

综述

肝脏祖细胞向肝癌干细胞恶变: 机制探索与研究进展

王婕 梁玉 杨鑫茂 杨雅倩 石丹宁 潘艳芳*

(陕西中医药大学基础医学院, 咸阳 712046)

摘要 原发性肝癌是全球高发的消化系统恶性肿瘤, 其高异质性、复发率及治疗抵抗性严重制约临床疗效。近年来, 肝癌干细胞(liver cancer stem cells, LCSCs)作为肿瘤发生发展的关键驱动因素备受关注, 而肝脏祖细胞(liver progenitor cells, LPCs)的恶性转化可能是LCSCs起源的重要机制。该综述系统解析了LPCs向LCSCs转化的分子调控网络: 包括Wnt/ β -catenin、Notch等信号通路异常激活, 通过影响相关靶基因表达推动LPCs恶变; 表观遗传和非编码RNA通过沉默抑癌基因或激活促癌基因, 重塑LPCs的恶性表型; 肿瘤微环境中巨噬细胞分泌的TWEAK、缺氧诱导的PI3K/Akt信号及肝星状细胞介导的免疫抑制, 共同营造促癌微环境; Oct3/4、Sox2、Nanog等干性转录因子异常表达或活化促进LPCs恶变。深入揭示上述机制不仅为肝癌靶向治疗提供新策略, 还提示LPCs移植、基因编辑及药物递送等治疗潜力。总之, 该文旨在阐述LPCs恶变为LCSCs的机制, 期望能为肝癌的早期诊断和治疗提供全新的视角与策略。

关键词 肝脏祖细胞; 肝癌干细胞; 恶变

Malignant Transformation of Liver Progenitor Cells into Liver Cancer Stem Cells: Mechanistic Insights and Research Advances

WANG Jie, LIANG Yu, YANG Xinmao, YANG Yaqian, SHI Danning, PAN Yanfang*

(Basic Medical College, Shaanxi University of Traditional Chinese Medicine, Xianyang 712046, China)

Abstract Primary hepatocellular carcinoma is a globally prevalent malignant tumor of the digestive system, whose high heterogeneity, recurrence rate, and therapy resistance severely limit clinical efficacy. In recent years, LCSCs (liver cancer stem cells), as key drivers of tumorigenesis and progression, have attracted significant attention, with the malignant transformation of LPCs (liver progenitor cells) being recognized as a crucial mechanism for LCSC origin. This review systematically deciphers the molecular regulatory network underlying LPCs-

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*通信作者: Tel: 18092722913, E-mail: panyanfang2000@163.com

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*Corresponding author. Tel: +86-18092722913, E-mail: panyanfang2000@163.com

to-LCSCs transformation: aberrant activation of Wnt/ β -catenin, Notch, and other signaling pathways promotes malignant transformation by modulating target gene expression; epigenetics and non-coding RNA remodels the malignant phenotype of LPCs through silencing tumor suppressor genes or activating oncogenes; the tumor microenvironment, including TWEAK secretion by macrophages, hypoxia-induced PI3K/Akt signaling, and immune suppression mediated by hepatic stellate cells, collaboratively fosters a pro-tumor niche; abnormal expression/activation of stemness-related transcription factors (Oct3/4, Sox2, Nanog) further drives malignancy. Elucidating these mechanisms not only provides novel strategies for targeted therapy but also highlights therapeutic potentials in LPCs transplantation, gene editing, and drug delivery. In summary, this review delineates the mechanisms of LPCs malignant transformation into LCSCs, aiming to offer fresh perspectives and strategies for early diagnosis and treatment of hepatocellular carcinoma.

Keywords liver progenitor cells; liver cancer stem cells; malignant transformation

原发性肝癌是常见消化系统恶性肿瘤,发病机制复杂、治疗难、复发率高且具异质性;其发病率居全球恶性肿瘤第六,死亡率第四,是癌症相关死亡第三大原因^[1]。肝细胞癌(hepatocellular carcinoma, HCC)是主要病理类型,占肝癌总数的75%~85%,是慢性肝病患者的主要死因之一^[2];肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICC)占15%~25%,起源于肝内胆管上皮,是第二大原发性肝脏恶性肿瘤^[3]。因高复发率和异质性,肝癌根治性治疗面临巨大挑战。当前肝癌治疗手段有手术切除、肝移植、局部消融及系统性药物治疗等^[4]。虽早期诊断有进展,但多数患者确诊时已处于中晚期,错过手术最佳时机,治疗效果不佳。手术切除后复发率高,肝移植因供体短缺、免疫排斥和费用高,仅适用于少数患者^[5],药物治疗对终末期患者效果有限。探索新型治疗策略对改善肝癌患者预后意义重大。

肝癌干细胞(liver cancer stem cells, LCSCs)作为肿瘤起始细胞备受关注,在肝癌发生发展中作用关键,是肝癌发生、进展、耐药及异质性的关键驱动因素,其耐药机制促进肝癌转移并提高复发率^[6]。最新研究表明,HCC和ICC可能源于共同细胞——肝脏祖细胞(liver progenitor cells, LPCs)^[7]。LPCs静息时分化缓慢,受特定刺激可迅速激活分化,其特性利于调控,或为肝癌治疗提供新方向^[8]。LPCs既能促进肝细胞再生、改善肝功能,又可能在信号通路失调时恶变为LCSCs,引发恶性肝肿瘤^[9]。深入研究LPCs向LCSCs转化机制,有助于揭示肝癌新的发病机制,为早期诊断和治疗提供新标志物与干预靶点。

1 LPCs的定义及功能

1.1 LPCs的定义及来源

LPCs是一类小型的上皮样细胞,其解剖学定位主要集中于肝小叶中央区域的Hering小管——肝细胞与胆管细胞交界处的特殊结构,该区域是肝脏再生的重要场所^[10]。此外,肝门静脉周围区域也被证实为LPCs的潜在来源之一^[11]。形态学上,LPCs介于成熟肝细胞与胆管细胞之间,处于一种中间状态^[12]。细胞体积较小,约为正常肝细胞的50%。胞质嗜碱性且含量稀少,核质比显著升高,细胞核呈卵圆形伴微小核仁,线粒体及核糖体等细胞器发育不完善^[13]。尽管LPCs与胆管上皮细胞均具有高核质比的特点,但LPCs的超微结构更接近原始未分化细胞,被认为是哺乳动物肝脏发育和组织修复的祖细胞^[14]。在肝实质严重受损时,LPCs可被激活并分化为功能性肝细胞,从而参与肝脏再生过程^[15]。

1.2 LPCs特征及功能

LPCs是具时空异质性的干性细胞群体,依据肝损伤背景或致癌因素,会向不同方向分化,同时伴随信号通路失调及优先表达干性生物标志物等调控因子^[16]。其具备自我更新特性,可分化为多种肝细胞,维持肝脏稳态^[17]。在合适培养条件下,LPCs能多向分化为肝细胞和胆管细胞,参与肝脏功能恢复与维持。LPCs具有强大的增殖能力和再生潜能,肝脏受损时可快速增殖分化以修复损伤。当肝脏受损时,LPCs凭借强大的增殖与分化能力,迅速参与肝再生,修复受损组织^[15]。基于LPCs的治疗在肝病领域潜力巨大,有望成为治疗肝纤维化、肝硬化和肝癌的新策略。

1.3 LPCs的信号通路和表面标志物

研究LPCs增殖与分化的信号通路对于解析其生物学行为至关重要。文献表明,在LPCs的增殖过程中,Wnt/ β -catenin信号通路处于持续激活状态,其核心效应分子 β -catenin及其下游靶基因(如*Cyclin D1*、*c-Myc*等)在增殖态LPCs中显著高表达,提示该通路对LPCs的激活和增殖具有关键调控作用^[18]。此外,Hedgehog信号通路通过协调细胞周期进程与谱系特异性基因表达,参与LPCs的增殖调控及分化终末命运的选择^[19]。

LPCs对维持肝脏正常生理功能、促进组织修复具有重要意义。然而,目前LPCs的标志物体系、调控信号通路,以及定向分化机制尚不明晰。深入研究LPCs在肝脏生理与病理状态下的作用机制、演变规律,以及其在肝脏疾病发生发展中的角色,将为临床运用LPCs治疗相关疾病提供理论依据。目前已知,CD133作为LPCs常见的表面标志物,可应用于LPCs群体的鉴定和分离^[20]。上皮细胞黏附分子(epithelial cell adhesion molecule, EpCAM)同样是LPCs的关键标志物^[21]。在生理过程中,EpCAM不仅介导LPCs的细胞黏附,维持细胞间稳定连接,还通过与细胞内信号分子相互作用,在信号转导中发挥关键作用,进而调控LPCs的增殖、分化等重要生理过程^[22]。

2 LCSCs的定义和功能

2.1 LCSCs定义及特点

LCSCs的概念起源于20世纪90年代,研究者在肝癌组织中发现一类具有异质性干细胞特性的细胞亚群,其不仅具备自我更新能力,还可分化为异质性肿瘤细胞,并直接参与肿瘤侵袭转移,后续研究将其命名为LCSCs^[23]。关于LCSCs的起源,目前存在多种假说:部分研究认为,正常LPCs因分化阻滞导致恶性转化,形成LCSCs^[23];另有观点提出,成熟肝细胞或胆管细胞通过基因突变及表观遗传重编程获得干性特征^[24];最新证据表明,干细胞谱系不同分化阶段的细胞(如祖细胞、前体细胞)均可能通过微环境压力或信号通路异常(如Wnt/ β -catenin持续激活)转化为LCSCs^[25-26]。

LCSCs在肝癌发生、转移及耐药中发挥核心作用。其生物学特征包括:(1)通过异常活化Wnt/ β -catenin等通路维持持续自我更新,驱动肿瘤组织持续性增

殖^[26];(2)分化为异质性肿瘤细胞亚群,导致肿瘤微环境复杂性增加^[27];(3)通过BCL-2家族蛋白高表达抵抗凋亡信号^[28];(4)激活EMT程序增强侵袭转移潜能,成为肝癌远处播散的关键驱动因素^[29]。

LCSCs呈现出四大显著特征:一是拥有强大的自我更新能力,能够持续推动肝癌组织的增殖;二是具备多向分化潜能,促使肿瘤的构成更加复杂;三是抗凋亡能力突出,能够有效抵御体内的凋亡信号;四是侵袭转移能力极强,成为肝癌转移的重要“助推器”^[25]。LCSCs通过基因突变、表观遗传破坏、信号通路失调或微环境改变,在调控肝癌干性、自我更新、致瘤性、转移、复发和治疗抵抗中发挥关键作用,而这些作用会导致肝癌预后不良^[30]。因此,深入研究LCSCs的特性,并探索能够抑制其自我更新的治疗方法,对改善肝癌治疗效果,提升患者生存质量具有极其重要的意义。

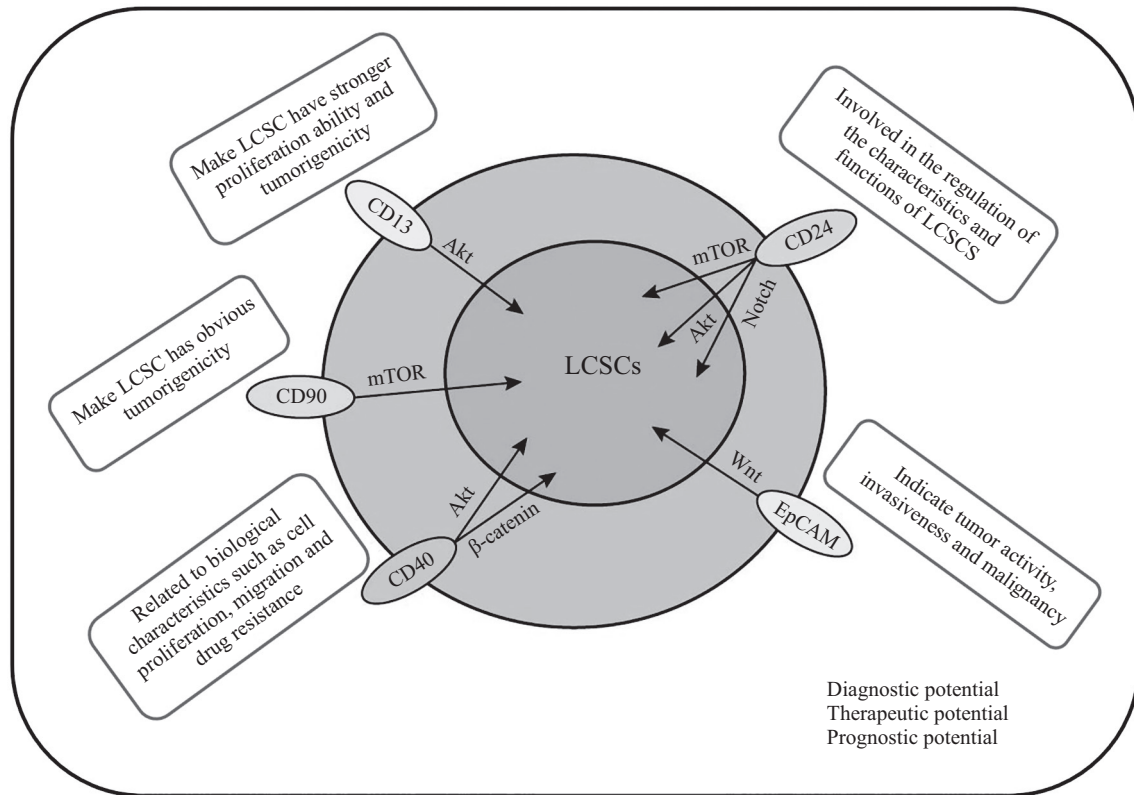
2.2 LCSCs的细胞表面标志物

研究LCSCs的细胞表面标志物对鉴定和研究这类细胞意义重大。已知的相关标志物有:EpCAM,在早期肝脏发育就有表达,其活化和高表达预示肿瘤活性高、侵袭能力强和恶性程度高;CD133在LCSCs自我更新和肿瘤形成中起重要作用,肿瘤组织中CD133⁺细胞增殖和致瘤性更强;CD90,癌前病变的肝脏组织及增殖胆管细胞中可检测到,动物移植实验显示CD90⁺细胞致瘤性明显增强;CD44在LCSCs中广泛表达,与细胞增殖、迁移和耐药性相关;CD24是潜在的标志物,参与调控肿瘤干细胞特性和功能^[31-32];CD13在某些LCSCs中表达,可能与增殖和侵袭能力相关^[33](图1)。

此外,OV6、K19、ABCG2和ALDH等也与LCSCs相关^[34]。这些标志物的研究有助于鉴定、分离LCSCs,探索其特性和功能,未来或有更多新标志物被发现,这将推动LCSCs研究的深入和相关治疗策略的发展。

2.3 调控LCSCs的信号通路

调控LCSCs的信号通路主要包括以下几种。(1)Wnt/ β -catenin信号通路:在LCSCs中,其异常活化与LCSCs增殖、自我更新能力增强相关,过度激活促进干性特征及肿瘤发生发展^[35]。(2)Notch信号通路:在LCSCs自我更新和分化中作用重要,异常激活增强LCSCs增殖与抗凋亡能力,促进肝癌发生发展^[36]。(3)Hedgehog信号通路:在LCSCs增殖、存活和侵



LCSCs的表面标记物(EpCAM、CD133、CD90、CD44和CD24)通过激活Wnt、 β -catenin、PI3K/Akt、mTOR和Notch等信号通路影响肺癌干细胞。深入研究肝细胞癌表面标记物对肝细胞癌的作用机制,在肝细胞癌的诊断、治疗及预后评估方面具有重要潜力。

The surface markers (EpCAM, CD133, CD90, CD44 and CD24) of LCSCs (liver cancer stem cells) affect LCSC through activated signaling pathways (Wnt, β -catenin, PI3K/Akt, mTOR, and Notch). In-depth study of the influence of surface markers of hepatocellular carcinoma on it has great potential for the diagnosis, treatment and prognosis of hepatocellular carcinoma.

图1 LCSCs的表面标志物对其影响
Fig.1 Impact of surface markers on LCSCs

衰方面作用关键,异常激活与LCSCs恶性转化和转移相关^[37]。(4) PI3K/Akt/mTOR信号通路:其调控与LCSCs细胞增殖、存活和代谢等密切相关,异常激活促进LCSCs干性特征和肿瘤发展^[38]。(5) TGF- β 信号通路:在细胞增殖、转移和侵袭方面发挥作用,异常激活可能促进LPCs向LCSCs转化^[39]。

3 LPCs与LCSCs的关系

LPCs作为正常肝脏干细胞,能自我更新与多向分化,参与肝脏修复再生;LCSCs属于肝癌干细胞亚群,可自我更新、增殖,推动肝癌生长与扩散,被视为低分化HCC来源,患者预后较差。二者在信号通路活性和表观遗传调控上有差异,前者参与正常生理,后者因突变或表观改变致使信号通路异常激活,进而引发肝癌^[30]。研究显示LCSCs可能源于LPCs恶变,它们在功能和分子特征上存在重叠,共享转录因子调控网络^[40]。LPCs恶变为LCSCs的机制涉及遗

传变异^[41]、表观调控改变^[42]及肿瘤微环境影响^[43]。LPCs在肝癌发生发展中作用关键,参与LCSCs生成与肝癌进展,对肝癌防治意义重大。

4 LPCs恶变为LCSCs的机制

LPCs向LCSCs的恶性转变是肝癌发病的关键。Wnt/ β -catenin等信号通路异常激活、非编码RNA的作用、肿瘤微环境改变以及Oct3/4等转录因子协同作用,多层面推动LPCs向LCSCs恶变,加速肝癌进程。

4.1 信号通路异常激活

在LPCs恶变为LCSCs的过程中,信号通路发挥着至关重要的作用。信号通路作为细胞内外信息传递的关键机制,对细胞的增殖、分化、凋亡等生命活动进行着精细调控。当LPCs向LCSCs转变时,多个信号通路会出现异常激活或失活的情况,共同参与这一恶变过程。

4.1.1 Wnt/ β -catenin信号通路 在LPCs恶变为LCSCs的进程中, Wnt/ β -catenin信号通路扮演着关键角色。在正常生理状态下, 该信号通路对LPCs的自我更新与分化起着调控作用, 维持肝脏细胞的稳态平衡^[44]。然而, 在肝癌发生时, 由于基因突变或表观遗传修饰的改变, Wnt/ β -catenin信号通路会出现异常激活^[45]。在静息状态下, 细胞内存在的降解复合体能够使 β -catenin发生磷酸化, 进而导致其被降解。但在异常情况下, Wnt配体的高表达或者表观遗传的改变会致使 β -catenin无法正常降解而在细胞内积累^[46]。积累的 β -catenin会进入细胞核, 与TCF/LEF家族转录因子相结合, 从而激活*c-Myc*、*Cyclin D1*等靶基因的转录过程^[47-48]。这些靶基因的激活, 推动了LPCs向LCSCs的转变, 同时也促进了肝癌的发展。

4.1.2 Notch信号通路 Notch信号通路同样参与了LCSCs的恶变过程。在正常的肝脏生理活动中, Notch信号通路对LPCs的增殖和分化进行着调控^[49]。而在肝癌发生时, 该信号通路常常会出现异常激活的现象。Notch信号通路异常激活可通过上调*Bcl-2*等抗凋亡蛋白的表达, 抑制细胞凋亡^[50]; 同时, 它还能促进*Cyclin D1*等细胞周期蛋白的表达, 加速细胞周期的进程。此外, Notch信号通路还会影响细胞分化相关基因的表达, 阻碍LPCs向正常肝细胞的分化, 促使其向LCSCs转变。

4.1.3 Hedgehog信号通路 在正常生理条件下, Hedgehog信号通路的核心蛋白SMO会受到PTCH的抑制。当Hedgehog配体与PTCH结合后, SMO被激活, 进而促使下游转录因子Gli家族蛋白进入细胞核, 对靶基因的转录进行调控^[51]。在LPCs恶变过程中, Hedgehog信号通路会异常激活。激活后的该信号通路会上调*Cyclin D1*、*Bcl-2*、*MMP2*等基因的表达, 这些基因的上调增强了LCSCs的增殖、存活和侵袭能力, 有力地推动了肝癌的发展^[52]。

4.1.4 PI3K/Akt信号通路 PI3K/Akt信号通路与细胞的生长、增殖等过程密切相关^[53]。在LPCs向LCSCs转变的过程中, PI3K/Akt信号通路会出现异常激活。激活后的Akt蛋白一方面能够抑制促凋亡蛋白Bax的活性, 发挥抗凋亡作用^[54]; 另一方面, Akt会激活mTOR通路, 促进蛋白质的合成, 为细胞生长提供物质基础^[55]。此外, PI3K/Ak信号通路还会上调*c-Myc*、*Nanog*等肿瘤生长相关基因的表达, 增强LCSCs的干性以及肿瘤发展能力^[56]。

上述信号通路在LPCs恶变为LCSCs的过程中, 各自发挥着关键作用, 并且它们之间还存在着相互作用。例如, Wnt/ β -catenin信号通路与Notch信号通路相互影响^[57], PI3K/Akt信号通路与Hedgehog信号通路可能存在协同作用^[58-59]。深入探究这些信号通路之间的相互关系, 对于理解LPCs恶变的分子机制以及开发针对肝癌的有效治疗策略具有重要意义。

4.2 表观遗传调控失衡

在LPCs恶变为LCSCs的过程中, 表观遗传调控失衡起了关键作用。LPCs恶性进展时, G α S的K28乙酰化水平和细胞质易位频率均显著增加, 这一过程由IL-6诱导的乙酰转移酶KAT7介导, 随后发生APT1介导的去棕榈酰化反应。细胞质中的乙酰化G α S与STAT3相关, 阻碍其与SOCS3相互作用, 进而促进LPCs对IL-6的反应, 推动癌前LPCs向LCSCs的转化, 这一机制为预防肝癌提供了潜在方向^[60]。组蛋白乳酸化在LCSCs的发生发展中发挥重要作用。去甲泽拉木醛能够降低乳酸表达水平, 抑制组蛋白乳酸化, 进而抑制LCSCs增殖与迁移、促进其凋亡。RNA表观遗传修饰也是潜在的遗传调控机制^[42]。YTHDF1通过mRNA m⁶A修饰与关键干细胞调控因子*Notch1*的mRNA结合, 提升其稳定性和翻译效率, 提高*Notch1*表达水平, 促进LCSCs的干性维持^[41]。

4.3 非编码RNA的作用

微小核糖核酸(microRNA, miRNA)作为一类重要的非编码RNA, 通过与靶信使核糖核酸(messenger RNA, mRNA)互补配对的方式, 在转录后水平对基因表达进行精准调控, 进而深刻影响细胞的功能与命运^[61]。在LPCs恶变为LCSCs的复杂进程中, 多种miRNA发挥着关键作用。例如, miR-21能够抑制抑癌基因*PTEN*的表达^[62]。由于PTEN对PI3K/Akt通路起负向调控作用, miR-21对PTEN的抑制会激活PI3K/Akt通路, 从而促进LPCs的增殖与存活, 并增强LCSCs的干性特征^[63]。miR-122在正常肝脏组织中呈现高表达状态, 但在LPCs恶变为LCSCs的过程中, 其表达水平下降, 这会导致细胞增殖、侵袭相关基因出现异常表达, 为LCSCs的形成创造有利条件^[64]。miR-34a则通过靶向调控*Sox2*等转录因子, 对LPCs向LCSCs的转变起到抑制作用。当miR-34a表达水平降低时, 细胞更容易获得干性并发生转化^[65]。

长链非编码RNA(long non-coding RNA, lncRNA)是一类重要的非编码RNA, 具有多样化的

功能和调控机制。在LCSCs的起源过程中,特定的lncRNA参与到转录因子表达和信号通路活性的调控中。以HOTAIR为例,它能与PRC2结合,介导H3K27me3修饰,进而沉默抑癌基因,这一过程促进了LPCs的增殖与恶变^[66]。此外,HOTAIR还与Wnt/ β -catenin通路相互作用,对LCSCs的干性维持以及肿瘤发生产生影响^[67]。MALAT1在肝癌组织中呈现高表达,它通过与蛋白质相互作用,对基因转录和mRNA加工过程进行调节。在LPCs恶变过程中,MALAT1调控细胞周期、凋亡相关基因,这不仅促进细胞的增殖与存活,还能增强LCSCs的迁移和侵袭能力^[68]。部分lncRNA作为竞争性内源RNA(competing endogenous RNA, ceRNA),可与miRNA结合,间接调控基因表达。比如,某lncRNA能够吸附miR-34a,从而促进LPCs向LCSCs的转变^[69]。

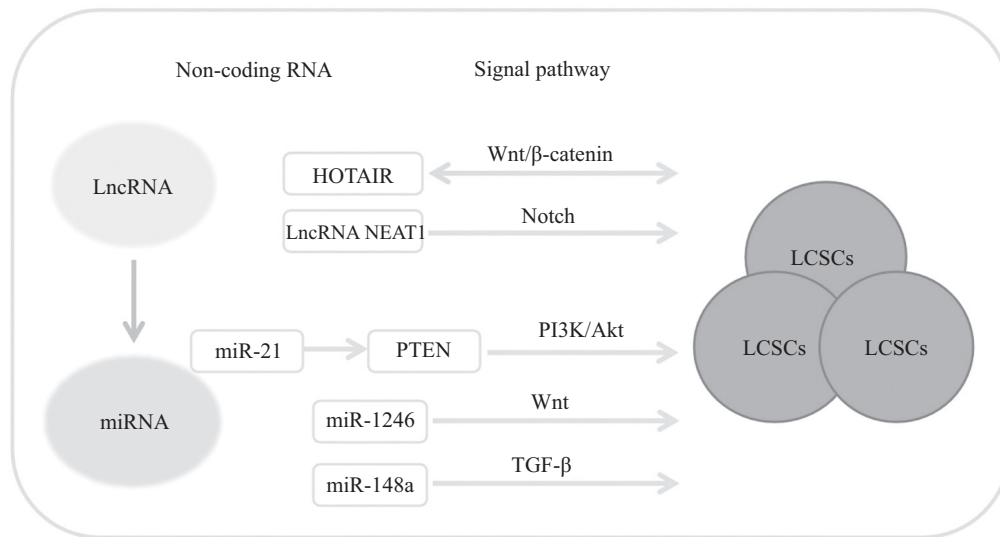
miRNA、lncRNA与信号通路及转录因子之间存在着错综复杂的协同作用。miR-21激活PI3K/Akt通路后,被活化的Akt会通过磷酸化激活下游转录因

子(如c-Myc)增强其蛋白稳定性及转录活性,miR-21与这些被激活的转录因子共同推动LPCs向LCSCs的转变^[63]。miR-1246激活Wnt通路,与异常激活的Wnt/ β -catenin通路协同作用,促进相关基因的转录激活,加速LPCs向LCSCs的转变进程^[70]。miR-148a增强TGF- β 通路,与其他相关因子协同作用,促进LPCs发生上皮-间质转化,进一步增强细胞的恶性程度^[71-72]。lncRNA NEAT1则通过增强Notch信号,与其他因子共同促进LPCs向LCSCs的转化^[73](图2)。

4.4 肿瘤微环境的影响

在肝脏慢性炎症的病程中,LPCs向LCSCs的转化是诱发肝癌的早期风险因素之一。

在肝脏的炎症反应过程中,先天免疫细胞和适应性免疫细胞对LPCs的激活都发挥着重要作用。在动物模型中,受到促炎细胞因子(如:IL-6、TNF- α 等)作用的鼠中的LPCs增殖水平显著升高^[74]。此外,淋巴细胞在LPCs向LCSCs转化的过程中也发挥着重要作用。研究显示,在炎症环境下,作为关键的免疫细胞因子,IL-17能够激活Th-17淋巴细胞参与



HOTAIR与Wnt/ β -连环蛋白信号通路相互作用,而长链非编码RNA NEAT1增强Notch信号,影响LCSCs干性的维持和肿瘤发生。微小RNA通过多种方式调节LCSCs: miR-21通过抑制其靶基因PTEN的表达激活PI3K/Akt信号通路,增强LCSCs的干性特征。miR-1246激活Wnt信号通路,加速LPCs向LCSCs的转化。miR-148a增强TGF- β 信号通路,促进LPCs的上皮-间质转化,增强细胞的恶性程度。miRNA与长链非编码RNA之间也存在相互作用,长链非编码RNA可作为竞争性内源RNA来调节miRNA。

HOTAIR interacts with the Wnt/ β -catenin signaling pathway, and lncRNA NEAT1 enhances Notch signaling, affecting the maintenance of LCSCs stemness and tumorigenesis. MiRNA regulates LCSCs through a variety of ways: miR-21 activates the PI3K/Akt signaling pathway by inhibiting the expression of its target gene *PTEN*, and enhances the stemness characteristics of liver cancer stem cells. After miR-1246 activates the Wnt signaling pathway, it accelerates the transformation of liver progenitor cells into liver cancer stem cells. After miR-148a enhances the TGF- β signaling pathway, it promotes the epithelial-mesenchymal transition of HPC and enhances the malignancy of cells. There is also interaction between miRNA and lncRNA, and lncRNA acts as ceRNA to regulate miRNA.

图2 LPCs恶变过程中,lncRNA和miRNA通过多种通路调控LCSCs

Fig.2 lncRNAs and miRNAs regulate LCSCs through multiple pathways during the malignant transformation of LPCs

先天性免疫和适应性免疫之间的相互作用、促进LPCs的活化,诱导LPCs转化为具有LCSCs表型的肝癌细胞,进而诱发肝癌的发生^[75]。这一现象不仅在体外动物实验中被证实,并且在肝硬化患者血浆中IL-17的表达水平也被证实能够预测肝癌的发病风险^[76]。

巨噬细胞作为肿瘤微环境的重要组成部分,所分泌的促炎因子TWEAK能够和LPCs表面受体FN14结合,通过NF- κ B信号转导,上调LPCs中ID1的表达。高表达的ID1抑制HNF4 α 和Rap1GAP的转录,破坏LPCs正常分化进程,转而推动其向LCSCs异常分化与增殖^[77]。不仅如此,门脉高压症患者脾脏分泌的异常细胞因子,会激活LPCs中的JAK/STAT通路。脾血清干预胎肝干细胞实验表明,被激活的JAK/STAT通路,加速LPCs增殖、提升克隆球形成能力,降低白蛋白表达水平,升高甲胎蛋白表达水平,诱导LPCs向LCSCs恶性转化^[78]。

肿瘤微环境中的缺氧和活化的肝星状细胞,同样对LPCs向LCSCs的转变影响深远。缺氧环境激活肿瘤细胞PI3K/Akt信号通路,促进细胞恶性增殖与免疫逃逸。活化的肝星状细胞分泌血管生成生长因子,协同VEGF刺激血管生成,为肿瘤提供养分^[79];活化的肝星状细胞还能抑制淋巴细胞活性,通过过表达PD-1并募集Tregs抑制CD8⁺ T细胞活化,营造免疫耐受环境^[80]。在这种适宜肿瘤生长的微环境下,LPCs更易发生恶变,向LCSCs转化。

4.5 转录因子的调控作用

转录因子在LPCs恶变为LCSCs进程中起关键作用。它们结合基因启动子或增强子,调控基因转录活性,影响细胞生长、分化和增殖。LPCs向LCSCs转变时,多个转录因子异常表达或活化,部分更是肝癌发生发展的关键调控因子。

4.5.1 转录因子的调控 Oct3/4作为一种重要的转录因子,在干细胞中对维持细胞的干性和自我更新能力起着不可或缺的作用^[81]。已有研究表明,Oct3/4在LPCs向LCSCs转变的进程中可能发挥着至关重要的作用^[82]。它或许是通过调控一系列相关基因的表达,来影响LPCs的增殖、分化以及干性维持,进而推动LCSCs的形成。

Sox2与干细胞的自我更新和分化密切相关^[81]。在LCSCs的起源过程中,Sox2可能参与调控干细胞标记物的表达,从而影响LPCs向干细胞状态的转变^[83]。

此外,Sox2还能够调控CD133等标志物的表达,并且与Wnt/ β -catenin等信号通路相互作用,共同对LCSCs的特性和功能进行调控^[84]。

Nanog与干细胞干性的维持以及自我更新紧密相连^[85]。在LPCs向LCSCs转变的过程中,Nanog极有可能发挥着重要作用。它通过调控细胞增殖、凋亡、分化等关键生物学过程,深刻影响着LPCs的干性以及LCSCs的特性^[86]。具体而言,在细胞增殖方面,Nanog能够促进细胞周期蛋白的表达,加速细胞周期进程;在细胞凋亡方面,它可以抑制促凋亡蛋白的表达,降低细胞的凋亡率;在细胞分化方面,Nanog会抑制LPCs向正常肝细胞分化,促使其朝着LCSCs的方向转化^[87]。

β -catenin作为Wnt/ β -catenin信号通路的核心组分,是肝癌发生发展过程中的重要转录因子。在正常生理状态下, β -catenin的稳态水平受到严格的调控,它参与细胞的增殖和分化过程^[88]。然而,在肝癌发生时,Wnt/ β -catenin信号通路出现异常激活,导致 β -catenin在细胞内过度积累^[89]。这种过度积累会致使一系列靶基因出现异常表达,进而促进LPCs向LCSCs的转变。

c-Myc在LPCs向LCSCs转变的过程中也发挥着重要作用,它参与细胞的自我更新和增殖过程。在LPCs恶变的过程中,c-Myc出现异常表达或活化,这种异常变化会促进肝癌祖细胞的增殖^[90-91]。c-Myc通过激活相关基因,为细胞的快速增殖提供充足的物质和能量基础,同时影响细胞的分化方向,促使肝癌祖细胞逐渐转化为癌细胞^[92]。

4.5.2 转录因子之间相互作用 在LPCs向LCSCs转变的过程中,转录因子之间存在着复杂且紧密的相互作用,主要体现在以下几个方面。(1) 协同促进干性维持与增殖: Oct3/4、Sox2和Nanog作为维持干细胞干性的关键转录因子,在LPCs向LCSCs转变过程中相互协作,共同调控干性维持及细胞增殖相关基因^[85]。当Wnt/ β -catenin信号通路异常激活后, β -catenin会进入细胞核,与TCF/LEF家族转录因子结合,进而激活Oct3/4、Nanog等靶基因,形成正反馈环路,显著强化LCSCs的干性和增殖能力^[93-94]。此外,c-Myc与Oct3/4等转录因子协同作用,共同激活相关基因的表达,加速LPCs向LCSCs的转变进程^[95]。(2) 调控分化方向: Sox2能够通过调控CD133、EpCAM等LPCs标志物的表达,改变细胞的生物学特性^[96]。

Oct3/4和Nanog则共同抑制LPCs向正常肝细胞分化相关基因的表达,促使细胞朝着LCSCs的方向转化^[97]。 β -catenin在这一过程中干扰正常细胞的分化程序^[98],而c-Myc通过影响细胞代谢和信号转导,推动细胞向肿瘤细胞方向分化^[99]。(3) 信号通路交叉与协同调控: Sox2与Wnt/ β -catenin信号通路协同,增强 β -catenin对靶基因的转录激活,促进LCSCs干性维持和增殖^[100]。Sox2还与Notch等信号通路相互作用,通过调控相关基因表达影响LPCs增殖分化,进而对LCSCs的形成产生影响^[101],由此,在LPCs恶变为LCSCs的过程中形成复杂紧密的调控网络。

综上所述,LPCs恶变为LCSCs是一个多因素协同作用的复杂过程。信号通路的异常激活、表观遗传调控失衡、肿瘤微环境改变以及转录因子的协同调控,共同驱动这一恶性转化进程。深入研究这些机制,不仅能增进人们对肝癌发生发展的理解,还能为开发靶向LPCs的新型治疗策略提供理论基础,有望攻克肝癌治疗的难题,改善患者预后。

5 应用前景及展望

在深入探究LPCs恶变为LCSCs机制的同时,本文也对LPCs在肝癌治疗领域的应用前景展开了探讨。一是通过LPCs移植治疗肝癌,促进肝脏再生修复以抑制肿瘤生长扩散,提高患者生存率与生活质量^[102];二是利用LPCs介导基因治疗,针对LCSCs特定基因进行干预,抑制肿瘤发展转移,降低治疗副作用^[103];三是利用LPCs介导药物递送,LPCs作为药物载体可提高药物靶向性与疗效,减少对正常组织的损伤。这些显示了LPCs在肝癌治疗中的巨大潜力^[104]。

在探究LPCs向LCSCs恶变机制方面,多组学联合剖析可能成为关键突破口。整合基因组学、转录组学、蛋白质组学等多组学数据,能够全面揭示恶变过程中的分子调控景观,为肝癌的精准治疗提供关键靶点^[105]。肿瘤微环境在LPCs恶变过程中起着重要作用。一方面,需要深入探究免疫细胞分泌的各类因子对LPCs干性维持以及恶变进程的调控机制^[106];另一方面,还需明确LCSCs的免疫逃逸机制。肿瘤微环境的改变可通过细胞表面受体向细胞内传递信号,进而调控LPCs的生物学行为^[107]。当明确这一过程中的关键分子后,通过靶向干预对肿瘤微环境进行重塑,该策略有望有效阻断LPCs的恶变进程。

6 总结

本文系统剖析LPCs向LCSCs恶变的分子机制(图3)。Wnt/ β -catenin、Notch等信号通路的异常激活,表观遗传失衡、非编码RNA调控异常、肿瘤微环境改变,以及Oct3/4等转录因子协同作用促进LPCs向LCSCs的恶性转化。对这些关键因子展开研究,有助于深入理解LCSCs的起源与发展,进而为肝癌治疗及干细胞治疗领域提供重要的理论支撑。但LPCs向LCSCs的转变机制复杂,仍有诸多未知机制待研究。深入探索更多转录因子、信号通路及非编码RNA的作用机制,对研究LCSCs治疗策略具有重大意义,有望为攻克肝癌难题开辟新径。

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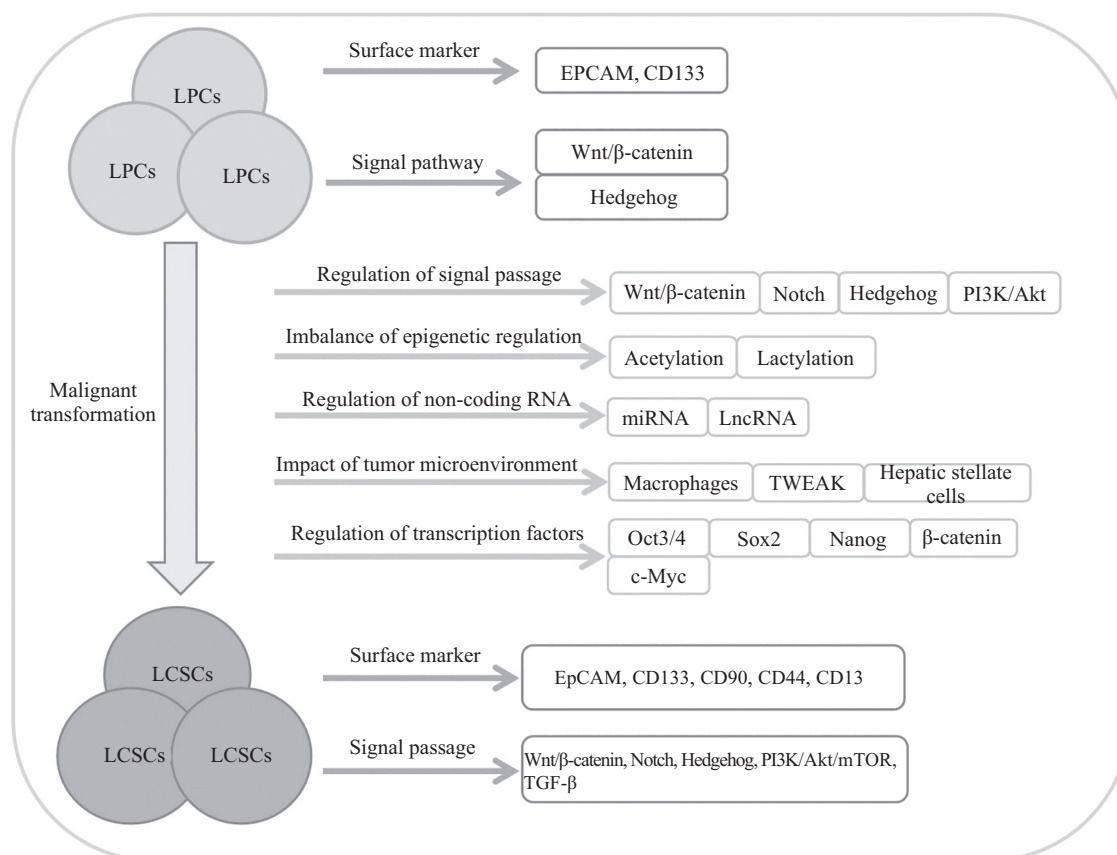


图3 LPCs向LCSCs恶变的分子机制研究

Fig.3 Molecular mechanisms underlying the malignant transformation of LPCs to LCSCs

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