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