附录 1　肝纤维化相关信号通路、受体、非编码 RNA 及通路拮抗剂/抗纤维化药物及相对应的实验模型类别总结

相关通路/分子	抗纤维化分子/药物	实验模型类别
TGFβ1/Smad		
Smad7	PZQ[1]	HSC－LX2
Smad2/3	罗格列酮[2]	蛋氨酸胆碱缺乏饮食诱导的小鼠 NASH 模型
Smad2/3	Lenvatinib[3]	HSC－LX2
JAK/STAT		
STAT3	芦可替尼(ruxolitinib)[4]	原代大鼠 HSC 模型
STAT3	STX－0119[5]	硫代乙酰胺和 CCl_4 诱导的小鼠肝纤维化模型
STAT3	索拉非尼[6]	硫代乙酰胺诱导的小鼠肝纤维化模型 胆管结扎小鼠肝纤维化模型
STAT1	利匹韦林[7]	原代 HSC 模型(人类)
Wnt /β－catenin		
GLI1－依赖性骨桥蛋白	PRC1[8]	CCl_4 诱导的小鼠肝纤维化模型
Wnt3a、Wnt10b	hBM－MSCs－Ex[9]	CCl_4 诱导的小鼠肝纤维化模型
RSPOs(Wnt 信号增强子)	OMP－131R10[10]	CCl_4 诱导的小鼠肝纤维化模型
Notch/ Hes1		
γ－分泌酶	GSI NPs[11]	饮食诱导的 NASH 小鼠模型
Notch2, Notch3, Hes1	Niclosamide[12]	胆管结扎诱导的胆汁淤积性肝纤维化大鼠模型
Sox9 依赖性骨桥蛋白	Ncst ASO[13]	饮食诱导的 NASH 小鼠模型
Hedgehog / Smo / Gli		
Gli2	MC－LR[14]	HSC－LX2
HIF－1a	PB2[15]	HSC－LX2
Gli1/2	GANT61[16]	CCl_4 诱导的小鼠肝纤维模型
Gli1	MDB5[17]	完全性胆总管结扎诱导的继发性胆汁性大鼠肝纤维化模型
ETA/B 受体		
ETA/BR	Bosentan[18]	CCl_4 诱导的肝纤维化模型
ETAR	LU－135252[19]	完全性胆总管结扎诱导的继发性胆汁性大鼠肝纤维化模型
FXR －Shp		
Shp	奥贝胆酸[20]	NASH 肝纤维化患者
PPARγ		
PPARγ		
α－SMA	TGZ[21]	完全性胆总管结扎诱导的继发性胆汁性大鼠肝纤维化模型
PPARα/γ		
TGFβ	Saroglitazar[22]	硫代乙酰胺诱导的大鼠肝纤维化模型
MiRNA		
TGFβ－Smad		
miR－17－5p －Smad7[23]	circRNA－MTO1[24]	CCl_4 诱导的小鼠肝纤维化模型
miR－34a－5p－Smad3[25]	Mirt2[26]	CCl_4 诱导的小鼠肝纤维化模型
miR－146－Smad4[27]	circRNA－RSF1[28]	CCl_4 诱导的小鼠肝纤维化模型
miR－155－ Smad3[29]	circRNA－0067835[30]	MCD 诱导的小鼠肝纤维化模型
Wnt/β－actenin		
miR－17－5p－WIF1(Wnt 抑制因子)[31]	lncRNA－p21[32]	HSC－T6 细胞,CCl_4 诱导的小鼠肝纤维化模型
miR－200a－β－catenin[33]	lncRNA－ATB[33]	HepG2－CORE 细胞
miR－378a－3p－Wnt10a[34]	lncRNA－SNHG7[35]	CCl_4 诱导的小鼠肝纤维化模型
Hedgehog (Hh)		
miR－152－DNMT1－PTCH1	PVT1[36]	原代 HSC 及 CCl_4 诱导的小鼠肝损伤模型
miR－212－Ptch1	MEG3[37]	CCl_4 诱导的小鼠肝纤维化模型
lncRNA		
TGFβ－Smad		
miR－27b－23b/24－Smad4	Gm5091[38]	小鼠酒精性肝纤维化模型
miR－148a－TGFβR1/2	HOTTIP[39]	CCl_4 诱导的小鼠肝纤维化模型

参考文献:

[1] LIU J, KONG D, QIU J, et al. Praziquantel ameliorates CCl_4 – induced liver fibrosis in mice by inhibiting TGF – β/Smad signalling via up – regulating Smad7 in hepatic stellate cells[J]. Br J Pharmacol, 2019, 176(24): 4666 – 4680. DOI: 10.1111/bph.14831.

[2] NI XX, LI XY, WANG Q, et al. Regulation of peroxisome proliferator – activated receptor – gamma activity affects the hepatic stellate cell activation and the progression of NASH via TGF – β1/Smad signaling pathway[J]. J Physiol Biochem, 2021, 77(1): 35 – 45. DOI: 10.1007/s13105 – 020 – 00777 – 7.

[3] OGAWA H, KAJI K, NISHIMURA N, et al. Lenvatinib prevents liver fibrosis by inhibiting hepatic stellate cell activation and sinusoidal capillarization in experimental liver fibrosis [J]. J Cell Mol Med, 2021, 25(8): 4001 – 4013. DOI: 10.1111/jcmm.16363.

[4] LYU L, YIN JK, ZHANG Z, et al. Role of ruxolitinib in the target inhibition of hepatic stellate cell activation and mechanism[J]. J Shanxi Med Univ, 2020, 51(2): 141 – 146. DOI: 10.13753/j.issn.1007 – 6611.2020.02.007.
律玲, 阴继凯, 张章, 等. 芦可替尼靶向抑制肝星状细胞活化的作用及机制[J]. 山西医科大学学报, 2020, 51(2): 141 – 146. DOI: 10.13753/j.issn.1007 – 6611.2020.02.007.

[5] CHOI S, JUNG H J, KIM M W, et al. A novel STAT3 inhibitor, STX – 0119, attenuates liver fibrosis by inactivating hepatic stellate cells in mice[J]. Biochem Biophys Res Commun, 2019, 513(1): 49 – 55. DOI: 10.1016/j.bbrc.2019.03.156.

[6] SU TH, SHIAU CW, JAO P, et al. Sorafenib and its derivative SC – 1 exhibit antifibrotic effects through signal transducer and activator of transcription 3 inhibition[J]. Proc Natl Acad Sci U S A, 2015, 112(23): 7243 – 7248. DOI: 10.1073/pnas.1507499112.

[7] MARTÍ – RODRIGO A, ALEGRE F, MORAGREGA ÁB, et al. Rilpivirine attenuates liver fibrosis through selective STAT1 – mediated apoptosis in hepatic stellate cells[J]. Gut, 2020, 69(5): 920 – 932. DOI: 10.1136/gutjnl – 2019 – 318372.

[8] RAO S, XIANG J, HUANG J, et al. PRC1 promotes GLI1 – dependent osteopontin expression in association with the Wnt/β – catenin signaling pathway and aggravates liver fibrosis [J]. Cell Biosci, 2019, 9: 100. DOI: 10.1186/s13578 – 019 – 0363 – 2.

[9] RONG X, LIU J, YAO X, et al. Human bone marrow mesenchymal stem cells – derived exosomes alleviate liver fibrosis through the Wnt/β – catenin pathway[J]. Stem Cell Res Ther, 2019, 10(1): 98. DOI: 10.1186/s13287 – 019 – 1204 – 2.

[10] ZHANG M, HAUGHEY M, WANG NY, et al. Targeting the Wnt signaling pathway through R – spondin 3 identifies an anti – fibrosis treatment strategy for multiple organs[J]. PLoS One, 2020, 15(3): e0229445. DOI: 10.1371/journal.pone.0229445.

[11] RICHTER LR, WAN Q, WEN D, et al. Targeted delivery of Notch Inhibitor attenuates obesity – induced glucose intolerance and liver fibrosis[J]. ACS Nano, 2020, 14(6): 6878 – 6886. DOI: 10.1021/acsnano.0c01007.

[12] ESMAIL MM, SAEED NM, MICHEL HE, et al. The ameliorative effect of niclosamide on bile duct ligation induced liver fibrosis via suppression of NOTCH and Wnt pathways[J]. Toxicol Lett, 2021, 347: 23 – 35. DOI: 10.1016/j.toxlet.2021.04.018.

[13] ZHU C, KIM K, WANG X, et al. Hepatocyte Notch activation induces liver fibrosis in nonalcoholic steatohepatitis[J]. Sci Transl Med, 2018, 10(468): eaat0344 . DOI: 10.1126/scitranslmed.aat0344.

[14] GU S, YAN M, WANG C, et al. Microcystin – leucine – arginine induces liver fibrosis by activating the Hedgehog pathway in hepatic stellate cells[J]. Biochem Biophys Res Commun, 2020, 533(4): 770 – 778. DOI: 10.1016/j.bbrc.2020.09.075.

[15] FENG J, WANG C, LIU T, et al. Procyanidin B2 inhibits the activation of hepatic stellate cells and angiogenesis via the Hedgehog pathway during liver fibrosis [J]. J Cell Mol Med, 2019, 23(9): 6479 – 6493. DOI: 10.1111/jcmm.14543.

[16] JIAYUAN S, JUNYAN Y, XIANGZHEN W, et al. Gant61 ameliorates CCl – induced liver fibrosis by inhibition of Hedgehog signaling activity[J]. Toxicol Appl Pharmacol, 2020, 387: 114853. DOI: 10.1016/j.taap.2019.114853.

[17] KUMAR V, DONG Y, KUMAR V, et al. The use of micelles to deliver potential hedgehog pathway inhibitor for the treatment of liver fibrosis[J]. Theranostics, 2019, 9(25): 7537 – 7555. DOI: 10.7150/thno.38913.

[18] ROCKEY DC, CHUNG JJ. Endothelin antagonism in experimental hepatic fibrosis. Implications for endothelin in the pathogenesis of wound healing[J]. J Clin Invest, 1996, 98(6): 1381 – 1388. DOI: 10.1172/JCI118925.

[19] CHO JJ, HOCHER B, HERBST H, et al. An oral endothelin – A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis[J]. Gastroenterology, 2000, 118(6): 1169 – 1178. DOI: 10.1016/s0016 – 5085(00)70370 – 2.

[20] YOUNOSSI ZM, RATZIU V, LOOMBA R, et al. Obeticholic acid for the treatment of non – alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo – controlled phase 3 trial [J]. Lancet, 2019, 394(10215): 2184 – 2196. DOI: 10.1016/S0140 – 6736(19)33041 – 7.

[21] MARRA F, DEFRANCO R, ROBINO G, et al. Thiazolidinedione treatment inhibits bile duct proliferation and fibrosis in a rat model of chronic cholestasis [J]. World J Gastroenterol, 2005, 11(32): 4931 – 4938. DOI: 10.3748/wjg.v11.i32.4931.

[22] MAKLED MN, SHARAWY MH, EL – AWADY MS. The dual PPAR – α/γ agonist saroglitazar ameliorates thioacetamide – induced liver fibrosis in rats through regulating leptin[J]. Naunyn Schmiedebergs Arch Pharmacol, 2019, 392(12): 1569 – 1576. DOI: 10.1007/s00210 – 019 – 01703 – 5.

[23] YU F, GUO Y, CHEN B, et al. MicroRNA – 17 – 5p activates hepatic stellate cells through targeting of Smad7[J]. Lab Invest, 2015, 95(7): 781 – 789. DOI: 10.1038/labinvest.2015.58.

[24] WANG W, DONG R, GUO Y, et al. CircMTO1 inhibits liver fibrosis via regulation of miR – 17 – 5p and Smad7[J]. J Cell Mol Med, 2019, 23(8): 5486 – 5496. DOI: 10.1111/jcmm.14432.

[25] FEILI X, WU S, YE W, et al. MicroRNA – 34a – 5p inhibits liver fibrosis by regulating TGF – β1/Smad3 pathway in hepatic stellate cells[J]. Cell Biol Int, 2018, 42(10): 1370 – 1376. DOI: 10.1002/cbin.11022.

[26] ZHANG B, LI H, LI D, et al. Long noncoding RNA Mirt2 upregulates USP10 expression to suppress hepatic steatosis by sponging miR-34a-5p[J]. Gene, 2019, 700: 139-148. DOI: 10.1016/j.gene.2019.02.096.

[27] HE Y, HUANG C, SUN X, et al. MicroRNA-146a modulates TGF-beta1-induced hepatic stellate cell proliferation by targeting SMAD4[J]. Cell Signal, 2012, 24(10): 1923-1930. DOI: 10.1016/j.cellsig.2012.06.003.

[28] CHEN Y, YUAN B, CHEN G, et al. Circular RNA RSF1 promotes inflammatory and fibrotic phenotypes of irradiated hepatic stellate cell by modulating miR-146a-5p[J]. J Cell Physiol, 2020, 235(11): 8270-8282. DOI: 10.1002/jcp.29483.

[29] CSAK T, BALA S, LIPPAI D, et al. MicroRNA-155 deficiency attenuates liver steatosis and fibrosis without reducing inflammation in a mouse model of steatohepatitis[J]. PLoS One, 2015, 10(6): e0129251. DOI: 10.1371/journal.pone.0129251.

[30] ZHU L, REN T, ZHU Z, et al. Thymosin-β4 mediates hepatic stellate cell activation by interfering with circRNA-0067835/miR-155/FoxO3 signaling pathway[J]. Cell Physiol Biochem, 2018, 51(3): 1389-1398. DOI: 10.1159/000495556.

[31] YU F, LU Z, HUANG K, et al. MicroRNA-17-5p-activated Wnt/β-catenin pathway contributes to the progression of liver fibrosis[J]. Oncotarget, 2016, 7(1): 81-93. DOI: 10.18632/oncotarget.6447.

[32] YU F, GUO Y, CHEN B, et al. LincRNA-p21 inhibits the Wnt/β-catenin pathway in activated hepatic stellate cells via sponging MicroRNA-17-5p[J]. Cell Physiol Biochem, 2017, 41(5): 1970-1980. DOI: 10.1159/000472410.

[33] FU N, ZHAO SX, KONG LB, et al. LncRNA-ATB/microRNA-200a/β-catenin regulatory axis involved in the progression of HCV-related hepatic fibrosis[J]. Gene, 2017, 618: 1-7. DOI: 10.1016/j.gene.2017.03.008.

[34] YU F, FAN X, CHEN B, et al. Activation of hepatic stellate cells is inhibited by microRNA-378a-3p via Wnt10a[J]. Cell Physiol Biochem, 2016, 39(6): 2409-2420. DOI: 10.1159/000452509.

[35] YU F, DONG P, MAO Y, et al. Loss of lncRNA-SNHG7 promotes the suppression of hepatic stellate cell activation via miR-378a-3p and DVL2[J]. Mol Ther Nucleic Acids, 2019, 17: 235-244. DOI: 10.1016/j.omtn.2019.05.026.

[36] ZHENG J, YU F, DONG P, et al. Long non-coding RNA PVT1 activates hepatic stellate cells through competitively binding microRNA-152[J]. Oncotarget, 2016, 7(39): 62886-62897. DOI: 10.18632/oncotarget.11709.

[37] YU F, GENG W, DONG P, et al. LncRNA-MEG3 inhibits activation of hepatic stellate cells through SMO protein and miR-212[J]. Cell Death Dis, 2018, 9(10): 1014. DOI: 10.1038/s41419-018-1068-x.

[38] ZHOU B, YUAN W, LI X. LncRNA Gm5091 alleviates alcoholic hepatic fibrosis by sponging miR-27b/23b/24 in mice[J]. Cell Biol Int, 2018, 42(10): 1330-1339. DOI: 10.1002/cbin.11021.

[39] LI Z, WANG J, ZENG Q, et al. Long noncoding RNA HOTTIP promotes mouse hepatic stellate cell activation via downregulating miR-148a[J]. Cell Physiol Biochem, 2018, 51(6): 2814-2828. DOI: 10.1159/000496012.