

m6A 识别蛋白 IGF2BPs 家族在头颈肿瘤中的研究进展

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摘要: RNA 表观遗传修饰在肿瘤的发生发展中发挥着重要的作用, N6-甲基腺苷 (N6-methyladenosine, m6A) 是真核生物中最常见的 mRNA 表观遗传修饰方式。近年来新发现的 m6A 阅读器-胰岛素样生长因子-2 mRNA 结合蛋白家族 (insulin-like growth factor-2 mRNA-binding protein 1, IGF2BPs), 可靶向结合 GG(m6A)C 序列, 增强 mRNA 稳定性, 促进肿瘤细胞的增殖、侵袭和迁移, 参与肿瘤的发生发展。本文将综述 IGF2BPs 家族在头颈肿瘤中的作用及其机制, 以期为 IGF2BPs 在临床的分子靶向治疗研究提供新的思路。

关键词: N6-甲基腺苷; IGF2BPs; 头颈部肿瘤; 鼻咽癌; 口腔鳞状细胞癌; 喉鳞状细胞癌; 下咽鳞状细胞癌; 食管鳞状细胞癌; 甲状腺癌

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Progress of m6A recognition protein IGF2BPs in head and neck cancer

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Abstract: RNA epigenetic modifications play a crucial role in tumor development, with N6-methyladenosine being the primary epigenetic modification found in all eukaryotic messenger RNAs. Recently discovered, the m6A reader family known as IGF2BPs targets GG(m6A)C sequences and enhances mRNA stability, thereby promoting tumor cell proliferation, invasion and migration, and contributing to tumorigenesis and development. This paper aims to review the involvement of IGF2BPs in head and neck tumors along with their underlying mechanisms, providing new insights for clinical molecular targeting therapy on IGF2BPs.

Key words: N6-methyladenosine; Insulin-like growth factor-2 mRNA-binding protein 1; Head and neck squamous cell carcinoma; Nasopharyngeal carcinoma; Oral squamous cell carcinoma; Laryngeal squamous cell carcinoma; Hypopharyngeal cancer; Esophageal squamous-cell carcinoma; Thyroid cancer

头颈部肿瘤 (head and neck squamous cell carcinoma, HNSCC) 是全球第六大恶性肿瘤, 多发生于喉部、咽部和口腔^[1-3]。由于发病部位隐匿, 早期不易发现, 多数患者初诊时已经是局部晚期并伴有区域淋巴结转移, 其中下咽鳞状细胞癌

(hypopharyngeal cancer, HSCC) 的预后最差^[3-4]。尽管随着诊疗技术的进步, 癌症的局部控制率得以改善, 但由于缺乏有效的早期监控指标, 致整体生存率在本质上并没有明显改善。目前头颈部肿瘤患者的 5 年总生存率仍然只有 50%, 晚期预后

不乐观^[3-5]。因此从分子水平出发,研究肿瘤的发生发展机制,寻找有效的肿瘤标记物和治疗靶点,将癌症预防和治疗干预相结合,是提高患者生活质量及生存时间的重要思路。

RNA 高通量测序技术和生物信息学方法的发展,使得 RNA 表观遗传修饰领域逐渐成为肿瘤学研究的热点。其中 N6-腺苷酸甲基化(N6-methyladenosine, m6A)在 mRNA 内部修饰碱基中占比例最大,主要发生在 mRNA 的终止密码子、3'非翻译区(3'UTR)等位置。作为真核生物信使 RNA (mRNA)中最普遍、最丰富且最保守的内部修饰之一,m6A 修饰影响了 RNA 的转录、加工、翻译等过程,在调节肿瘤发生发展方面起着重要作用^[6]。m6A 甲基化修饰需要 3 种调控因子的参与:①甲基化转移酶(writers),如 METTL3/14、WTAP 等,主要催化 mRNA 上腺苷酸发生 m6A 修饰;②去甲基化酶(erasers),如 FTO 和 ALKBH3/5 等,主要介导 m6A 的去甲基化过程,擦除甲基化修饰信号;③阅读器(readers),如 YTHDF1-3 和 EIF3 等,可以促进靶基因的翻译效率,增强稳定性^[7-12]。胰岛素样生长因子-2mRNA 结合蛋白家族(insulin-like growth factor-2 mRNA-binding protein1, IGF2BPs),家族作为近些年新发现的 m6A“reader”,在各种肿瘤中的作用和机制研究日益增多,已经成为肿瘤发生发展的研究热点。

1 IGF2BPs

作为高度保守的单链 RNA 结合蛋白家族 IGF2BPs,由 2 个 RNA 识别基元域和 4 个 K 同源域组成,参与调控 RNA 的加工和代谢,并参与各种细胞的病理生理过程^[13-16]。lncRNAs、环状 RNAs(circRNAs)和 microRNAs(miRNAs)等非编码 ncRNAs 是肿瘤发生和进展的关键调控因子^[17]。IGF2BPs 依靠其特有的 KH 结构域识别 ncRNA 上的 m6A 信号,从而维持其稳定性^[18]。IGF2BPs 家族识别靶 mRNA 的 m6A 修饰,干扰 miRNA 对 mRNA 的调控,缩短癌细胞的 G1 细胞周期,加快 mRNA 的出核速度,参与下游 mRNA 的翻译和降解,并参与介导肿瘤免疫微环境^[19-21]。IGF2BPs 家族中的 3 个蛋白 IGF2BP1、IGF2BP2 和 IGF2BP3,分别位于人类染色体 17q21.32^[22]、3q27.2^[23] 和 7p15.3^[24] 上。IGF2BPs 主要集中在细胞质颗粒中,在核周区域更加显著^[25]。这表明该蛋白家族的亚细胞分类本质上受

特定 RNA 底物的相关调节^[26]。IGF2BPs 家族在多种癌症中发挥至关重要的作用,其中 IGF2BP1 的致癌作用最强且作用靶点多样^[27]。本文将对 IGF2BPs 在各种头颈肿瘤中的作用机制进行综述,以期到头颈部肿瘤的早期诊断和治疗提供新的思路。

2 IGF2BPs 在头颈肿瘤中的作用机制

已有研究证明 IGF2BPs 家族与头颈肿瘤的淋巴结转移、肿瘤分期及患者生存期有显著相关性,通过识别 mRNA 和非编码 RNA(ncRNAs)上的 m6A 修饰,促进其稳定性或翻译,影响癌症干细胞的自我更新、血管生成、凋亡、代谢重编程、免疫逃逸等推动肿瘤发生发展与转移,介导免疫微环境^[28-33](图 1):①管理癌症干细胞的相关基因,MYC 是促进癌症干细胞自我更新的最常激活的癌基因之一,已被证实是 IGF2BPs 的重要靶标^[15]。体内和体外实验表明,在鼻咽癌(nasopharyngeal carcinoma, NPC)、口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)、甲状腺癌(thyroid cancer, TC)等中,IGF2BPs 可增强 m6A 对 MYC 的识别,增强并维持 MYC 的稳定性,促进癌症干细胞的自我更新^[34-36];②参与癌症干细胞相关信号通路,如 Wnt/ β -catenin、MAPK、PI3K/AKT 等信号通路,促进头颈肿瘤干细胞自我更新,使其获得逃避细胞凋亡的能力^[37-40];③IGF2BPs 可以通过调节肿瘤血管生成、上皮间质转化等诱导头颈肿瘤转移^[41-42];④影响癌细胞的代谢和死亡形式,铁死亡是一种新发现的铁依赖性细胞死亡形式,在食管鳞状细胞癌(esophageal squamous-cell carcinoma, ESCC)中 IGF2BP2 抑制铁死亡并促进其发展^[43]。在 OSCC 中影响自噬相关基因 RB1CC1 并抑制 OSCC 进展^[44]。Warburg 效应或有氧糖酵解是肿瘤中最常见的代谢重编程途径。IGF2BP2 促进口腔鳞状细胞癌进展的 Warburg 效应^[45]。IGF2BP2 识别并上调 m6A 修饰的载脂蛋白 E(APOE),促进甲状腺乳头状癌的糖酵解和肿瘤生长^[46];⑤IGF2BPs 可以直接或间接调节免疫检查点,促进免疫逃逸。IGF2BP2 可提高 PD-L1 的稳定性和表达,介导 HSCC 的免疫逃逸^[47]。

因此以 IGF2BPs 为目标,扰乱肿瘤细胞状态和肿瘤微环境,从而抑制肿瘤生长,IGF2BPs 有望成为 HNSCC 新的预后生物标志物和潜在的治疗靶点。

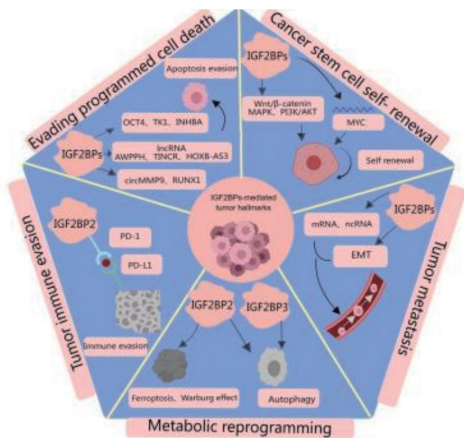


图 1 IGF2BPs 在头颈肿瘤中的机制
Figure 1 Mechanisms of IGF2BPs in Head and neck squamous cell carcinoma

2.1 NPC

NPC 是一种早期易转移、侵袭性高的原发性头颈部恶性肿瘤^[48-49]。Wang 等^[50]研究发现 IGF2BPs 在 NPC 组织中高表达。雷公藤内酯通过干扰 Lnc-THOR-IGF2BP1 信号通路,在体外和体内均可抑制人 NPC 细胞的生长,从而减缓 NPC 的进展。基因组学结合预后生存分析证实 3 个 m6A 相关基因 IGF2BP1 / IGF2BP2 / METTL3 是 NPC 的独立预后标志物^[51]。长链非编码 RNA- LncRNA AWPPH 在 NPC 的细胞中高表达,通过 AWPPH/IGF2BP1/LSD1 轴促进 NPC 细胞的增殖和迁移,AWPPH 稳定 LSD1 mRNA,增强 LSD1 在 NPC 中的表达,推动 NPC 的进展^[52]。WTAP 在 NPC 中表达明显上调,且通过 IGF2BP2 增强 LncRNA DIAPH1-AS1 的稳定性,促进 NPC 细胞生长和转移^[53]。IGF2BP3 在 NPC 组织和细胞中升高,且与 NPC 临床分期、淋巴结转移和预后不良呈正相关。IGF2BP3 通过激活 AKT/mTOR 信号通路调控上皮-间质转化 (epithelial-mesenchymal transition, EMT) 关键调控因子的表达,从而刺激 NPC 细胞的迁移和侵袭^[41]。MYC 有效地结合到 IGF2BP3 的启动子上通过影响 m6A 修饰的 KPNA2 的稳定性来促进 NPC 细胞的增殖和转移^[34]。IGF2BP3 还可通过 Notch3 轴促进肿瘤转移^[54]。Zheng 等^[39]研究发现 LncRNA TINCR 在 NPC 中显著上调,介导 PADI1-MAPK-MMP2/9 信号通路促进鼻咽癌的进展,在化疗耐药中起着关键作用,而 IGF2BP3 可以稳定 TINCR 的表达,增加其在 NPC 中的表达,进而促进 NPC 进展。

2.2 OSCC

OSCC 是头颈部常见恶性肿瘤,侵袭性强、转移

和复发率高^[55-56]。研究表明 IGF2BPs 在 OSCC 中高表达,通过促进肿瘤发生、转移与免疫浸润,从而影响患者的预后与生存率^[57]。Qiu 等^[58] circBICD2 通过 miR-149-5p/IGF2BP1 轴,下调 IGF2BP1 表达,可以抑制 OSCC 细胞增殖、迁移、侵袭和谷氨酰胺水解,促进细胞凋亡。THOR 和 IGF2BP1 在舌鳞状细胞癌 (tongue squamous cell carcinoma, TSCC) 组织中显著高表达,通过 THOR/IGF2BP1/IGF2-MEK-ERK 轴调节 TSCC 细胞的增殖促进 TSCC 发生^[59]。IGF2BP2 可以稳定 HK2 稳定性,加速 OSCC 进展的 Warburg 效应^[45]。METTL3 通过结合 IGF2BP2 增强 SLC7A11 mRNA 的稳定性,从而促进 OSCC 的生长和转移^[60]。METTL14 以 m6A-IGF2BP2 依赖的方式靶向调控自噬相关基因 RB1CC1,抑制 OSCC 进展^[44]。IGF2BP2 激活 FAK/Src 信号通路上调 EREG 表达从而促进细胞侵袭和 EMT,在 OSCC 中发挥促癌作用^[42]。长链非编码 RNA HOXB-AS3 与 IGF2BP2 结合,维持 c-Myc mRNA 的稳定性,从而促进 OSCC 细胞的增殖和活力^[35]。IGF2BP2-AS1 下调可通过 Wnt/ β -catenin 通路抑制 OSCC 细胞的生长和迁移,为 OSCC 治疗提供了新的分子靶点^[38]。Liu 等研究表明^[61],circ-IGHG 通过 miR-142-5p 诱导 IGF2BP3 介导的 EMT 并促进 OSCC 的转移、进展。EGF 以 EGF 受体 (EGFR) 依赖的方式诱导 IGF2BP3、PDPN 高表达并与 OSCC 患者的 T 分期、淋巴结转移及总生存率有显著相关性^[62]。IGF2BP3 或 PDPN 的缺失可抑制 OSCC 细胞中白细胞介素 IL-6 和 IL-8 的表达,并使 OSCC 异种移植肿瘤组织中 NF- κ B 配体受体激活剂低表达,从而抑制 OSCC 细胞侵袭能力、肿瘤发生和局部骨破坏^[30]。

2.3 喉鳞状细胞癌 (laryngeal squamous cell carcinoma, LSCC)

LSCC 是头颈部最常见的癌症之一,过去 30 年全球喉癌的发病率和患病率分别增加了 12%、24%,同时其 5 年生存率呈现下降趋势^[63-64]。IGF2BP2 通过促进 CDK6 mRNA 的稳定表达,在体内、体外均可促进 LSCC 细胞的增殖和侵袭^[65]。Li 等^[40]研究发现真核翻译起始因子 4a3 (EIF4A3) 诱导的 circCDK1 在 LSCC 组织中表达上调并与患者预后不良呈正相关。通过 EIF4A3-circCDK1-IGF2BP2-CPPED1 轴激活 PI3K-AKT 信号通路,进而促进 LSCC 转移。IGF2BP2 以 m6A 依赖的方式稳定 CircMMP9,募集 ETS1 刺激 TRIM59 的转录,激活 PI3K/AKT 信号通路加速 LSCC 的进展^[66]。

IGF2BP3 在良性喉病变和喉发育不良中表达较低,而在 LSCC 中可见细胞质弥漫性和强染色,因此 IGF2BP3 可以作为区分浸润性和非浸润性癌病变的标志^[67]。IGF2BP3 介导的 TMA7 m6A 修饰通过 UBA2-PI3K 通路抑制自噬,促进 LSCC 进展和顺铂耐药^[68]。上调 RBM15,通过 IGF2BP3 靶向增强 TMBIM6 mRNA 的稳定性,促进 LSCC 的增殖、侵袭、迁移和凋亡^[69]。目前尚未发现 IGF2BP1 在 LSCC 中的相关报道。

2.4 下咽鳞状细胞癌(hypopharyngeal squamous cell carcinoma, HSCC)

HSCC 发病部位隐匿,早期无明显特异性症状,并易发生粘膜下扩散和局部淋巴结转移,预后极差^[70]。IGF2BP2 在 HSCC 中高表达,下调 IGF2BP2 的表达可以通过 PD-1/PD-L1 轴,抑制 HSCC 细胞的增殖活力、转移、侵袭,从而调控 HSCC 的发生发展,同时证明 IGF2BP2 可以与免疫检查点 PD-L1 相互作用,为 HSCC 的免疫治疗提供新的靶点^[47]。

2.5 ESCC

ESCC 预后极差、死亡率高,是全球第六大癌症死亡原因,目前缺乏有效的治疗策略^[1,71]。研究表明 IGF2BPs 在 ESCC 肿瘤组织中高表达。miR-454-3p 通过 ERK/AKT 信号通路靶向下调 IGF2BP1,从而在 ESCC 中发挥抑癌作用^[72]。miR-98-5p 在 ESCC 组织和细胞中表达降低,高表达 miR-98-5p 可以下调 IGF2BP1/UHRF2 表达延缓 ESCC 进展过程,抑制细胞增殖和凋亡^[73]。RPS15 通过 IGF2BP1 介导 MKK6 和 MAPK14 mRNA 的 m6A 修饰,促进 ESCC 的发展^[74]。IGF2BP1 结合并稳定了 INHBA mRNA,激活 Smad2/3 信号通路,促进 ESCC 恶性表型的发生^[75]。IGF2BP2 过表达可抑制细胞凋亡,促进细胞增殖、迁移^[76]。环状 RNA(circRNAs)—circRUNX1 作为一种致癌因子通过 miR-449b-5p 增强 FOXP3 表达,IGF2BP2 与 circRUNX1 的结合稳定其表达,增强其致癌效果^[77]。长链非编码 RNA(lncRNA)TMEM44-AS1 在 ESCC 组织和细胞中高表达,并抑制 ESCC 细胞铁死亡,TMEM44-AS1 通过 IGF2BP2/GPX4 轴影响铁死亡,促进 ESCC 的恶性进展^[43]。LIPH-4 与 ESCC 患者预后不良呈正相关,通过与 miR-216b 竞争性结合并靶向 IGF2BP2 在 ESCC 中发挥致癌作用,在体外促进 ESCC 细胞生长,介导细胞周期进程,抑制细胞凋亡^[78]。在 ESCC 细胞和组织中,CCAT2、IGF2BP2 和 TK1 表达上调,miR-200b 表达下调。CCAT2 与 miR-200b 结合并使其表达下调,IGF2BP2 高表达。IGF2BP2

通过识别 TK1 mRNA 的 m6A 修饰,增强 TK1 mRNA 的稳定性,导致 TK1 表达升高,进而促进 ESCC 的发展^[79]。IGF2BP2 通过稳定 OCT4 mRNA,在 ESCC 中发挥致癌作用^[80]。LINC01305 通过与 IGF2BP2 和 IGF2BP3 发生相互作用,促进 HTR3A mRNA 的表达和 ESCC 细胞的转移和增殖^[81]。IGF2BP3 通过正向调控 KIF18A,促进食管癌(Esophageal cancer, ESCA)细胞的增殖、迁移、侵袭和辐射抗性,加速 ESCA 进程^[82]。IGF2BP3 可以靶向结合锌指 e-box 结合同源盒 1(Zeb1) mRNA,抑制其降解,促进 ESCC 细胞的迁移、侵袭和上皮-间质转化^[83]。

2.6 TC

TC 作为一种常见恶性肿瘤,近年来的发病率和死亡率急剧上升^[84]。IGF2BP2 在 TC 肿瘤组织中高表达,长链非编码 RNA MALAT1 通过调控 miR-204/IGF2BP2/m6A-MYC 信号通路在 TC 中发挥致癌作用^[36]。抑制 IGF2BP2 可以通过 m6A 依赖性降低 TC 细胞中 HAGLR 的表达和转录物的稳定性,诱导细胞凋亡和细胞周期阻滞,抑制 TC 的发生^[85]。甲状腺腺瘤相关基因(THADA)与位于 IGF2BP3 基因的 LOC389473 基因之间存在复发性融合,过表达 IGF2BP3 可以激活 PI3K 和 MAPK 通路促进 TC 的增殖、侵袭和转移,这说明通过基因融合和扩增操纵 IGF2BP3 使其过表达可能成为新的抗肿瘤靶点,为诊治 TC 提供新的见解^[86]。在最常见的甲状腺乳头状癌(papillary thyroid carcinomas, PTC)中,FTO 通过 IGF2BP2 介导的 m6A 修饰抑制载脂蛋白 E(apolipoprotein E, APOE)的表达,并通过调节 IL-6/JAK2/STAT3 信号通路抑制 PTC 糖酵解代谢,从而抑制肿瘤生长^[46]。淋巴结转移是 PTC 复发最主要的原因,现有研究表明 IGF2BP2 以 m6A 依赖的方式通过稳定 DPP4 促进 PTC 淋巴转移,为切断淋巴结转移途径提供新的方案^[87]。甲状腺间变性癌(anaplastic thyroid carcinoma, ATC)也叫甲状腺未分化癌,是一种罕见的甲状腺癌,恶性程度高、侵袭性强、治疗反应及预后差^[88]。通过 RNA 测序和免疫组织化学分析证实 IGF2BP1 可以单基因标记 ATC 来区分 ATC 和低分化甲状腺癌^[89]。放射性碘难治性甲状腺乳头状癌(RR-PTC)是临床面临的一大难题,有研究表明 AhR 拮抗剂通过抑制 circSH2B3/miR-4640-5p/IGF2BP2 轴促进 RR-PTC 分化^[90]。靶向抑制 IGF2BP2 与 RUNX2 mRNA 的结合,促进 RR-PTC 分化,为 PTC 分化提供了一种新的治疗方法和潜在的标记物^[91]。IGF2BP2 依赖

性 ERBB2 信号的激活有助于获得对酪氨酸激酶抑制剂 (tyrosine kinase inhibitors, TKI) 的抗性, 形成获得性耐药, 因此抑制 IGF2BP2 促进 RR-PTC 分化, 将会构建新的分化策略^[92]。

3 小结与展望

综上所述, IGF2BPs 家族作为 m6A 修饰的重要读取器参与 mRNA 稳定和翻译的调控。除 mRNA 外, 还有多种 ncRNAs、转录因子 (TFs) 和翻译后修饰 (PTMs) 通过操纵 IGF2BPs 使头颈肿瘤发生和发展的过程失调并发挥关键作用。当前的研究表明, IGF2BPs 可通过影响癌症干细胞的相关基因、信号通路、代谢途径促进头颈肿瘤细胞增殖、侵袭、转移、维持血管生成、细胞程序性死亡、能量代谢失调和免疫逃逸。目前针对 IGF2BPs 靶向通路的精准治疗甚少, 在放射性碘难治性甲状腺癌 (RR-PTC) 中, 研究表明分化疗法与 I131 共同治疗放射性碘难治性甲状腺癌 (RR-PTC) 是一种很有前景的替代治疗方法, TKI、芳烃受体 (AhR) 拮抗剂抑制 IGF2BP2 通路可以增强 PTC 的分化^[90,92]。雷公藤内酯 (trip-tolide) 是雷公藤中的一种二萜环氧化物, 通过 MET-TL3-m6A-IGF2BP2 轴介导 SLC7A11 RNA 稳定性抑制铁凋亡影响 OSCC 进展^[60]。也可干扰 Lnc-THOR-IGF2BP1 信号通路, 抑制人鼻咽癌细胞的生长^[50]。叶酸可以治疗 RPS15 介导的 IGF2BP1-MKK6/MAPK14-p38 MAPK 通路, 从而抑制 ESCC 的发展, 并与顺铂联合增强了这种作用^[74]。敲低 IGF2BP2 在一定程度上增加了 PTC 细胞对顺铂治疗的敏感性^[87]。IGF2BP3 稳定 TINCR 激活 PA-DII-MAPK-MMP2/9 途径最终促进 NPC 增殖、转移和顺铂耐药^[39]。IGF2BPs 是肿瘤进展、化疗耐药和免疫治疗反应的关键因素。我们可以将未来研究的重点放在肿瘤细胞能量代谢方面, 探究癌细胞的转移和化疗抵抗, 完善 IGF2BPs 调控机制网络图, 将为头颈肿瘤的精准靶向治疗提供新的方向。然而目前关于 IGF2BPs 在驱动癌症基因转录、转录后修饰和翻译等复杂调控机制的研究尚未完全阐明, 存在很多局限性, 同时对 IGF2BPs 家族治疗头颈恶性肿瘤的靶向研究也处于临床前阶段, 需要大量的实验验证继而投入临床药物应用。关于 IGF2BPs 与免疫抑制细胞 (如 MDSCs 和 Tregs) 之间关系的研究尚未开展, 继续探索这一领域也可能有助于我们了解头颈肿瘤发生机制, 加深对免疫抑制的认识。因此我们应积极开发作用于 IGF2BPs 调控机制轴的小分子抑制剂, 精确且有效地调控 IGF2BPs 及其调

控的靶基因表达水平, 或联合应用 IGF2BPs 上游调控基因的抑制剂, 使得 IGF2BPs 相关基因治疗成为更有力的癌症治疗手段, 也可以特异性抑制 IGF2BPs 与 RNA 结合的分子, 从而更有效地治疗癌症。当今社会医学不断进步, 人们对生活水平要求不断提高的同时对微创诊断方法的要求越来越高, 因此对患者外周血标志物的检测越来越受到重视。我们可以检测外周血中是否存在抗 IGF2BPs 自身抗体、是否可以将 IGF2BPs 作为肿瘤标志物作为诊断 HNSCC 的依据, 为 HNSCC 患者提供新的诊断方法, 帮助我们更好地制定个性化的癌症治疗策略。

参考文献:

- [1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. *CA Cancer J Clin*, 2021, 71 (3): 209-249. doi: 10.3322/caac.21660
- [2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018 [J]. *CA A Cancer J Clinicians*, 2018, 68 (1): 7-30. doi: 10.3322/caac.21442
- [3] Johnson DE, Burtneess B, Leemans CR, et al. Head and neck squamous cell carcinoma [J]. *Nat Rev Dis Primers*, 2020, 6 (1): 92. doi: 10.1038/s41572-020-00224-3
- [4] Garneau JC, Bakst RL, Miles BA. Hypopharyngeal cancer: a state of the art review [J]. *Oral Oncol*, 2018, 86: 244-250. doi: 10.1016/j.oraloncology.2018.09.025
- [5] Galloway TJ, Ridge JA. Management of squamous cancer metastatic to cervical nodes with an unknown primary site [J]. *J Clin Oncol*, 2015, 33 (29): 3328-3337. doi: 10.1200/JCO.2015.61.0063
- [6] Sun T, Wu RY, Ming L. The role of m6A RNA methylation in cancer [J]. *Biomed Pharmacother*, 2019, 112: 108613. doi: 10.1016/j.biopha.2019.108613
- [7] Fu Y, Dominissini D, Rechavi G, et al. Gene expression regulation mediated through reversible m⁶A RNA methylation [J]. *Nat Rev Genet*, 2014, 15 (5): 293-306. doi: 10.1038/nrg3724
- [8] Hu YY, Wang SM, Liu J, et al. New sights in cancer: Component and function of N6-methyladenosine modification [J]. *Biomed Pharmacother*, 2020, 122: 109694. doi: 10.1016/j.biopha.2019.109694
- [9] Chen B, Li Y, Song RF, et al. Functions of RNA N6-methyladenosine modification in cancer progression [J]. *Mol Biol Rep*, 2019, 46 (2): 2567-2575. doi: 10.1007/s11033-019-04655-4
- [10] Tuncel G, Kalkan R. Importance of m⁶A-methyladenosine (m6A) RNA modification in cancer [J]. *Med On-*

- col, 2019, 36(4): 36. doi:10.1007/s12032-019-1260-6
- [11] 周子寒, 周先果, 陈佩琴, 等. m6A 结合蛋白 IGF2BP1 在肝细胞癌中的基因调控网络分析[J]. 中国癌症防治杂志, 2020, 12(6): 675-680. doi: 10.3969/j.issn.1674-5671.2020.06.14
 ZHOU Zihan, ZHOU Xianguo, CHEN Peiqin, et al. Gene regulatory network analysis of m6A reader IGF2BP1 in hepatocellular carcinoma[J]. Chinese Journal of Oncology Prevention and Treatment, 2020, 12(6): 675-680. doi:10.3969/j.issn.1674-5671.2020.06.14
- [12] Jiang XL, Liu BY, Nie Z, et al. The role of m6A modification in the biological functions and diseases[J]. Signal Transduct Target Ther, 2021, 6(1): 74. doi: 10.1038/s41392-020-00450-x
- [13] Huang XW, Zhang H, Guo XR, et al. Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in cancer [J]. J Hematol Oncol, 2018, 11(1): 88. doi:10.1186/s13045-018-0628-y
- [14] Du QY, Zhu ZM, Pei DS. The biological function of IGF2-BPs and the irrolein tumor igenesis [J]. Investig New Drugs, 2021, 39(6): 1682-1693. doi: 10.1007/s10637-021-01148-9
- [15] Huang HL, Weng HY, Sun WJ, et al. Recognition of RNA N6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation[J]. Nat Cell Biol, 2018, 20(3): 285-295. doi:10.1038/s41556-018-0045-z
- [16] Wächter K, Köhn M, Stöhr N, et al. Subcellular localization and RNP formation of IGF2BPs (IGF2 mRNA-binding proteins) is modulated by distinct RNA-binding domains[J]. Biol Chem, 2013, 394(8): 1077-1090. doi:10.1515/hsz-2013-0111
- [17] Dai LR, Liang WL, Shi ZM, et al. Systematic characterization and biological functions of non-coding RNAs in glioblastoma[J]. Cell Prolif, 2023, 56(3): e13375. doi:10.1111/cpr.13375
- [18] Liu HT, Zou YX, Zhu WJ, et al. lncRNA THAP7-AS1, transcriptionally activated by SP1 and post-transcriptionally stabilized by METTL3-mediated m6A modification, exerts oncogenic properties by improving CUL4B entry into the nucleus[J]. Cell Death Differ, 2022, 29(3): 627-641. doi:10.1038/s41418-021-00879-9
- [19] Liu Y, Guo Q, Yang H, et al. Allosteric regulation of IGF2BP1 as a novel strategy for the activation of tumor immune microenvironment[J]. ACS Cent Sci, 2022, 8(8): 1102-1115. doi:10.1021/acscentsci.2c00107
- [20] Roundtree IA, Evans ME, Pan T, et al. Dynamic RNA modifications in gene expression regulation [J]. Cell, 2017, 169(7): 1187-1200. doi:10.1016/j.cell.2017.05.045
- [21] Han DL, Liu J, Chen CY, et al. Anti-tumour immunity controlled through mRNA m6A methylation and YTH-DF1 in dendritic cells [J]. Nature, 2019, 566(7743): 270-274. doi:10.1038/s41586-019-0916-x
- [22] Bell JL, Turlapati R, Liu T, et al. IGF2BP1 harbors prognostic significance by gene gain and diverse expression in neuroblastoma[J]. J Clin Oncol, 2015, 33(11): 1285-1293. doi:10.1200/JCO.2014.55.9880
- [23] Gu TW, Horová E, Möllsten A, et al. IGF2BP2 and IGF2 genetic effects in diabetes and diabetic nephropathy [J]. J Diabetes Complications, 2012, 26(5): 393-398. doi:10.1016/j.jdiacomp.2012.05.012
- [24] Mancarella C, Scotlandi K. IGF2BP3 from physiology to cancer: novel discoveries, unsolved issues, and future perspectives[J]. Front Cell Dev Biol, 2019, 7: 363. doi:10.3389/fcell.2019.00363
- [25] Farina KL, Huttelmaier S, Musunuru K, et al. Two ZBP1 KH domains facilitate beta-actin mRNA localization, granule formation, and cytoskeletal attachment[J]. J Cell Biol, 2003, 160(1): 77-87. doi: 10.1083/jcb.200206003
- [26] Nielsen J, Adolph SK, Rajpert-De Meyts E, et al. Nuclear transit of human zipcode-binding protein IMP1[J]. Biochem J, 2003, 376(Pt 2): 383-391. doi: 10.1042/BJ20030943
- [27] Nielsen J, Kristensen MA, Willemoës M, et al. Sequential dimerization of human zipcode-binding protein IMP1 on RNA: a cooperative mechanism providing RNP stability[J]. Nucleic Acids Res, 2004, 32(14): 4368-4376. doi:10.1093/nar/gkh754
- [28] Tang H, Zhao JJ, Liu JP. Comprehensive analysis of the expression of the IGF2BPs gene family in head and neck squamous cell carcinoma: association with prognostic value and tumor immunity[J]. Heliyon, 2023, 9(10): e20659. doi:10.1016/j.heliyon.2023.e20659
- [29] Lin SH, Lin CW, Lu JW, et al. Cytoplasmic IGF2BP2 protein expression in human patients with oral squamous cell carcinoma: prognostic and clinical implications[J]. Int J Med Sci, 2022, 19(7): 1198-1204. doi:10.7150/ijms.74751
- [30] Hwang YS, Ahn SY, Moon S, et al. Insulin-like growth factor-II mRNA binding protein-3 and podoplanin expression are associated with bone invasion and prognosis in oral squamous cell carcinoma[J]. Arch Oral Biol, 2016, 69: 25-32. doi:10.1016/j.archoralbio.2016.05.008
- [31] Gu YM, Niu SX, Wang Y, et al. DMDRMR-Mediated regulation of m6A-Modified CDK4 by m6A reader IGF2BP3 drives ccRCC progression [J]. Cancer Res, 2021, 81(4): 923-934. doi:10.1158/0008-5472.CAN-20-1619
- [32] Xu WH, Lai YN, Pan YQ, et al. m6A RNA methylation-mediated NDUFA4 promotes cell proliferation and

- metabolism in gastric cancer[J]. Cell Death Dis, 2022, 13(8): 715. doi:10.1038/s41419-022-05132-w
- [33] Liu Y, Guo Q, Yang H, et al. Allosteric regulation of IGF2BP1 as a novel strategy for the activation of tumor immune microenvironment[J]. ACS Cent Sci, 2022, 8(8): 1102-1115. doi:10.1021/acscentsci.2c00107
- [34] Du MY, Peng Y, Li Y, et al. MYC-activated RNA N6-methyladenosine reader IGF2BP3 promotes cell proliferation and metastasis in nasopharyngeal carcinoma[J]. Cell Death Discov, 2022, 8(1): 53. doi:10.1038/s41420-022-00844-6
- [35] Leng F, Miu YY, Zhang Y, et al. A micro-peptide encoded by HOXB-AS3 promotes the proliferation and viability of oral squamous cell carcinoma cell lines by directly binding with IGF2BP2 to stabilize c-Myc[J]. Oncol Lett, 2021, 22(4): 697. doi:10.3892/ol.2021.12958
- [36] Ye M, Dong S, Hou HT, et al. Oncogenic role of long noncoding RNAMALAT1 in thyroid cancer progression through regulation of the miR-204/IGF2BP2/m6A-MYC signaling[J]. Mol Ther Nucleic Acids, 2021, 23: 1-12. doi:10.1016/j.omtn.2020.09.023
- [37] Bugter JM, Fenderico N, Maurice MM. Mutations and mechanisms of WNT pathway tumour suppressors in cancer[J]. Nat Rev Cancer, 2021, 21(1): 5-21. doi:10.1038/s41568-020-00307-z
- [38] Tong SQ, Wang XY, Guo XR, et al. Knockdown of lncRNA IGF2BP2-AS1 inhibits proliferation and migration of oral squamous cell carcinoma cells via the Wnt/ β -catenin pathway[J]. J Oral Pathol Med, 2022, 51(3): 272-280. doi:10.1111/jop.13248
- [39] Zheng ZQ, Li ZX, Guan JL, et al. Long noncoding RNA TINCR-mediated regulation of acetyl-CoA metabolism promotes nasopharyngeal carcinoma progression and chemoresistance[J]. Cancer Res, 2020, 80(23): 5174-5188. doi:10.1158/0008-5472.CAN-19-3626
- [40] Li JL, Cao H, Yang JW, et al. CircCDK1 blocking IGF2BP2-mediated m6A modification of CPPED1 promotes laryngeal squamous cell carcinoma metastasis via the PI3K/AKT signal pathway[J]. Gene, 2023, 884: 147686. doi:10.1016/j.gene.2023.147686
- [41] Xu Y, Guo ZB, Peng HW, et al. IGF2BP3 promotes cell metastasis and is associated with poor patient survival in nasopharyngeal carcinoma[J]. J Cell Mol Med, 2022, 26(2): 410-421. doi:10.1111/jcmm.17093
- [42] Lin CW, Yang WE, Su CW, et al. IGF2BP2 promotes cell invasion and epithelial-mesenchymal transition through Src-mediated upregulation of EREG in oral cancer[J]. Int J Biol Sci, 2024, 20(3): 818-830. doi:10.7150/ijbs.91786
- [43] Yang RT, Wan JH, Ma LW, et al. TMEM44-AS1 promotes esophageal squamous cell carcinoma progression by regulating the IGF2BP2-GPX4 axis in modulating ferroptosis[J]. Cell Death Discov, 2023, 9(1): 431. doi:10.1038/s41420-023-01727-0
- [44] Liang JF, Cai HS, Hou C, et al. METTL14 inhibits malignant progression of oral squamous cell carcinoma by targeting the autophagy-related gene RB1CC1 in an m6A-IGF2BP2-dependent manner[J]. Clin Sci, 2023, 137(17): 1373-1389. doi:10.1042/CS20230219
- [45] Xu K, Dai XJ, Wu JK, et al. N6-methyladenosine (m6A) reader IGF2BP2 stabilizes HK2 stability to accelerate the Warburg effect of oral squamous cell carcinoma progression[J]. J Cancer Res Clin Oncol, 2022, 148(12): 3375-3384. doi:10.1007/s00432-022-04093-z
- [46] Huang JP, Sun W, Wang ZH, et al. FTO suppresses glycolysis and growth of papillary thyroid cancer via decreasing stability of APOE mRNA in an N6-methyladenosine-dependent manner[J]. J Exp Clin Cancer Res, 2022, 41(1): 42. doi:10.1186/s13046-022-02254-z
- [47] Yang XD, Liu JS. Targeting PD-L1 (Programmed death-ligand 1) and inhibiting the expression of IGF2BP2 (Insulin-like growth factor 2 mRNA-binding protein 2) affect the proliferation and apoptosis of hypopharyngeal carcinoma cells[J]. Bioengineered, 2021, 12(1): 7755-7764. doi:10.1080/21655979.2021.1983278
- [48] Chua MLK, Wee JTS, Hui EP, et al. Nasopharyngeal carcinoma[J]. Lancet, 2016, 387(10022): 1012-1024. doi:10.1016/S0140-6736(15)00055-0
- [49] Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma[J]. N Engl J Med, 2019, 381(12): 1124-1135. doi:10.1056/NEJMoa1905287
- [50] Wang SS, Lv Y, Xu XC, et al. Triptonide inhibits human nasopharyngeal carcinoma cell growth via disrupting lnc-RNA THOR-IGF2BP1 signaling[J]. Cancer Lett, 2019, 443: 13-24. doi:10.1016/j.canlet.2018.11.028
- [51] Lu SS, Yu ZZ, Xiao ZQ, et al. Gene signatures and prognostic values of m6A genes in nasopharyngeal carcinoma[J]. Front Oncol, 2020, 10: 875. doi:10.3389/fonc.2020.00875
- [52] Guo DQ, Liu F, Zhang L, et al. Long non-coding RNA AWPPH enhances malignant phenotypes in nasopharyngeal carcinoma via silencing PTEN through interacting with LSD1 and EZH2[J]. Biochem Cell Biol, 2021, 99(2): 195-202. doi:10.1139/bcb-2019-0497
- [53] Li ZX, Zheng ZQ, Yang PY, et al. WTAP-mediated m6A modification of lncRNA DIAPH1-AS1 enhances its stability to facilitate nasopharyngeal carcinoma growth and metastasis[J]. Cell Death Differ, 2022, 29(6): 1137-1151. doi:10.1038/s41418-021-00905-w

- [54] Chen BY, Huang RD, Xia TL, 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. doi:10.1038/s41388-023-02865-6
- [55] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. *CA Cancer J Clin*, 2018, 68(6): 394-424. doi:10.3322/caac.21492
- [56] Bhattacharya A, Roy R, Snijders AM, et al. Two distinct routes to oral cancer differing in genome instability and risk for cervical node metastasis [J]. *Clin Cancer Res*, 2011, 17(22): 7024-7034. doi:10.1158/1078-0432.CCR-11-1944
- [57] Wang XP, Xu HY, Zhou Z, et al. IGF2BP2 maybe a novel prognostic biomarker in oral squamous cell carcinoma [J]. *Biosci Rep*, 2022, 42(2): BSR20212119. doi:10.1042/BSR20212119
- [58] Qiu LH, Zheng LL, Gan CW, et al. circBICD2 targets miR-149-5p/IGF2BP1 axis to regulate oral squamous cell carcinoma progression [J]. *J Oral Pathol Med*, 2021, 50(7): 668-680. doi:10.1111/jop.13156
- [59] Yang HJ, Fu GL, Liu FN, et al. LncRNA THOR promotes tongue squamous cell carcinomas by stabilizing IGF2BP1 downstream targets [J]. *Biochimie*, 2019, 165: 9-18. doi:10.1016/j.biochi.2019.06.012
- [60] Xu L, Li QX, Wang YF, et al. m6A methyltransferase METTL3 promotes oral squamous cell carcinoma progression through enhancement of IGF2BP2-mediated SLC7A11 mRNA stability [J]. *Am J Cancer Res*, 2021, 11(11): 5282-5298
- [61] Liu JP, Jiang X, Zou AL, et al. circIGHG-induced epithelial-to-mesenchymal transition promotes oral squamous cell carcinoma progression via miR-142-5p/IGF2BP3 signaling [J]. *Cancer Res*, 2021, 81(2): 344-355. doi:10.1158/0008-5472.CAN-20-0554
- [62] Zhang XL, Jung IH, Hwang YS. EGF enhances low-invasive cancer cell invasion by promoting IMP-3 expression [J]. *Tumour Biol*, 2016, 37(2): 2555-2563. doi:10.1007/s13277-015-4099-2
- [63] Nocini R, Molteni G, Mattiuzzi C, et al. Updates on larynx cancer epidemiology [J]. *Chin J Cancer Res*, 2020, 32(1): 18-25. doi:10.21147/j.issn.1000-9604.2020.01.03
- [64] Badwal JS. Total laryngectomy for treatment of T4 laryngeal cancer: trends and survival outcomes [J]. *Pol Przegl Chir*, 2018, 91(3): 30-37. doi:10.5604/01.3001.0012.2307
- [65] Tang XJ, Tang QL, Li SS, et al. IGF2BP2 acts as a m6A modification regulator in laryngeal squamous cell carcinoma through facilitating CDK6 mRNA stabilization [J]. *Cell Death Discov*, 2023, 9(1): 371. doi:10.1038/s41420-023-01669-7
- [66] Li JL, Cao H, Yang JW, et al. IGF2BP2-m6A-circMMP9 axis recruits ETS1 to promote TRIM59 transcription in laryngeal squamous cell carcinoma [J]. *Sci Rep*, 2024, 14(1): 3014. doi:10.1038/s41598-024-53422-4
- [67] Maržić D, Marijić B, Braut T, et al. IMP3 protein overexpression is linked to unfavorable outcome in laryngeal squamous cell carcinoma [J]. *Cancers*, 2021, 13(17): 4306. doi:10.3390/cancers13174306
- [68] Yang LK, Yan BR, Qu LM, et al. IGF2BP3 regulates TMA7-mediated autophagy and cisplatin resistance in laryngeal cancer via m6A RNA methylation [J]. *Int J Biol Sci*, 2023, 19(5): 1382-1400. doi:10.7150/ijbs.80921
- [69] Wang X, Tian LL, Li YS, et al. RBM15 facilitates laryngeal squamous cell carcinoma progression by regulating TMBIM6 stability through IGF2BP3 dependent [J]. *J Exp Clin Cancer Res*, 2021, 40(1): 80. doi:10.1186/s13046-021-01871-4
- [70] An CM, Sun Y, Miao SS, et al. Retropharyngeal lymph node metastasis diagnosed by magnetic resonance imaging in hypopharyngeal carcinoma: a retrospective analysis from Chinese multi-center data [J]. *Front Oncol*, 2021, 11: 649540. doi:10.3389/fonc.2021.649540
- [71] Yang T, Hui RT, Nouws J, et al. Untargeted metabolomics analysis of esophageal squamous cell cancer progression [J]. *J Transl Med*, 2022, 20(1): 127. doi:10.1186/s12967-022-03311-z
- [72] Yan AT, Wang CZ, Zheng LF, et al. microRNA-454-3p inhibits cell proliferation and invasion in esophageal cancer by targeting insulin-like growth factor 2 mRNA-binding protein 1 [J]. *Oncol Lett*, 2020, 20(6): 359. doi:10.3892/ol.2020.12223
- [73] Fang XY, Sun JJ, Chen SY, et al. IGF2BP1/UHRF2 axis mediated by miR-98-5p to promote the proliferation of and inhibit the apoptosis of esophageal squamous cell carcinoma [J]. *Ann Clin Lab Sci*, 2021, 51(3): 329-338
- [74] Zhao YH, Li Y, Zhu R, et al. RPS15 interacted with IGF2BP1 to promote esophageal squamous cell carcinoma development via recognizing m6A modification [J]. *Signal Transduct Target Ther*, 2023, 8(1): 224. doi:10.1038/s41392-023-01428-1
- [75] Wang JJ, Chen DX, Zhang Y, et al. Elevated expression of the RNA-binding protein IGF2BP1 enhances the mRNA stability of INHBA to promote the invasion and migration of esophageal squamous cancer cells [J]. *Exp*

- Hematol Oncol, 2023, 12 (1): 75. doi: 10.1186/s40164-023-00429-8
- [76] Lu FY, Chen WC, Jiang TW, et al. Expression profile, clinical significance and biological functions of IGF2BP2 in esophageal squamous cell carcinoma [J]. *Exp Ther Med*, 2022, 23 (4): 252. doi:10.3892/etm.2022.11177
- [77] Wang C, Zhou MX, Zhu PY, et al. IGF2BP2-induced circRUNX1 facilitates the growth and metastasis of esophageal squamous cell carcinoma through miR-449b-5p/FOXP3 axis [J]. *J Exp Clin Cancer Res*, 2022, 41 (1): 347. doi:10.1186/s13046-022-02550-8
- [78] Xiao YH, Tang JM, Yang DS, et al. Long noncoding RNA LIPH-4 promotes esophageal squamous cell carcinoma progression by regulating the miR-216b/IGF2BP2 axis [J]. *Biomark Res*, 2022, 10 (1): 60. doi:10.1186/s40364-022-00408-x
- [79] Wu XD, Fan YH, Liu YP, et al. Long non-coding RNA CCAT2 promotes the development of esophageal squamous cell carcinoma by inhibiting miR-200b to upregulate the IGF2BP2/TK1 axis [J]. *Front Oncol*, 2021, 11: 680642. doi:10.3389/fonc.2021.680642
- [80] Zhao R, Li T, Zhao X, et al. The m6A reader IGF2BP2 promotes the progression of esophageal squamous cell carcinoma cells by increasing the stability of OCT4 mRNA [J]. *Biochem Cell Biol*, 2024, 102 (2): 169-178. doi:10.1139/bcb-2023-0067
- [81] Huang GW, Chen QQ, Ma CC, et al. linc01305 promotes metastasis and proliferation of esophageal squamous cell carcinoma through interacting with IGF2BP2 and IGF2BP3 to stabilize HTR3A mRNA [J]. *Int J Biochem Cell Biol*, 2021, 136: 106015. doi:10.1016/j.biocel.2021.106015
- [82] Qian LX, Cao X, Du MY, et al. KIF18A knockdown reduces proliferation, migration, invasion and enhances radiosensitivity of esophageal cancer [J]. *Biochem Biophys Res Commun*, 2021, 557: 192-198. doi:10.1016/j.bbrc.2021.04.020
- [83] Feng YD, Lin YB, Jiang ZY, et al. Insulin-like growth factor-2 mRNA-binding protein 3 promotes cell migration, invasion, and epithelial-mesenchymal transition of esophageal squamous cell carcinoma cells by targeting zinc finger E-box-binding homeobox 1 mRNA [J]. *Mol Carcinog*, 2023, 62 (4): 503-516. doi: 10.1002/mc.23502
- [84] Kim J, Gosnell JE, Roman SA. Geographic influences in the global rise of thyroid cancer [J]. *Nat Rev Endocrinol*, 2020, 16 (1): 17-29. doi:10.1038/s41574-019-0263-x
- [85] Dong LP, Geng ZS, Liu Z, et al. IGF2BP2 knockdown suppresses thyroid cancer progression by reducing the expression of long non-coding RNA HAGLR [J]. *Pathol Res Pract*, 2021, 225: 153550. doi:10.1016/j.prp.2021.153550
- [86] Panebianco F, Kelly LM, Liu PY, et al. THADA fusion is a mechanism of IGF2BP3 activation and IGF1R signaling in thyroid cancer [J]. *Proc Natl Acad Sci USA*, 2017, 114 (9): 2307-2312. doi:10.1073/pnas.1614265114
- [87] Wang WL, Ding Y, Zhao YZ, et al. m6A reader IGF2BP2 promotes lymphatic metastasis by stabilizing DPP4 in papillary thyroid carcinoma [J]. *Cancer Gene Ther*, 2024, 31 (2): 285-299. doi: 10.1038/s41417-023-00702-2
- [88] Molinaro E, Romei C, Biagini A, et al. Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies [J]. *Nat Rev Endocrinol*, 2017, 13 (11): 644-660. doi:10.1038/nrendo.2017.76
- [89] Haase J, Misiak D, Bauer M, et al. IGF2BP1 is the first positive marker for anaplastic thyroid carcinoma diagnosis [J]. *Mod Pathol*, 2021, 34 (1): 32-41. doi:10.1038/s41379-020-0630-0
- [90] Sa R, Guo ML, Liu DY, et al. AhR antagonist promotes differentiation of papillary thyroid cancer via regulating circSH2B3/miR-4640-5P/IGF2BP2 axis [J]. *Front Pharmacol*, 2021, 12: 795386. doi: 10.3389/fphar.2021.795386
- [91] Sa R, Liang R, Qiu X, et al. Targeting IGF2BP2 promotes differentiation of radioiodine refractory papillary thyroid cancer via destabilizing RUNX2 mRNA [J]. *Cancers*, 2022, 14 (5): 1268. doi: 10.3390/cancers14051268
- [92] Sa R, Liang R, Qiu X, et al. IGF2BP2-dependent activation of ERBB2 signaling contributes to acquired resistance to tyrosine kinase inhibitor in differentiation therapy of radioiodine-refractory papillary thyroid cancer [J]. *Cancer Lett*, 2022, 527: 10-23. doi: 10.1016/j.canlet.2021.12.005