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述评 EDITORIAL

肝细胞癌中上皮间质转化及其相关信号通路的研究进展

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Epithelial-mesenchymal transition and related signaling pathways in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common forms of liver cancer and the third leading cause of cancer-related mortality in the world. Although numerous therapeutic strategies have been employed to treat this fatal disease, the prognosis of HCC patients remains dismal with a low 5-year survival rate of approximately 30%. Postoperative recurrence and metastasis of HCC are the leading cause of poor prognosis. Metastasis has been thought to rely on non-motile epithelial tumor cells acquiring characteristics of mesenchymal cells, which are more migratory. This change is known as the epithelial-to-mesenchymal transition (EMT). EMT has been considered one of the main reasons for the invasion and metastasis of HCC. Notably, increasing evidence indicates that several signaling pathways participate in the regulation of EMT in HCC. In the current review, we will discuss the current progress in research of EMT and its related signaling pathways in HCC.

Key Words: Hepatocellular carcinoma; Epithelial-mesenchymal transition; Invasion and metastasis; Signaling pathway

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摘要

肝细胞癌(hepatocellular carcinoma, HCC)是一种最常见的肝癌, 世界上癌症相关死亡的第3大常见原因. 尽管各种治疗手段已经用

背景资料
目前肝细胞癌(hepatocellular carcinoma, HCC)患者的预后仍然很不理想, 术后复发转移是HCC患者预后不良的主要因素, 上皮间质转化(epithelial-mesenchymal transition, EMT)已经被认为是导致HCC侵袭转移的主要因素之一, 为研发靶向阻断HCC侵袭转移的治疗策略, 最终达到改善患者预后的目标, 迫切需要深入研究EMT在HCC中的作用及精确分子机制.

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研发前沿
HCC侵袭转移的分子机制是近年来的研究热点, EMT与HCC侵袭转移的关联已经证实, 但相关的信号通路还有待进一步研究. 当前研究证据主要来源于调控EMT相关转录因子或者移植瘤实验, EMT在自发肿瘤进展中的有何作用? 是否可以通过靶向阻断EMT来缓解HCC侵袭转移? 这些问题都有待进一步研究.

于处理该致死性疾病, HCC患者的预后仍然很不理想, 术后5年生存率大约为30%. 术后复发转移是HCC患者预后不良的主要因素, 这一过程被认为依赖于非运动性上皮肿瘤细胞获得间质细胞特征, 称为上皮间质转化(epithelial-mesenchymal transition, EMT), EMT已经被认为是导致HCC侵袭转移的主要因素之一. 值得注意的是, 越来越多的证据表明多个信号通路参与调节HCC的EMT进展, 本文将对近年来HCC中EMT及其相关信号通路的研究进展进行简要综述.

关键词: 肝细胞癌; 上皮间质转化; 侵袭转移; 信号通路

核心提示: 肝细胞癌(hepatocellular carcinoma, HCC)侵袭转移是导致预后不良的主要因素, 肝癌细胞发生上皮间质转化(epithelial-mesenchymal transition)后侵袭及迁移能力显著增强, 从而更容易出现肝内及肝外转移. 人为干预这些病理过程有可能促进HCC的治疗及改善患者预后.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是世界上最常见的恶性肿瘤之一, 全球发病率位居第6位, 每年约70万的新发病例, 在全球癌症相关死亡中HCC高居第3位, 每年约60万患者死亡[1]. 持续增长的HCC发病率已经成为影响全球健康的重大威胁, 各种各样的致病因素已经被证实, 如肝炎病毒、黄曲霉素B1、吸烟、酒精摄入、非酒精性脂肪肝、糖尿病和肥胖等. 尽管HCC的诊断方法得到很大的提高, 但大多数患者在诊断时已为晚期, 超过60%的患者失去了可能的治疗机会如外科切除和肝移植[2]. HCC患者的5年生存率只有7%, 有症状的患者生存率很少大于1年[3]. HCC患者预后差的潜在原因主要是因为常见的肝内外转移, 因此, 阐明HCC转移的分子机制有助于研发有效的转移相关靶向治疗, 从而提高晚期HCC患者的生存率.

上皮间质转化(epithelial-mesenchymal transition, EMT)是细胞失去上皮样极性, 表现出间质表型的一种生物学进程, 已经被认为是肿瘤转移的一种最重要的机制. 本综述将总结EMT的分子机制并讨论HCC中EMT相关信号通路的研究进展.

1 EMT的基础

EMT是一个可逆的上皮细胞向间质细胞转化的细胞进程[4]. 在此过程中, 上皮细胞将经历持续的细胞活动, 包括失去顶-底极性结构, 细胞间连接受到破坏, 细胞骨架重构, 改变细胞形态并最终呈现出间质及侵袭表型, 从而增加细胞运动性并提高其降解细胞外基质的能力[5].

为实现该表型转变, 细胞需要重组他们的基因表达[4-6]. EMT相关基因重组的特征是E-钙黏蛋白(E-cadherin)下调促进细胞连接分离. 同时, 间质型N-钙黏蛋白(N-cadherin)表达增加, 以上过程被认为是“钙黏蛋白转化”. 促使上皮表型向间质表型转化也需要改变编码细胞骨架的基因表达, 特别是能形成中间纤维并调节细胞器和蛋白质运输的波形蛋白(Vimentin)表达激活, 在向间质细胞转化过程中, 上皮细胞失去与基底膜的交互作用并与其他的细胞外基质成分建立新的连接. 因此, 上皮整合蛋白表达被抑制, 而其他整合蛋白表达增加, 整合蛋白表达的变化对EMT至关重要. 在细胞发生EMT进程中, 为促进更具侵袭性的行为, 蛋白酶家族包括基质金属蛋白酶2(matrix metalloproteinases, MMP2)、MMP3及MMP9均表达上调. 目前, E-cadherin, N-cadherin及Vimentin的表达已被广泛定义为EMT发生的分子标记.

迄今为止, 有3个完善的转录调节因子组被确定为调节EMT分子标记表达的重要因素[6]. 第一组转录因子是Snail锌指蛋白家族, 包括Snail1和Snail2(Slug). 第二组是锌指E-box结合同源框家族, 包括Zeb1和Zeb2. 第三组是基础helix-loop-helix家族, 包括Twist1、Twist2、E12、E47以及分化抑制蛋白. 这些转录因子可以单独的或协同抑制上皮基因和激活间质基因的表达, 从而调节细胞的EMT. 转录因子Snail和Zeb家族可以通过结合E-cadherin启动子的E-box框从而抑制E-cadherin的转录. 另外, 一些新的EMT相关转录因子也被发现. 这些

新的EMT调节因子包括叉头盒(forkhead box, FOX)转录因子家族, GATA家族成员和SOX转录因子[5,6].

2 EMT的类型

基于其生物背景及功能意义, EMT可以分为3种类型[7]: (1) Ⅰ型EMT与着床、胚胎形成和器官发育有关, 促使不同类型的间质样细胞形成具有各种各样功能的组织. 来源于Ⅰ型EMT的间质细胞保持着向上皮转化的间质上皮化的潜在能力; (2) Ⅱ型EMT与组织损伤, 炎症反应, 组织再生和器官纤维化相关. 在创伤和/或炎症损伤过程中, Ⅱ型EMT产生成纤维细胞, 从而促进组织再生和重构. 关于器官纤维化, 此型EMT对炎症过程产生持续反应, 最终引起器官衰竭; (3)Ⅲ型EMT发生于恶性细胞的遗传或表观遗传改变中, 在恶性细胞的转移播散过程中起重要作用. 下面我们将详细讨论Ⅲ型EMT.

3 EMT在肿瘤及HCC中的作用

近年来, EMT在肿瘤中的意义被广泛研究. 发生EMT的恶性细胞获得增强的迁移及侵袭能力并侵入周围的细胞外基质, 最终向远处位点转移. EMT调控因子包括Snail1和Snail2的表达增加了恶性肿瘤细胞的侵袭性并与肿瘤复发和癌症患者的生存率显著相关[5,8]. EMT表型改变在结肠癌、甲状腺癌及乳腺癌的侵袭表型中发挥重要作用, 这些研究均表明EMT参与了肿瘤转移过程[5]. 另外, 越来越多的证据表明EMT参与了促进肿瘤进展的其他方面[6]. 发生EMT的细胞具有抵抗细胞凋亡、衰老、化疗和免疫治疗的能力, EMT通过诱导免疫耐受使恶性肿瘤细胞逃避免疫监视, 也有研究[9-13]表明EMT与肿瘤干细胞的特性相关. 近期Fischer等[14]以及Zheng等[15]在乳腺癌和胰腺癌中研究发现EMT形成不是肿瘤转移的必备条件, 而是耐药的决定因素. 然而上述研究存在局限性, 因为肿瘤是一种异质性疾病, 不同肿瘤类型中癌细胞转移相关机制可能不一致, 例如, 研究发现*Neu*或者*PyMT*癌基因诱导的乳腺癌小鼠模型中检测不到EMT发生, 而myc诱发的乳腺癌中则存在EMT[16]. 因此, 尽管Fischer等[14]和Zheng等[15]在他们构建的乳腺癌和胰腺癌模型中发现EMT不是肿瘤进展的必要因素, 仍然有必要在其他肿瘤模型和肿瘤类型中明确以上结论是否具有普遍性.

在HCC中, E-cadherin作为EMT最重要的分子标记, 其在69%的HCC标本中表达下调并与肝内转移和包膜侵犯相关[17]. 在发生转移的患者标本中, E-cadherin的表达明显低于未发生转移的患者[18]. 进一步的研究[19]表明, Snail和Twist是诱导HCC发生EMT的主要调节因子. 在HCC患者中, Snail和Twist过表达与较大的肿瘤体积、复发率升高、更短的无瘤生存率及总生存率相关[19]. 另外, HCC中Snail或Twist的表达与E-cadherin表达下调相关. 体外实验证实, 过表达Snail或Twist可促进肿瘤细胞的侵袭能力及增加细胞的间质表型. 在Huh7细胞中过表达Snail或Twist抑制E-cadherin表达, 并且诱导EMT表型转化[19]. 除了增加细胞的侵袭性, EMT也保护肝细胞逃避细胞外信号诱导的细胞凋亡. 例如, EMT可以激活表皮生长因子受体(epidermal growth factor receptor, EGFR)通路并帮助肝细胞逃避转化生长因子-β1(transforming growth factor-β1, TGF-β1)诱导的细胞凋亡[20]. 另外, 研究[21-23]已经发现EMT导致分化不良的HCC细胞系化疗抗性增加. Wu等[24]构建吉西他滨(Gemcitabine)抵抗肝癌细胞系, 研究发现吉西他滨抵抗肝癌细胞获得了EMT表型. 而且5-氟尿嘧啶(5-fluorouracil, 5-Fu)抵抗的肝癌细胞也存在典型的EMT形态学表型, 如细胞与细胞间黏附缺失、纺锤状形态和伪足的形成增加, 实时定量PCR检测发现E-cadherin表达下调以及Twist1表达增加, 进一步证实了EMT的形成[25].

4 HCC中EMT相关信号通路及其功能

由于其在肿瘤生物学中各方面的基础作用, EMT的调节网络机制正在广泛研究中. 众多的信号通路已经被证实与EMT相关, 包括TGF-β信号通路、Wnt信号通路、Notch信号通路、Hedgehog(Hh)信号通路、受体络氨酸激酶(receptor tyrosine kinase, RTK)相关信号通路如磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)/Akt通路、促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)通路、Jun氨基末端激酶(Jun N-terminal kinase, JNK)通路和Src通路, 以及炎症信号通路如细胞核因子κB(nuclear factor-κB, NF-κB)通路和白介素6(interleukin-6, IL6)/信号传导蛋白和转

创新盘点

本文对HCC中EMT的研究进展进行阐述, 重点说明EMT相关信号通路, 且对近年来的研究热点进行总结, 可以更深入的了解EMT在HCC中的功能及相关信号通路在EMT形成中的作用.

应用要点
本文旨在通过了解HCC中EMT形成的作用及相关分子机制, 探讨新的研究方向和治疗策略: 即如何通过敲除EMT相关转录因子和阻断相关信号通路等来缓解HCC的进展.

录激活物3(signal transducers and activators of transcription 3, STAT3)通路. 这些信号通路能单独或协同其他信号通路触发EMT, 而几乎所有信号通路均与HCC的发生和发展相关. 下面, 我们将回顾HCC中与EMT明确相关的信号通路并揭示其功能.

4.1 TGF-β信号通路 TGF-β信号通路是一个EMT的关键调控因子和主要诱导因子, 其在发育、伤口愈合、纤维化和肿瘤中发挥至关重要的作用. TGF-β家族包含33个家族成员, 包括TGF-β的各亚型(TGF-β1、TGF-β2、TGF-β3)、激活素类、骨形态发生蛋白质类(bone morphogenetic proteins, BMPs)以及生长和分化因子(growth and differentiation factors, GDFS). 这条途径通过TGF-β家族成员与细胞表面受体形成复合物而启动, 细胞表面受体是两个Ⅱ型(TβRⅡ)和两个Ⅰ型(TβRⅠ)跨膜蛋白激酶受体组成的四聚体. 这种结合先使得TβRⅡ受体磷酸化, 随后激活TβRⅠ受体. 活化的TβRⅠ受体随后招募和磷酸化细胞内的Smad2和Smad3蛋白. 这两个受体激活后的Smad蛋白与Smad4相互作用形成三聚Smad复合物进入细胞核内, 并与其他转录因子协同调节靶基因的表达. Smad信号已经发现可以调节EMT的转录因子包括Snail1/Snail2[26,27]、ZEB1/ZEB2[28-30]及Twist[31]的表达, 从而导致EMT的发生. 除了经典的Smad信号, TGF-β也可以通过其他的非Smad信号通路, 包括Rho样GTP酶[32,33]、PI3K/Akt/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)[34-36]、细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)[37,38]、p38[39]和JNK[39,40]途径来诱发EMT.

众所周知, TGF-β信号通路在肿瘤中具有双重作用. 在肿瘤的早期阶段, 他可以发挥抑癌作用, 而在晚期癌症中, TGF-β信号通路发挥促癌作用. 研究[41]表明虽然TGF-β1抑制肝细胞生长, 但在HCC患者血清和尿液中TGF-β1的水平是升高的, 另外TGF-β1表达水平升高与HCC患者的更短的生存期相关. 对HCC组织进行免疫组织化学分析也发现TGF-β1、TGF-β2、TGF-β3是高表达的[42]. 通过对野生型的肝脏及TβRⅡ表达缺失的肝脏组织中进行基因表达的比较发现[43]: TGF-β早期效应功能的基因可以诱导细胞周期阻滞和凋亡, TGF-β晚期转录效应的基因可以激活EMT和基质重塑密切相关的一些基因. 此外, TGF-β的早期和晚期效应基因的表达已在HCC样本中的得到验证: 具有TGF-β晚期特征的患者具有更多肿瘤侵袭性的表型, 更高的肿瘤复发率及更少的生存时间. 在HCC中, TGF-β诱导的EMT是TGF-β信号通路逃避肿瘤抑制效应的重要原因. TGF-β信号通路活化与HCC细胞E-cadherin表达减少、运动性增加和侵袭行为增强相关. 同时有研究[44]发现: TGF-β可以与细胞外基质蛋白层黏连蛋白5(laminin-5, Ln-5)共同作用促进EMT过程. 在发生EMT的时候, TGF-β可以通过上调血小板衍生生长因子(platelet-derived growth factor, PDGF)-A和PDGF受体促进PDGF信号通路, 进而产生一个具有肿瘤干细胞特征的新生肿瘤细胞亚群[45]. HCC细胞选择性的失去对TGF-β信号通路生长抑制效应的应答, 而对TGF-β1刺激则表现出增强的迁移和侵袭能力的具体机制尚未完全阐明. 在HCC中, TGF-β信号的功能角色转变也可能与TGF-β对肿瘤微环境的作用相关. 已经有研究表明, TGF-β可以调节肿瘤微环境免疫监视进而促进肿瘤的发展和转移. Yang等[46]发现TGF-β信号通路也可以被乙型肝炎病毒(hepatitis B virus, HBV)感染激活, 产生趋化因子2(chemotactic factor-2, CLL-2)及募集Treg细胞. 免疫抑制Treg细胞可以造成对肿瘤细胞的免疫反应破坏, 从而促进HCC细胞的肝内静脉转移. 此外, TGF-β信号通路也与在HCC形成过程中通过Akt激活的肿瘤起始细胞的生成相关[47].

由于TGF-β信号通路在HCC的发生发展中起着重要作用, 他也成为了HCC治疗的理想靶点. 对HCC细胞用TGF-β受体激酶抑制剂LY2157299处理后, 可以抑制肿瘤的生长和迁移[48,49]. 现在LY2157299的功效正处于Ⅱ期临床试验研究阶段(NCT01246986). 患者接受了LY2157299治疗后, 血浆中的TGF-β, E-cadherin和甲胎蛋白(α-fetoprotein, AFP)水平会有所降低[50]. 另一种TβRⅠ受体激酶抑制剂LY2109761, 可以通过上调E-cadherin逆转HCC细胞EMT表型, 并降低HCC细胞的侵袭和转移能力[18]. 他也可以抑制HCC细胞和内皮细胞之间的旁分泌途径, 从而抑制肿瘤新生血管的形成和肿瘤的生长[51]. 通过抑制结缔组织生长因子(connective tissue growth factor, CTGF)合成和释放, LY2109761干扰了HCC细胞和癌相关

成纤维细胞之间的相互作用, 从而减少HCC的生长和扩散[52].

4.2 Wnt/β-catenin信号通路 过去的二十年里, Wnt信号通路参与细胞增殖、分化、运动、干细胞的自我更新以及肿瘤形成已经被广泛研究[53]. 到目前为止, 在人类中已发现有19种不同的Wnt配体(Wnts)和11个跨膜Frizzled受体(FZD). 与细胞外的分泌Wnts配体结合并与细胞表面受体Frizzled和低密度脂蛋白受体相关蛋白(low-density lipoprotein receptor related protein, LRP)5/6L相结合可以启动下游信号通路. 他们的相互作用分别可以激活经典级联反应(Wnt/β-catenin信号通路)和非经典的级联反应: JNK和蛋白激酶C(protein kinase C, PKC)通路[54]. 在典型的通路中, 这种相互作用可以通过降解结肠腺瘤性息肉病(adenomatous polyposis coli, APC)蛋白、Axin、激酶糖原合成酶激酶-3β(glycogen synthase kinase-3β, GSK-3β)和酪蛋白激酶I(casein kinase I, CKI)组成的复合体阻止β-catenin被磷酸化, 进而防止β-catenin泛素化并促进其在细胞质中蓄积. 细胞质β-catenin进入细胞核内, 与淋巴增强因子/T细胞因子(lymphoid enhancing factor/T-cell factor, LEF/TCF)复合物相互作用, 最终导致β-catenin靶基因的激活. β-catenin入核后可以激活LEF-1的转录[55], LEF-1也同时是EMT发生的重要分子[56]. 研究[57]已发现β-catenin/LEF-1复合物可以下调E-cadherin的表达. 使用PDGF治疗后, 核内的β-catenin可以与磷酸化的p68相互作用并且促进EMT过程[58]. 此外, 研究[59]表明: 该通路在缺氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)诱导的EMT中也发挥重要作用.

在肝脏中, Wnt信号通路具有多种生物学功能[60], 包括胎肝发育、肝再生、肝区划分、肝脏代谢及肝纤维化等. Wnt信号通路遗传和/或表观遗传的变化导致的异常活化对于由正常肝细胞向恶性表型的转变是必不可少的. 在95%的HCC中Wnt信号通路已证实是失调的[61], 这提示其在HCC的发生中具有重要意义. 研究发现: 在30%-70%的HCC中, β-catenin在细胞质和核内高表达. β-catenin在细胞质和核内的异常表达水平与肿瘤分级, 临床病理参数及患者的预后相关. 8%-30%HCC具有β-catenin的基因突变(CTNNB1), 这也是β-catenin高表达的部分原因. 此外, Axin1/2突变[62]、GSK-3β的失活[63]、肿瘤抑制因子*APC*基因异常甲基化及FZD受体的高表达[64]也是Wnt/β-catenin信号通路在HCC中异常激活的潜在机制. *APC*基因失活导致的β-catenin信号活化对于小鼠肝肿瘤发生也是必需的[65]. 研究发现Wnt/β-catenin信号通路也可被HBV[66,67]或HCV[68]激活, 在病毒性肝炎发展为HCC进程中起着重要的作用. 并且, Wnt信号通路也可以通过调节炎症参与HCC的进展. Anson等[69]发现, Wnt/β-catenin信号可以NF-κB信号并产生促进肿瘤侵袭性的炎症微环境. 值得注意的是, 硫酸乙酰肝素糖蛋白(heparan sulfate proteoglycan, HSPG)已证实可以作为Wnt配体的共同受体或储存场所, 他们之间与Wnts的相互作用可以调节下游信号通路的活性. Lai等[70]已经提出过表达的硫酸酯酶2可以将HSPGs上存储的Wnt3a释放, 促进与Wnt配体及Frizzled受体的结合, 并最终激活Wnt/β-catenin信号通路. Gao等[71]发现利用人单克隆抗体(HS20)可以阻断Wnt3a的积累及与HSPGs的结合, 通过减少该配体与FZD受体之间的通道, 从而破坏Wnt3a/β-catenin信号的级联反应.

4.3 Notch信号通路 Notch信号通路在生长发育及疾病发生发展等多个生理病理过程中均发挥着至关重要的作用. 到目前为止, 有4个Notch受体(Notch 1-4)和5个Notch配体(Delta-like1、3、4和Jagged1, 2)被发现. Notch的配体和受体都是跨膜蛋白, 这种结构是细胞间接触所需要的. Notch的配体与其相应的受体结合后, Notch受体被γ-分泌酶裂解, 然后释放Notch的一个胞内结构域, 即NotchIC. 随后, NotchIC进入细胞核, 与DNA结合蛋白质CSL(CBF1, Hairless抑制子, Lag1)、Mastermind(Mam)以及其他辅助因子形成一个转录复合子, 继而调节靶基因的表达和转录活性[72]. 目前已经证实的Notch信号通路[61]下游靶点包括HES(hairy enhancer of split)家族[73]、Hes相关抑制蛋白(hes-related repressor protein, HERP)[62]、Notch的受体和配体[74]、细胞周期蛋白D1(cyclin D1, CCND1)及细胞周期素依赖性激酶2(cyclin-dependent kinase, CDK2)[75], 还有MYC[76]. Notch的激活也可以调节Snail和血管内皮钙黏蛋白(vascular endothelial cadherin, VE-cadherin)的表达, 进而促进了永生化内皮细胞

名词解释

钙黏蛋白转化: 在同一肿瘤中, 同时存在的E-cadherin表达减少与N-cadherin表达增加被称为E-N钙黏蛋白转化. E-N钙黏蛋白转化与EMT的关系密切.

同行评价
本文阐述了近年来肝癌细胞EMT形成与HCC恶性行为的关系, 重点分析细胞内各种信号途径对EMT形成的影响, 对肝癌的靶向治疗有一定的指导意义.

的EMT并伴随着致癌基因的转换[77]. 除了已证实的Notch依赖性激活, Notch通路也可以由Notch配体在没有与Notch受体相互作用的情况下激活[78,79].

虽然Notch信号通路是一个跨物种的高度保守的信号通路, 但是这条多效的信号通路的功能严格上说是与生物背景息息相关的. Notch信号通路在恶性肿瘤中的作用与癌症类型有关. 他在胰腺癌[80]、乳腺癌[81]、前列腺癌[82]和肺癌[83]中具有致癌作用. 但是, 在皮肤癌中他被认为是一种肿瘤抑制因子[84,85]. 从原理上讲, Notch信号通路在调节细胞周期、细胞凋亡、细胞分化、血管生成、EMT和肿瘤干细胞中均有作用[74]. 而且Notch信号通路也可与其他信号通路共同作用, 包括PI3K/AKT信号通路[86,87]、NF-κB信号通路[88,89]、Wnt信号通路[85,90]、RAS-MAPK信号通路[91,92]和TGF-β信号通路[93,94]等, 他们的共同作用决定其功能的结果. 然而, Notch在HCC中作用的研究却显示出相互矛盾的结果. 早期的研究[95]表明, Notch1可以通过抑制细胞周期和诱导细胞凋亡来抑制HCC的生长. Notch1的过表达能下调CyclinA1、CyclinD1、CyclinE和CDK2的表达, 抑制Rb蛋白的磷酸化, 并增加p21的表达[95,96]. Notch1也可通过防止蛋白酶体降解调控p53蛋白表达, 从而使HCC细胞对肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)敏感继而诱导细胞凋亡[97]. 还有研究[98]证实Notch信号通路的激活可以负反馈调节Rb的失活进而抑制HCC生长. 然而, Notch信号通路在HCC的致癌作用也被证实. 在HCC中Notch3和Notch1的表达比正常肝组织多, 这表明在HCC中Notch的信号通路被激活[99]. 另一项研究[100]表明, 在1/3的HCC中发现了代表Notch活性的基因标签. 使用转基因小鼠模型可以发现Notch信号通路能促进HCC发生[100]. 体外研究[101]显示Notch3可以通过调节内源性p53水平以防止HCC细胞的阿霉素诱导死亡, 并且Notch3敲除会降低HepG2和SNU398细胞的耐药性并抑制其周期进展. 阻断Notch信号通路可以降低Notch信号通路的活性并减少HCC细胞的增殖. 更重要的是, 在HepG2中过表达HBx可以激活Notch信号通路[102], 这表明Notch信号通路在HBV相关HCC中有潜在作用. 这些证据表明, Notch信号通路在HCC的确切作用依赖于通路激活的生物背景.

4.4 Hh信号通路 Hh信号通路可以调节细胞分化、增殖和迁移等多种生物功能. 他在胚胎发育过程中参与器官形成, 在成熟组织中参与伤口愈合反应. Hh信号通路可以被自分泌、旁分泌, 甚至内分泌的Hh配体[包括Sonic hedgehog(Shh)、Indian hedgehog(Ihh)和Desert hedgehog(Dhh)]所触发[103]. EGF[104]、PDGF[105]、瘦素[106]和TGF-β[107]可以诱导Hh配体的表达. 分泌型Hh配体与12次跨膜的细胞表面受体Patched(PTCH)的结合, 进而抵消PTCH对Smo蛋白的抑制作用. 活化的Smo蛋白作用于由Cos 2、Fu和SuFu组成的多蛋白复合体, 然后释放Glis蛋白(Gli1、Gli2和Gli3). 这样就导致了Glis蛋白的堆积和细胞核定位, 进而调节Hh反应基因的转录从而影响细胞的增殖、生存和EMT. 除了配体依赖性激活, Hh信号通路也可以被配体非依赖机制激活. 内源性RAS-MEK/AKT信号通路可以调节Gli1的细胞核定位和转录活性[108]. 也有发现证实Gli1是TGF-β信号通路[109]和Wnt信号通路[110]的下游靶点.

Hh信号通路的过度活化可以导致各种癌症包括HCC的发生和发展[111-113]. Hh信号通路的激活与临床病理特征的恶性程度和HCC患者的不良预后有关. 与Wnt信号通路一样, Hh信号通路也涉及HBV相关HCC的发生和进展[114]. 在HBV感染患者的肝脏组织样本中, HBx的表达与Hh信号通路的标记蛋白成正相关. 阻断Hh信号通路可以抑制HBx刺激的HCC细胞生长、转移以及HBx转基因老鼠的肿瘤发展[114]. Gli1的过表达与HCC肿瘤手术后的快速复发有关[109]. 体外研究表明, Gli1的过表达可以促进HCC细胞的增殖、迁移和侵袭. Hh信号通路可以通过ERK通路上调MMP-9表达进而促进HCC的浸润和转移. Hh信号通路促进HCC侵袭的其他机制依赖于Hh信号通路可以促进HCC的EMT. 现在已经发现Gli1可以通过结合到*SNAIL1*启动子区域来调节SNAIL1的转录, 进而导致EMT[109]. 此外, Hh信号通路通过调节自噬以调控HCC细胞的存活和凋亡进而参与HCC的发展过程[115]. 用重组的Shh或其激动剂(SAG和Purmorphamine)处理HCC细胞可以抑制自噬, 从而导致HCC细胞的凋亡减少. 除了影响肿瘤细胞的生物活性, Hh信号通路也是肝

星状细胞(hepatic stellate cell, HSC)的主要调节因子. Hh信号通路的激活能促进静止的HSC向肌成纤维细胞样的HSC转化[116]. 现在已经证实, HCC细胞分泌的Hh配体可以刺激肌成纤维细胞的糖酵解, 从而导致肌成纤维细胞来源的乳酸堆积为恶性肝细胞提供能量来源[117].

4.5 其他的信号通路 其他多种生长因子, 包括纤维母细胞生长因子(fibroblast growth factor, FGF)、EGF、肝细胞生长因子(hepatocyte growth factor, HGF)、胰岛素样生长因子(insulin-like growth factor, IGF)和PDGF, 在HCC的发生发展及EMT过程中发挥重要作用. 这些生长因子与RTKs结合, 并诱导这些受体的自身磷酸化, 进而激活PI3K/Akt信号通路、MAPK信号通路、JNK信号通路和SRC信号通路, 这些生长因子就是通过上述途径诱导EMT, 并发挥他们对HCC的影响作用[6,8,118]. 此外, 炎症信号通路包括与EMT相关的NF-κB信号通路和IL-6/STAT3通路也与HCC的发展紧密相关[119]. 这些信号通路参与EMT和HCC的发生发展的具体分子机制在其他综述已经被详述[6,8,118,119], 在此不再重复论述.

5 结论

进展期HCC患者的预后仍然不好, 这主要是由于HCC容易出现转移. 目前, 对于进展期HCC患者而言, 唯一被证明有效的化疗药物是索拉非尼. 但是, 索拉菲尼仅仅可以延长总生存期3 mo. 因此, 研究HCC转移的调控机制迫在眉睫. EMT是癌症转移的一个重要机制, 并在HCC的发展中起着基础性作用. 深入研究EMT相关的信号通路及其对HCC的作用具有重要意义, 将有助于开发新型的可以预防和抑制HCC转移的靶向制剂, 对晚期患者十分有利.

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