

• 综 述 •

IGF2BP3 在肝癌中的研究进展^{*}

杨宛林¹, 叶宇璐¹, 宁登冲¹, 叶霞¹, 蓝金艳¹, 易廷庄^{2△}

(1. 右江民族医学院研究生学院, 广西 百色 533000; 2. 右江民族医学院附属医院, 广西 百色 533000)

[摘要] 胰岛素样生长因子 2 mRNA 结合蛋白 3(IGF2BP3)也称为 IMP3,是一种在原始胚胎中表达而在成人中低表达或不表达的癌胚抗原。近期研究表明,IGF2BP3 在多种肿瘤中的表达异常,尤其是在肝癌中,不仅影响肿瘤的增殖、侵袭、转移等生物学行为,还在调控铁死亡、塑造免疫微环境、介导化疗耐药等方面发挥重要作用。此外,IGF2BP3 与肝癌患者的预后也明显相关,为肝癌的诊治提供了新的视角。但 IGF2BP3 在肝癌中的作用机制及其临床意义尚未完全阐明。该文总结了近年来 IGF2BP3 在肝癌发生、发展中的研究进展,并系统性地综述了其在肝癌中的恶性进展、免疫浸润、耐药性等方面的作用。

[关键词] 肝肿瘤; 胰岛素样生长因子 2 mRNA 结合蛋白 3; 癌胚抗原; 免疫浸润; 综述

DOI:10.3969/j.issn.1009-5519.2025.05.034 **中图法分类号:**R735.7

文章编号:1009-5519(2025)05-1214-05 **文献标识码:**A

Research progress of IGF2BP3 in liver cancer^{*}

YANG Wanlin¹, YE Yulu¹, NING Dengchong¹, YE Xia¹, LAN Jinyan¹, YI Tingzhuang^{2△}

(1. Graduate School, Youjiang Medical University For Nationalities, Baise, Guangxi 533000, China; 2. Affiliated Hospital of Youjiang Medical University For Nationalities, Baise, Guangxi 533000, China)

[Abstract] Insulin-like Growth Factor 2 mRNA Binding Protein 3 (IGF2BP3), also known as IMP3, is a cancer embryonic antigen that is expressed during early embryonic development but is expressed at low levels or absent in adults. Recent studies have shown that IGF2BP3 is abnormally expressed in various tumors, particularly in hepatocellular carcinoma (HCC). It not only influences tumor biological behaviors such as proliferation, invasion, and metastasis, but also plays a significant role in regulating ferroptosis, shaping the immune microenvironment, and mediating chemotherapy resistance. Moreover, IGF2BP3 is closely associated with the prognosis of HCC patients, providing new insights into the diagnosis and treatment of liver cancer. However, the precise mechanisms of IGF2BP3 in HCC and its clinical significance remain to be fully elucidated. This article summarizes the recent research progress on IGF2BP3 in the occurrence and development of HCC, and systematically reviews its role in malignant progression, immune infiltration, and drug resistance in liver cancer.

[Key words] Liver neoplasms; Insulin-like growth factor 2 mRNA binding protein 3; Carcinoembryonic antigen; Immune infiltration; Review

原发性肝癌在全球癌症发病率中排第 6 位,同时,也是导致癌症患者死亡的第三大原因。原发性肝癌主要包括肝细胞癌(HCC)、肝内胆管癌、混合型肝癌 3 种类型,HCC 占据了原发性肝癌的绝大部分(75%~85%),是最常见的亚型^[1]。目前,药物治疗、经皮消融、经动脉化疗栓塞、嵌合抗原受体工程 T 淋巴细胞免疫治疗、肝癌切除术、肝移植等多种治疗模式均不同程度地抑制了肝癌进展,延长了患者生存

期^[2-3]。分子靶向药物,如索拉非尼、仑伐替尼已成为肝癌一线治疗的重要选择,贝伐珠单抗联合阿替珠单抗的免疫治疗方案近年来显示出明显的临床获益,成为推荐治疗晚期肝癌患者的一线方案之一。然而,肝癌患者病死率仍居高不下,且易产生耐药性^[4-6],为肝癌治疗带来了新的挑战。因此,进一步明确肝癌的分子机制对寻找新的治疗方向至关重要。

在探索肝癌分子机制的过程中胰岛素样生长因

^{*} 基金项目:国家自然科学基金项目(82460475)。

[△] 通信作者, E-mail: ytz20070101@163.com。

网络首发 [https://link.cnki.net/urlid/50.1129.R.20250331.1305.031\(2025-03-31\)](https://link.cnki.net/urlid/50.1129.R.20250331.1305.031(2025-03-31))

子家族的调控蛋白逐渐引起了广泛关注^[7]。作为 RNA 结合蛋白家族的重要成员,胰岛素样生长因子 2 mRNA 结合蛋白(IGF2BP)家族参与了多种癌症中 mRNA 的稳定性、剪接、翻译和降解过程,深刻影响了肿瘤的发生、发展^[8]。IGF2BP 家族成员中的 IGF2BP3 因在肿瘤中的异常高表达及其与肿瘤生物学行为的密切相关性逐渐成为研究的重点^[9]。IGF2BP3 是一种 RNA 结合蛋白,参与了调控 mRNA 的稳定性、剪接、翻译和降解过程,在肿瘤细胞增殖、侵袭、迁移、耐药等生物学过程中具有关键作用^[10-12]。近年来,随着分子生物学的迅猛发展,人们对肿瘤分子机制的认识日益加深。IGF2BP3 作为在多种肿瘤中表达异常的基因,在肝癌中的作用机制和临床意义逐渐成为研究热点^[13]。众多研究揭示了 IGF2BP3 在肝癌中的重要作用,包括对肝癌细胞生物学行为的调控,与铁死亡分子、干性标志物的相关性,以及对肿瘤微环境的影响等^[14-17]。现综合分析 IGF2BP3 在肝癌中的作用机制,探讨其作为潜在治疗靶点的可能性,为未来的研究方向提供参考依据。

1 IGF2BP3 基因的结构及功能

1.1 IGF2BP3 的结构特征 IGF2BP3 是一种含有 580 个氨基酸的癌胎 RNA 结合蛋白,具有 2 个 N 端 RNA 识别基序——核糖核苷酸还原酶 M1 和核糖核苷酸还原酶 M2,4 个 C 端核内不均一核糖蛋白 K 同源(KH)结构域——KH1~KH4 和 2 个链接区域——L1 和 L2^[12]。IGF2BP3 基因位于 7p 11.5 染色体上,克隆的 IGF2BP3 互补 DNA 包含 1 个 250 碱基对的 5'-非翻译区(UTR),1 个 1 740 碱基对的开放阅读框和 1 个 2 168 碱基对的 3'-UTR。IGF2BP3 富含 AU 的 3' UTR,覆盖 8 个 AUUUA 和 4 个 AUUUUUA 重复基序^[18]。IGF2BP3 存在于细胞质中,以颗粒状结构积聚,通常在核周区域富集^[19]。

1.2 IGF2BP3 在胚胎发育中的核心作用 IGF2BP3 在胚胎发育过程中发挥了至关重要的作用。早期研究表明,在人和小鼠胚胎发生的早期阶段 IGF2BP3 在上皮细胞、肌肉、胎盘中高表达^[20]。在成年小鼠中 IGF2BP3 在肺、脾脏、肌肉、肠道、胰腺、肾脏、大脑、卵巢、睾丸中均表达^[21-22]。在成人组织中 IGF2BP3 可表达在胎盘、淋巴结、扁桃体、睾丸等部位^[11]。更为重要的是根据对非洲爪蟾的同源物——RNA 结合蛋白 vgl。有研究表明,IGF2BP3 在神经发育中具有重要作用^[22]。类似地在斑马鱼中 IGF2BP3 对胚胎发育至关重要,并能维持母体 RNA 的稳定性^[23]。

1.3 IGF2BP3 在肿瘤发生、发展中的多重作用 近年来,有研究证实,IGF2BP3 在多种肿瘤中的异常高表达与肿瘤的发生、发展和侵袭高度相关^[24]。有研究表明,IGF2BP3 可能以哺乳动物雷帕霉素靶蛋白控制的方式促进 IGF2 的合成^[25-27]。虽然 IGF2BP3 在控

制 IGF2 mRNA 翻译中的作用仍存在矛盾,但最近的研究发现,在人类癌症中上调该蛋白可能通过促进 IGF2 的表达促进肿瘤生长;此外,IGF2BP3 还通过与细胞核中的核内不均一核糖蛋白 M 协同作用,导致细胞周期蛋白表达增强,从而促进肿瘤细胞增殖,并促进了肿瘤细胞的免疫逃逸^[28-29]。还有研究发现,IGF2BP3 的异常高表达与患者预后也密切相关^[30]。表明 IGF2BP3 不仅参与了胚胎发育过程中 mRNA 的稳定性、细胞生长及迁移,还对癌症的诊治也具有重要意义。

2 IGF2BP3 在肝癌增殖、侵袭、迁移、凋亡中的作用机制

2.1 IGF2BP3 调控肝癌细胞增殖与凋亡 IGF2BP3 通过结合并稳定某些关键 mRNA,如细胞周期蛋白依赖性激酶和细胞周期蛋白促进这些分子的翻译,从而明显加速细胞周期进程,增强肝癌细胞的增殖能力^[28,31]。同时,IGF2BP3 通过抑制促凋亡基因的表达,削弱细胞内凋亡信号,增强肿瘤细胞的生存优势。体外研究表明,IGF2BP3 通过与凋亡相关 mRNA 的 3'-UTR 区域结合,调节 mRNA 稳定性并下调其表达,从而明显抑制肿瘤细胞的凋亡^[32]。这种通过 RNA 结合的方式削弱细胞内的凋亡通路进一步增强了肿瘤细胞的存活能力。这些功能使 IGF2BP3 成为肝癌增殖与凋亡的核心调控因子之一。

2.2 IGF2BP3 促进肝癌细胞迁移与侵袭 IGF2BP3 通过调控上皮-间质转化相关基因的表达明显增强肝癌细胞的迁移与侵袭能力^[33]。有研究表明,IGF2BP3 通过抑制上皮钙黏蛋白的表达、上调波形蛋白等间质标志物的表达加速肝癌细胞从上皮表型向侵袭性表型转变。这一作用是肝癌细胞获得高度侵袭性的重要分子基础^[34]。此外,YAN 等^[35]研究表明,下调 IGF2BP3 可明显减轻环状 RNA-0098823 过表达引起的肝癌细胞过度迁移、侵袭、凋亡等。

2.3 IGF2BP3 通过非编码 RNA 的调控网络的关系 非编码 RNA(微小 RNA、长非编码 RNA 和环状 RNA)通过与 IGF2BP3 的相互作用共同参与了肝癌的发生、发展,微小 RNA-129-1 作为肿瘤抑制因子通过靶向 IGF2BP3 和丝裂原活化蛋白激酶 1 明显延缓肝癌细胞的 G₁~S 期转变,从而抑制其增殖和发展^[36-37]。长链非编码 RNA00467 通过增强肿瘤坏死因子受体相关因子 5 mRNA 的稳定性,明显促进肝癌细胞的增殖与转移^[38]。环状 RNA-0098823 与 IGF2BP3 相互作用,增强动力蛋白相关蛋白 1 的稳定性,从而调控肝癌细胞的迁移、侵袭、凋亡等^[35]。

3 IGF2BP3 在肝癌免疫调节中的核心作用

3.1 IGF2BP3 调控免疫细胞浸润与功能 肝癌的免疫微环境在其发生、发展、治疗抵抗方面具有至关重要的作用。多项研究证实,IGF2BP3 的高表达与多种

免疫细胞(B 淋巴细胞、CD4⁺ T 淋巴细胞、CD8⁺ T 淋巴细胞、巨噬细胞、中性粒细胞和树突状细胞)的浸润呈正相关^[13]。然而这种免疫细胞浸润并非普遍带来抗肿瘤效果,反而可能通过塑造免疫抑制性微环境促进肿瘤进展。有研究表明,IGF2BP3 通过与 C-C 基序趋化因子配体 5、转化生长因子-β1(TGF-β1)mRNA 结合,增强这些分子的稳定性和表达,诱导巨噬细胞向 M2 型极化,从而抑制 CD8⁺ T 淋巴细胞活性,并削弱抗肿瘤免疫反应^[16,39]。

3.2 IGF2BP3 介导的免疫逃逸机制 越来越多的研究表明,N6-腺苷酸甲基化(m6A)修饰可通过调节免疫细胞浸润、促瘤炎症、免疫抑制、免疫监视、抗肿瘤免疫应答等方式改变多种肿瘤的免疫应答^[40]。IGF2BP3 作为一种关键的 m6A 阅读器不仅在肿瘤细胞的生长、转移中发挥作用,还可能通过影响肿瘤微环境和免疫细胞功能促进免疫逃逸。IGF2BP3 通过 m6A 依赖性机制上调免疫抑制分子的表达,直接削弱 CD8⁺ T 淋巴细胞的杀伤能力,从而赋予肿瘤细胞更强的生存优势^[39,41]。此外,IGF2BP3 增强 C-C 基序趋化因子配体 5、TGF-β1 的表达,进一步促进免疫抑制性细胞 M2 型巨噬细胞、调节性 T 淋巴细胞的募集,强化肝癌免疫逃逸能力^[16]。

4 IGF2BP3 参与肝癌的干性调节

4.1 IGF2BP3 通过 m6A 依赖性机制调控肝癌干性 肿瘤干细胞是指癌细胞的干细胞样表型,在肝癌的发生、发展中发挥了重要作用^[42]。有研究表明,m6A 修饰能通过调节与肿瘤干性相关的基因 mRNA 的表达水平,进而影响肝癌干细胞的发展和维持^[43]。IGF2BP3 作为 m6A 阅读蛋白可通过与特定的 m6A 修饰的 mRNA 结合,影响肝癌干细胞的自我更新和多能性,这种作用可能通过调节关键的干细胞标志物和信号通路来实现^[44]。有研究发现,敲低 IGF2BP3 会明显抑制肝癌细胞的增殖、集落形成和侵袭能力,同时,IGF2BP3 与干性标志物——转录因子 2 的表达水平呈正相关,进一步表明其在肝癌干细胞特性维持中的重要性^[13]。IGF2BP3 通过 m6A 依赖性增强真核翻译起始因子 5B mRNA 的稳定性,促进肝癌干细胞表型的维持,揭示了 IGF2BP3 在 m6A 调控网络中的中心作用^[45]。

4.2 IGF2BP3 通过协同非编码 RNA 调控肝癌干性 IGF2BP3 通过与非编码 RNA 的相互作用共同调控肝癌细胞的干性特性。有研究表明,IGF2BP3 通过抑制微小 RNA 的靶向降解,增强高迁移率族蛋白 A2 的表达,从而与高迁移率族蛋白 A2 协同促进肝癌细胞的侵袭和迁移能力^[46]。IGF2BP3 还可通过与非编码 RNA 协作增强细胞黏附分子 44 等干性相关分子的稳定性^[47]。有研究表明,在肝癌组织中 IGF2BP3 与细胞黏附分子 44 的表达呈正相关,协同

促进肝癌细胞的干性表型^[13]。

4.3 乙型肝炎病毒(HBV)感染与 IGF2BP3 调控网络的关系 慢性 HBV 感染是肝癌的重要致病因素。有研究发现,HBV-pgRNA 可通过上调 IGF2BP3 的表达明显增强肝癌细胞的干性特性,不仅揭示了 HBV 感染与肝癌干性调控的分子关联,还进一步强调了 IGF2BP3 在 HBV 相关肝癌中的特殊作用^[48]。

5 IGF2BP3 参与肝癌铁死亡的调节

IGF2BP3 调控肝癌铁死亡的分子机制为 IGF2BP3 通过 m6A 依赖性机制调控多种铁死亡关键因子的表达水平,在肝癌细胞中形成对铁死亡的复杂调控网络。IGF2BP3 通过结合核因子 E2 相关因子 2(NRF2)mRNA 的 m6A 位点明显增强其稳定性和翻译水平,从而上调 NRF2 蛋白的表达。这一过程赋予了肝癌细胞更强的抗氧化能力,减少了脂质过氧化损伤,明显抑制铁死亡的发生^[15]。有研究表明,IGF2BP3 通过直接或间接调控长链脂肪酸合成酶 4、溶质载体家族 1 成员 5 参与了调控肝癌细胞的铁死亡。IGF2BP3 与溶质载体家族 1 成员 5 呈正相关,与抗氧化分子 NFE2L2(NRF2)呈负相关,进一步表明其在铁死亡调控中的双重作用^[49]。

6 IGF2BP3 在肝癌耐药性中的作用机制与治疗潜力

6.1 IGF2BP3 通过 m6A 依赖性机制调控肝癌耐药性 近年来,肝癌的治疗手段不断进步,包括手术、化疗、靶向治疗等,但肝癌细胞的耐药性问题仍是制约疗效的关键因素^[50]。IGF2BP3 作为一种在多种肿瘤中表达异常的蛋白,近年来的研究表明,与肿瘤细胞的耐药性密切相关。IGF2BP3 能以 m6A 阅读蛋白的身份稳定某些促耐药相关基因的 mRNA,明显增强肿瘤细胞对化疗药物的耐受性。有研究表明,IGF2BP3 结合 NRF2 mRNA 的 m6A 修饰位点增强其稳定性和翻译效率,从而上调 NRF2 蛋白水平。这一过程赋予了肝癌细胞更强的抗氧化能力,降低了化疗药物——索拉非尼诱导的铁死亡效应^[15]。IGF2BP3 通过 m6A 依赖性机制稳定表皮生成因子受体 mRNA,促进肿瘤细胞生长,并在结直肠癌中介导西妥昔单抗的耐药性^[51]。这一机制可能在肝癌耐药中同样适用。

6.2 IGF2BP3 通过调控代谢重编程增强化疗耐药 IGF2BP3 能通过调控肿瘤细胞的代谢重编程增强化疗耐药性。有研究表明,IGF2BP3 能通过细胞色素 C 氧化酶亚基 6B2 介导线粒体能量重编程,从而促进非小细胞肺癌对表皮生长因子受体-酪氨酸激酶抑制剂的耐药性^[45]。CD133⁺ 肿瘤干细胞亚群表现出较高的化疗耐药性^[52],而 IGF2BP3 被发现与肿瘤干性标志物的高表达明显相关。通过抑制 CD133⁺ 细胞比例可明显增强这些细胞对索拉非尼的化疗响应^[52-53]。相关研究发现,IGF2BP3 作为肿瘤启动性干细胞中的功能癌基因,当沉默 IGF2BP3 时可恢复 TGF-β 信号,消

除肿瘤启动性干细胞对肝癌的化学耐药^[54]。有研究证实,靶向 IGF2BP3 基因的小干扰 RNA 负载的脂质体原位异种移植模型靶向 IGF2BP3 可有效恢复仑伐替尼对 HCC 的敏感性。这些发现强调了代谢重编程和表观遗传调控的联系,并提示 IGF2BP3 可能为克服 HCC 的仑伐替尼耐药提供新的策略^[55]。

7 小结与展望

肝癌是一个早期诊断率低、复发率高且预后差的疾病。目前,在肝癌的诊断方面仍缺乏特异性生物标志物;在治疗方面肝癌对放化疗均不敏感,靶向治疗、免疫治疗的疗效尚有待于进一步提高。IGF2BP3 作为一个在肝癌发展中具有多重作用的分子已成为肝癌研究领域的热点。IGF2BP3 在肝癌的恶性进展中扮演了重要角色,IGF2BP3 作为一个多功能的 RNA 结合蛋白通过影响 mRNA 的稳定性和翻译效率参与了调控肝癌细胞的多种生物学行为。IGF2BP3 不仅对肝癌铁死亡、免疫微环境等产生深远的影响,在其恶性表型中也具有重要作用。IGF2BP3 表达水平与肝癌患者的预后紧密相关,有望成为一个有潜力的预后生物标志物和治疗靶点。尽管目前针对 IGF2BP3 的治疗策略仍处于初步阶段,但已有的研究结论为未来的临床应用提供了坚实的基础。然而 IGF2BP3 在肝癌中的作用机制仍复杂且尚未完全清楚,其在肿瘤微环境、肿瘤代谢方面的认识仍十分有限。因此,需更多的研究阐明其在肿瘤发展中的具体角色。此外,IGF2BP3 作为治疗靶点的安全性、有效性也需在今后的临床试验中进一步验证。随着对 IGF2BP3 功能和作用机制的深入了解,以及新药物和治疗方法的开发期待 IGF2BP3 相关的治疗策略能尽快用于临床,为肝癌患者带来新的希望。

参考文献

[1] BRAY F, LAVERSANNE M, SUNG H, et al. Global cancer statistics 2022; GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2024, 74(3): 229-263.

[2] VITALE A, TREVISANI F, FARINATI F, et al. Treatment of hepatocellular carcinoma in the precision medicine era: from treatment stage migration to therapeutic hierarchy[J]. Hepatology, 2020, 72(6): 2206-2218.

[3] QIN S, MAO Y, CHEN X, et al. The functional roles, cross-talk and clinical implications of m6A modification and circRNA in hepatocellular carcinoma[J]. Int J Biol Sci, 2021, 17(12): 3059-3079.

[4] YI C, CHEN L, LIN Z, et al. Lenvatinib targets FGF receptor 4 to enhance antitumor immune response of Anti-Programmed cell death-1 in HCC[J]. Hepatology, 2021, 74(5): 2544-2560.

[5] FINN R S, IKEDA M, ZHU A X, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresect-

able hepatocellular carcinoma[J]. J Clin Oncol, 2020, 38(26): 2960-2970.

[6] TANG W, CHEN Z, ZHANG W, et al. The mechanisms of sorafenib resistance in hepatocellular carcinoma: theoretical basis and therapeutic aspects[J]. Signal Transduct Target Ther, 2020, 5(1): 87.

[7] ADACHI Y, NOJIMA M, MORI M, et al. Insulin-Like growth factor 2 and incidence of liver cancer in a nested case-control study [J]. Cancer Epidemiol Biomarkers Prev, 2021, 30(11): 2130-2135.

[8] CAI Y, WANG Y, MAO B, et al. Targeting insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) for the treatment of cancer [J]. Eur J Med Chem, 2024, 268: 116241.

[9] LIU X, CHEN J, CHEN W, et al. Targeting IGF2BP3 in Cancer [J]. Int J Mol Sci, 2023, 24(11): 9423.

[10] JOSHNA C R, SAHA P, ATUGALA D, et al. Plant PUF RNA-binding proteins: a wealth of diversity for post-transcriptional gene regulation [J]. Plant Sci, 2020, 297: 110505.

[11] MANCARELLA C, SCOTLANDI K. IGF2BP3 from physiology to cancer: novel discoveries, unsolved issues, and future perspectives[J]. Front Cell Dev Biol, 2019, 7: 363.

[12] LEDERER M, BLEY N, SCHLEIFER C, et al. The role of the oncofetal IGF2 mRNA-binding protein 3 (IGF2BP3) in cancer[J]. Semin Cancer Biol, 2014, 29: 3-12.

[13] QIN S, JIN H, LI Y, et al. Comprehensive analysis of IGF2BP3 with expression features, prognosis, immune modulation and stemness in hepatocellular carcinoma and pan-cancer[J]. J Cancer, 2024, 15(9): 2845-2865.

[14] GAO Y, LUO T, OUYANG X, et al. IGF2BP3 and miR191-5p synergistically increase HCC cell invasiveness by altering ZO-1 expression[J]. Oncol Lett, 2020, 20(2): 1423-1431.

[15] LU Z, YANG H, SHAO Y, et al. IGF2BP3-NRF2 axis regulates ferroptosis in hepatocellular carcinoma[J]. Biochem Biophys Res Commun, 2022, 627: 103-110.

[16] MA L, JIANG J, SI Q, et al. IGF2BP3 enhances the growth of hepatocellular carcinoma tumors by regulating the properties of macrophages and CD8⁺ T cells in the tumor microenvironment [J]. J Clin Transl Hepatol, 2023, 11(6): 1308-1320.

[17] WANG H, WANG R, FANG J. A spliceosome-associated gene signature aids in predicting prognosis and tumor microenvironment of hepatocellular carcinoma [J]. Aging (Albany NY), 2023, 15(11): 4906-4925.

[18] YANTISS R K, WODA B A, FANGER G R, et al. KOC (K homology domain containing protein overexpressed in cancer): a novel molecular marker that distinguishes between benign and malignant lesions of the pancreas[J]. Am J Surg Pathol, 2005, 29(2): 188-195.

[19] WÄCHTER K, KÖHN M, STÖHR N, et al. Subcellular localization and RNP formation of IGF2BPs (IGF2 mR-

NA-binding proteins) is modulated by distinct RNA-binding domains [J]. *Biol Chem*, 2013, 394 (8): 1077-1090.

[20] MUELLER-PILLASCH F, POHL B, WILDA M, et al. Expression of the highly conserved RNA binding protein KOC in embryogenesis[J]. *Mech Dev*, 1999, 88 (1): 95-99.

[21] HAMMER N A, HANSEN T V, BYSKOV A G, et al. Expression of IGF- II mRNA-binding proteins (IMPs) in gonads and testicular cancer[J]. *Reproduction*, 2005, 130 (2): 203-212.

[22] BELL J L, WÄCHTER K, MÜHLECK B, et al. Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression? [J]. *Cell Mol Life Sci*, 2013, 70(15): 2657-2675.

[23] REN F, LIN Q, GONG G, et al. Igf2bp3 maintains maternal RNA stability and ensures early embryo development in zebrafish[J]. *Commun Biol*, 2020, 3(1): 94.

[24] TANGPRASITTIPAP A, KAEWPROMMAL P, SRI-PICHAI O, et al. Comparison of gene expression profiles between human erythroid cells derived from fetal liver and adult peripheral blood[J]. *PeerJ*, 2018, 6: e5527.

[25] DAI N, RAPLEY J, ANGEL M, et al. mTOR phosphorylates IMP2 to promote IGF2 mRNA translation by internal ribosomal entry [J]. *Genes Dev*, 2011, 25 (11): 1159-1172.

[26] DAI N, CHRISTIANSEN J, NIELSEN F C, et al. mTOR complex 2 phosphorylates IMP1 cotranslationally to promote IGF2 production and the proliferation of mouse embryonic fibroblasts[J]. *Genes Dev*, 2013, 27(3): 301-312.

[27] LIAO B, HU Y, HERRICK D J, et al. The RNA-binding protein IMP-3 is a translational activator of insulin-like growth factor II leader-3 mRNA during proliferation of human K562 leukemia cells[J]. *J Biol Chem*, 2005, 280 (18): 18517-18524.

[28] RIVERA VARGAS T, BOUDOUKHA S, SIMON A, et al. Post-transcriptional regulation of cyclins D1, D3 and G1 and proliferation of human cancer cells depend on IMP-3 nuclear localization[J]. *Oncogene*, 2014, 33 (22): 2866-2875.

[29] SCHMIEDEL D, TAI J, YAMIN R, et al. The RNA binding protein IMP3 facilitates tumor immune escape by downregulating the stress-induced ligands ULPB2 and MICB[J]. *Elife*, 2016, 5: e13426.

[30] SHANTHA KUMARA H, KIRCHOFF D, CABALLERO O L, et al. Expression of the cancer testis antigen IGF2BP3 in colorectal cancers; IGF2BP3 holds promise as a specific immunotherapy target[J]. *Oncoscience*, 2015, 2 (6): 607-614.

[31] DEFORZH E, VARGAS T R, KROPP J, et al. IMP-3 protects the mRNAs of cyclins D1 and D3 from GW182/AGO2-dependent translational repression[J]. *Int J Oncol*, 2016, 49(6): 2578-2588.

[32] LOU K, CHEN N, LI Z, et al. MicroRNA-142-5p overexpression inhibits cell growth and induces apoptosis by regulating FOXO in hepatocellular carcinoma cells[J]. *Oncol Res*, 2017, 25(1): 65-73.

[33] WANG J, ZHANG B, CHEN X, et al. Cell mechanics regulate the migration and invasion of hepatocellular carcinoma cells via JNK signaling[J]. *Acta Biomater*, 2024, 176: 321-333.

[34] LOH C Y, CHAI J Y, TANG T F, et al. The E-Cadherin and N-Cadherin Switch in Epithelial-to-Mesenchymal transition: signaling, therapeutic implications, and challenges[J]. *Cells*, 2019, 8(10): 1118.

[35] YAN J, WANG X, FAN Z, et al. Circ_0098823 binding with IGF2BP3 regulates DNMT1 stability to promote metastasis of hepatocellular carcinoma via mitochondrial fission[J]. *Apoptosis*, 2024, 29(5/6): 709-725.

[36] KOUHKAN F, MOBARRA N, SOUFI-ZOMORROD M, et al. MicroRNA-129-1 acts as tumour suppressor and induces cell cycle arrest of GBM cancer cells through targeting IGF2BP3 and MAPK1[J]. *J Med Genet*, 2016, 53(1): 24-33.

[37] LI J, ZHU Y. Recent advances in liver cancer stem cells: non-coding RNAs, oncogenes and oncoproteins[J]. *Front Cell Dev Biol*, 2020, 8: 548335.

[38] JIANG W, CHENG X, WANG T, et al. LINC00467 promotes cell proliferation and metastasis by binding with IGF2BP3 to enhance the mRNA stability of TRAF5 in hepatocellular carcinoma[J]. *J Gene Med*, 2020, 22 (3): e3134.

[39] LIU Z, WANG T, SHE Y, et al. N⁶-methyladenosine-modified circIGF2BP3 inhibits CD8⁺ T-cell responses to facilitate tumor immune evasion by promoting the deubiquitination of PD-L1 in non-small cell lung cancer[J]. *Mol Cancer*, 2021, 20(1): 105.

[40] RAMESH-KUMAR D, GUIL S. The IGF2BP family of RNA binding proteins links epitranscriptomics to cancer [J]. *Semin Cancer Biol*, 2022, 86(Pt 3): 18-31.

[41] CHEN B, HUANG R, XIA T, et al. The m6A reader IGF2BP3 preserves NOTCH3 mRNA stability to sustain Notch3 signaling and promote tumor metastasis in nasopharyngeal carcinoma[J]. *Oncogene*, 2023, 42(48): 3564-3574.

[42] ZHOU H, TAN L, LIU B, et al. Cancer stem cells: Recent insights and therapies [J]. *Biochem Pharmacol*, 2023, 209: 115441.

[43] GAO R, YE M, LIU B, et al. m6A modification: a Double-Edged sword in tumor development [J]. *Front Oncol*, 2021, 11: 679367.

[44] DENG L, DI Y, CHEN C, et al. Depletion of the N⁶-Methyladenosine(m6A) reader protein IGF2BP3 induces ferroptosis in glioma by modulating the expression of GPX4[J]. *Cell Death Dis*, 2024, 15(3): 181.

Chemother, 2023, 29(1):105-108.

[20] BUKIRI H, VOLKMANN E R. Current advances in the treatment of systemic sclerosis[J]. Curr Opin Pharmacol, 2022, 64:102211.

[21] HOZUMI H, HASEGAWA H, MIYASHITA K, et al. Efficacy of corticosteroid and intravenous cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a propensity score-matched analysis[J]. Respirology, 2019, 24(8):792-798.

[22] NACCACHE J M, JOUNEAU S, DIDIER M, et al. Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial[J]. Lancet Respir Med, 2022, 10(1):26-34.

[23] INOUE Y, WELLS A U, SONG J W, et al. Nintedanib in Asian patients with progressive fibrosing interstitial lung diseases: results from the INBUILD trial[J]. Respirology, 2023, 28(5):465-474.

[24] RICHELDI L, DU BOIS R M, RAGHU G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis [J]. N Engl J Med, 2014, 370(22):2071-2082.

[25] RODRÍGUEZ-PORTAL J A. Efficacy and safety of nintedanib for the treatment of idiopathic pulmonary fibrosis: an update[J]. Drugs R D, 2018, 18(1):19-25.

[26] ITO Y, TAZAKI G, KONDO Y, et al. Therapeutic effect of nintedanib on acute exacerbation of interstitial lung diseases[J]. Respir Med Case Rep, 2019, 26:317-320.

[27] KULKARNI T, CRINER G J, KASS D J, et al. Design of the STRIVE-IPF trial-study of therapeutic plasma exchange, rituximab, and intravenous immunoglobulin for acute exacerbations of idiopathic pulmonary fibrosis[J]. BMC Pulm Med, 2024, 24(1):143.

[28] DOWMAN L, HILL C J, MAY A, et al. Pulmonary rehabilitation for interstitial lung disease[J]. Cochrane Database Syst Rev, 2021, 2(2):CD006322.

[29] RUSH B, WISKAR K, BERGER L, et al. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: a nationwide retrospective cohort analysis[J]. Respir Med, 2016, 111:72-76.

[30] YANG L, XIANG Z, DAI M, et al. Prognosis of lung transplantation in patients with acute exacerbations of interstitial lung disease: a meta-analysis based on cohort studies[J]. Ann Thorac Cardiovasc Surg, 2024, 30(1):24-00086.

[31] HAYAT SEO M K, BRUCK O, KUMAR A, et al. Acute exacerbation of interstitial lung disease in the intensive care unit: principles of diagnostic evaluation and management[J]. World J Crit Care Med, 2023, 12(3):153-164.

(收稿日期:2024-04-23 修回日期:2024-12-20)

(上接第 1218 页)

[45] LIN Z, LI J, ZHANG J, et al. Metabolic reprogramming driven by IGF2BP3 promotes acquired resistance to EGFR inhibitors in non-small cell lung cancer[J]. Cancer Res, 2023, 83(13):2187-2207.

[46] ENNAJDAOUI H, HOWARD J M, STERNE-WEILER T, et al. IGF2BP3 modulates the interaction of invasion-associated transcripts with RISC[J]. Cell Rep, 2016, 15(9):1876-1883.

[47] PRICE D, MUTERSPAUGH R, CLEGG B, et al. IGFBP-3 blocks Hyaluronan-CD44 signaling, leading to increased acetylcholinesterase levels in A549 cell media and apoptosis in a p53-dependent manner[J]. Sci Rep, 2020, 10(1):5083.

[48] SHI L, GUO G, ZHOU J, et al. Identification of a potent and specific retinoic acid-inducible gene 1 pathway activator as a hepatitis B virus antiviral through a novel cell-based reporter assay[J]. J Virol Methods, 2024, 325:114875.

[49] LI X, LI Y, ZHANG W, et al. The IGF2BP3/notch/jag1 pathway: a key regulator of hepatic stellate cell ferroptosis in liver fibrosis[J]. Clin Transl Med, 2024, 14(8):e1793.

[50] PETROWSKY H, FRITSCH R, GUCKENBERGER M, et al. Modern therapeutic approaches for the treatment of malignant liver tumours[J]. Nat Rev Gastroenterol Hepatol, 2020, 17(12):755-772.

[51] CHEN L J, LIU H Y, XIAO Z Y, et al. IGF2BP3 promotes the progression of colorectal cancer and mediates cetuximab resistance by stabilizing EGFR mRNA in an m6A-dependent manner[J]. Cell Death Dis, 2023, 14(9):581.

[52] MA S, LEE T K, ZHENG B J, et al. CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway[J]. Oncogene, 2008, 27(12):1749-1758.

[53] SHAO W, ZHAO H, ZHANG S, et al. A pan-cancer landscape of IGF2BPs and their association with prognosis, stemness and tumor immune microenvironment[J]. Front Oncol, 2023, 12:1049183.

[54] WANG C, DONG R, YANG F, et al. LARP4B promotes hepatocellular carcinoma progression and impairs sorafenib efficacy by activating SPINK1-mediated EGFR pathway[J]. Cell Death Discovery, 2024, 10(1):208.

[55] LU Y, ZHU J, ZHANG Y, et al. Lactylation-driven IGF2BP3-mediated serine metabolism reprogramming and RNA m6A-modification promotes lenvatinib resistance in HCC [J]. Adv Sci (Weinh), 2024, 11(46):e2401399.

(收稿日期:2024-05-26 修回日期:2024-11-28)