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·综 述·

异质核糖核蛋白F在肿瘤发生发展及治疗中的研究进展

Research progress on heterogeneous nuclear ribonucleoprotein F in tumorigenesis, progression, and therapeutics

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[摘 要] 异质核糖核蛋白F(HNRNPF)是一种在细胞核内表达丰富的RNA结合蛋白,通过结合富含鸟嘌呤(G)的RNA调控转录与转录后加工过程影响细胞生物学行为。HNRNPF在多种恶性肿瘤中呈高表达,且其表达水平与患者预后有关。本文就HNRNPF对肿瘤细胞恶性生物学行为的影响及其免疫调控机制进行综述,并展望HNRNPF作为潜在治疗靶点的潜力,以期为肿瘤的靶向干预提供理论依据。

[关键词] 异质核糖核蛋白F;肿瘤;选择性剪接;增殖;治疗
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恶性肿瘤严重威胁人类生命。近年来,研究发现RNA结合蛋白功能失调可导致原癌基因和抑癌基因表达异常而促进肿瘤的发生。异质核糖核蛋白(heterogeneous nuclear ribonucleoprotein, HNRNP)是一类广泛表达于真核细胞的RNA结合蛋白家族,包括约30个成员。HNRNP家族蛋白中常见四种RNA结合域,即RNA识别基序、类RNA识别基序、富含甘氨酸的RGG盒、KH结构域,RNA结合域旁还有辅助结构[1]。HNRNP家族中的异质核糖核蛋白F(heterogeneous nuclear ribonucleoprotein F, HNRNPF)通过与RNA结合,调控基因表达中的多个环节,包括转录、pre-mRNA选择性剪接、mRNA稳定性、翻译等过程[2-4]。其中pre-mRNA选择性剪接是真核细胞基因表达转录后调控的关键步骤,其异常调控与许多肿瘤发生发展密切相关[5-6]。本文重点综述HNRNPF在选择性剪接和免疫调控中的作用,探讨其对肿瘤恶性生物学行为的影响及作用机制(图1),以期为肿瘤靶向治疗和预后评估提供理论依据。

1 HNRNPF的表达

HNRNPF基因位于10号染色体q11.21。HNRNPF主要分布于细胞核,广泛表达于甲状腺、胃、小肠、输尿管和前列腺等组织,并调控其正常生理功能。HNRNPF在这些组织中的分布特征提示其可能参与调控内分泌、消化及生殖等生理过程。HNRNPF主要参与转录调控、pre-mRNA的选择性剪接过程,这些功能对于维持基因表达的稳定性和准确性至关重要,从而进一步影响肿瘤的发生发展过程。HNRNPF在多种恶性肿瘤中高表达,与患者不良预后有关[7-9],有望作为肿瘤诊断和预后评估的潜在标志物[10-12]。

2 HNRNPF调节转录

研究[13-14]发现,HNRNPF是转录依赖性核质穿梭蛋白,通过甘氨酸-酪氨酸-精氨酸富集域,即GYR结构域与核转运蛋白1(transportin-1, TRN1)相互作用,实现核转位。同时,HNRNPF可与转录起始蛋白相互作用,提示其可能参与转录起始过程[15],如HNRNPF参与缺氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)和乳铁蛋白的转录激活作用。HNRNPF在缺氧条件下被诱导表达并发生核转位,通过结合HIF-1α反义长链非编码RNA(HIF-1α antisense long non-coding RNA, HIFAL)的240~300 nt区域,将HIFAL/PKM2/PHD3复合物导入细胞核,促进HIF-1α转录复合物的组装及靶基因转录,促进肿瘤细胞的无氧糖酵解,使其适应缺氧微环境[16]。乳铁蛋白(lactotransferrin, LTF)是一种铁结合蛋白,可通过提高细胞内铁水平和脂质活性氧诱导铁死亡,从而抑制前列腺癌进展。HNRNPF还可与乳铁蛋白增强子RNA(lactotransferrin-enhancer RNA, LTFe)结合,通过促进增强子-启动子染色质环的形成来调控靶基因LTF的转录,进而促进铁死亡过程,抑制前列腺癌进展[17]。

3 HNRNPF调控pre-mRNA的剪接

剪接是真核细胞基因表达的关键步骤。Wang

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等[18]研究发现，在少突胶质细胞中，HNRNPF可通过募集U1 snRNP促进DM20的剪接。选择性剪接在细胞分化发育中发挥重要作用[19-21]。HNRNPF空间结构包括三个非经典的RNA识别基序（RNA recognition motif, RRM），也称qRRM。HNRNPF通过qRRM与pre-mRNA富含鸟嘌呤的RNA序列（G-tracts）结合，促进剪接体特异性结合剪接位点[5]，从而调节pre-mRNA的选择性剪接过程[22-23]，最终影响细胞生物学行为。

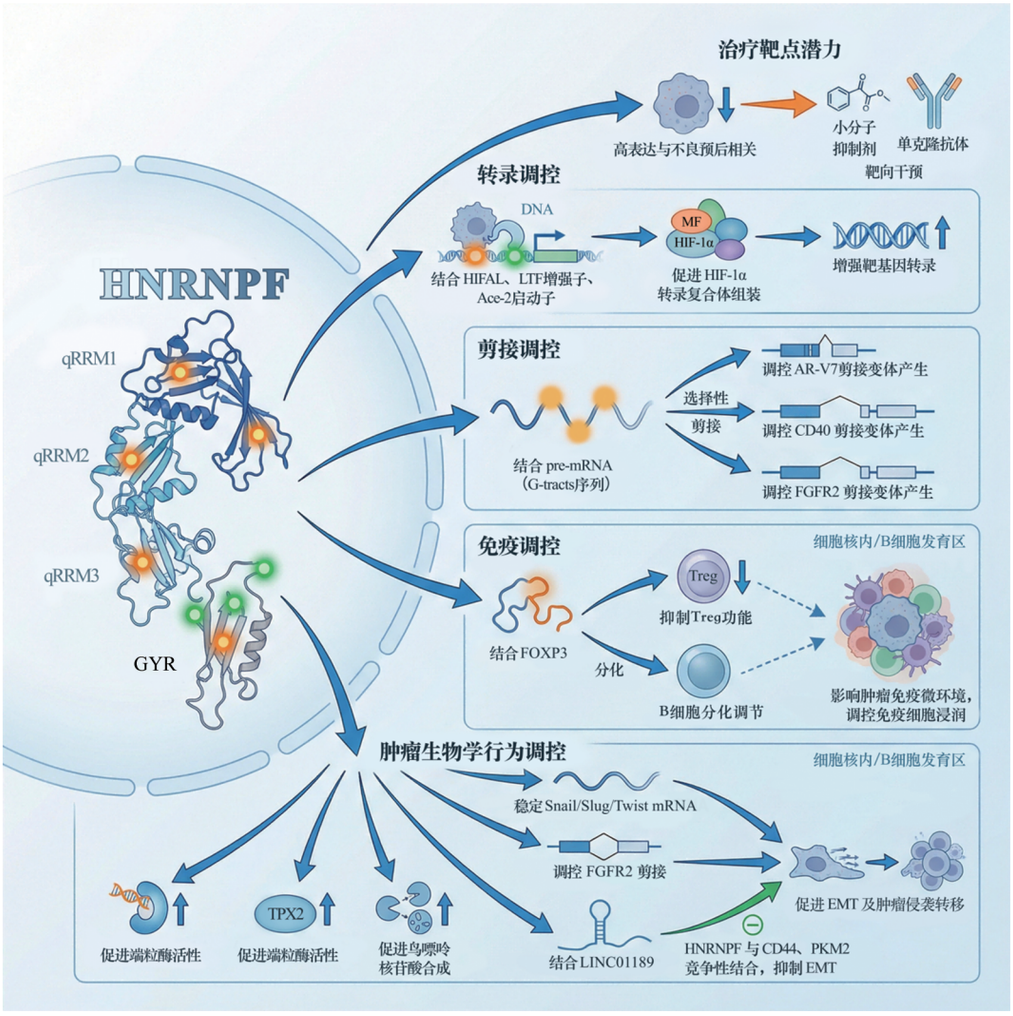


图1　HNRNPF调控肿瘤发生发展及免疫微环境核心机制图

[采用BioRender绘图软件（biorender.com）绘制]

非受体酪氨酸蛋白激酶Src（proto-oncogene tyrosine-protein kinase Src, c-Src）广泛存在于真核生物中，参与调控细胞增殖、分化、迁移及信号转导等生物学过程，可因C-末端结构域突变或缺失而被激活，促进肿瘤的发生和发展[24]。髓样细胞白血病蛋白-1（myeloid cell leukemia 1, MCL-1）属于B细胞淋巴瘤-2（B-cell lymphoma-2, Bcl-2）家族的抗凋亡蛋白，在肿瘤发生发展以及化疗耐药中发挥重要作用[25]。研究[26]表明HNRNPF可通过结合poly（rG）调控c-Src、MCL-1编码基因SRC、Mcl-1的外显子跳跃。此外，HNRNPF还通过结合pre-mRNA的poly（A）位点区域（即经典RG3序列，常存在于应激反应相关基因）等，调控选择性多聚腺苷酸化和mRNA稳定性。因此，HNRNPF不仅促进选择性剪接和促凋亡产物生成，还通过选择聚腺苷酸化位点抑制细胞的应激反应。

雄激素受体（androgen receptor, AR）是属于类固醇激素受体家族的一种核受体，是前列腺癌发生发展中关键的一环。AR主要包括DNA结合域、铰链区、配体结合域和N端结构域等4个结构域。AR pre-mRNA经选择性剪接可产生多种剪接变体，其剪接位点多见于配体结合域。其中雄激素受体剪接变体7（androgen receptor splice variant 7, AR-V7）在没有配体的情况下即可进入细胞核并激活下游信号通路，

从而产生去势抵抗性前列腺癌表型。HNRNPF通过与AR的pre-mRNA剪接位点结合，介导AR-V7的产生，最终促进前列腺癌发生发展[27-28]。

4　HNRNPF的免疫调控作用

4.1　HNRNPF调控B细胞的分化

B淋巴细胞在生发中心中经历快速增殖、抗体基因突变以及亲和选择等过程，最终分化为效应B细胞和记忆B细胞，该阶段是适应性免疫应答、体液免疫记忆形成的基础[29]。研究[30-31]表明HNRNPF通过直接结合CD40 pre-mRNA的G-tracts，促进CD40外显子6的包含和内含子7的去除，从而调控CD40分子的表达。敲除HNRNPF可导致CD40表达下降，从而影响B细胞的分化成熟和抗体类型转换。

4.2　HNRNPF调控Treg细胞的功能

FOXP3是调节性T细胞（regulatory T cell, Treg）的谱系特异性转录因子，对Treg的发育和功能至关重要。FOXP3外显子2编码的区域可与HNRNPF的qRRM结合，导致HNRNPF对其靶pre-mRNA（包括BCL-X，Tarbp2）的选择性剪接作用受到抑制，而在Treg中过表达HNRNPF后，该抑制作用减弱，最终抑制Treg的免疫抑制功能，为肿瘤免疫治疗提供了新的思路和潜在靶点[32]。

4.3　HNRNPF调控肿瘤相关巨噬细胞（tumor-associated macrophage, TAM）功能

部分实体瘤中的TAM以促癌的M2型为主。M2型TAM通过产生促炎症因子或趋化因子，在肿瘤免疫抑制微环境、肿瘤血管形成和肿瘤转移中发挥重要作用，其中CCL13是M2型TAM产生的重要促瘤趋化因子。研究[33]发现HNRNPF可结合CCL13 mRNA并增强其稳定性，从而维持CCL13水平，促进肿瘤转移。

血管紧张素转换酶2（angiotensin-converting enzyme 2, ACE2）是肾素-血管紧张素系统（renin-angiotensin system, RAS）的重要酶，ACE2/Ang-（1-7）轴在抑制肝癌进展和耐药中发挥重要作用。HNRNPF可通过结合ACE2基因启动子增强其转录活性[34]。ACE2可通过抑制巨噬细胞的PD-L1和血管内皮生长因子A的表达，阻断巨噬细胞浸润和M2型极化，从而重塑肿瘤免疫微环境。

4.4　HNRNPF影响肿瘤微环境

在多数肿瘤组织中，HNRNPF与T辅助细胞、NK细胞、$CD8^+$ T细胞和中性粒细胞等免疫细胞的浸润程度显著相关[7]。长期慢性炎症可能通过损伤细胞、基因突变、改变微环境等方式增加肿瘤发生风险。在溃疡性结肠炎关联的结肠癌中，常涉及HNRNPF等基因突变，并伴随IL-17等促炎信号通路下调[35]，因而推测HNRNPF可能通过参与调控IL-17等促炎细胞因子或受体基因的mRNA稳定性影响肿瘤的发生发展。非霍奇金淋巴瘤（non-Hodgkin's lymphoma, NHL）可发生于免疫抑制状态患者。研究[36]显示，EB病毒（EBV）阳性NHL患者通常具有较显著的免疫抑制性微环境特征，包括较高水平的$CD8^+$ T细胞、Treg细胞和M2型巨噬细胞浸润，以及免疫负调控分子上调。此外在其分析的NHL病例中，HNRNPF突变仅见于EBV阳性病例。上述结果提示HNRNPF异常可能与EBV阳性NHL的免疫微环境密切相关，但其具体机制及作为肿瘤免疫治疗的靶点的潜在价值有待进一步研究。

5　HNRNPF促进肿瘤细胞增殖

细胞癌变过程中，端粒酶活性通常会增强。人端粒酶RNA组分（human telomerase RNA component, hTERC）和人端粒酶逆转录酶（human telomerase reverse transcriptase, hTERT）是端粒酶的两个核心组分。研究[37]发现，HNRNPF基因多态性与白细胞端粒长度显著相关。进一步研究[1,38-39]发现，HNRNPF对端粒酶RNA的5'端UUAGG重复序列有较高的亲和力，通过与hTERC及端粒酶复合物相互作用，增强端粒酶活性和端粒长度，从而促进细胞增殖。

微管相关蛋白爪蟾驱动蛋白样蛋白2靶蛋白（targeting protein for xenopus kinesin-like protein 2, TPX2）在有丝分裂和染色体分离中发挥关键作用。研究[40-42]发现，在膀胱癌细胞中，HNRNPF和TPX2表达均上调。HNRNPF通过与TPX2相互作用并维持其表达水平，促进细胞周期蛋白Cyclin D1表达并抑制p21的表达，最终促进膀胱癌细胞增殖；而敲低HNRNPF后，TPX2表达下调，Cyclin D1随之表达减弱，而p21表达增强，最终抑制膀胱癌细胞增殖。

Wang等[43]发现HNRNPF通过结合circPFKP侧翼Alu元件，调控肌苷单磷酸脱氢酶2活性，上调前列腺癌细胞内鸟嘌呤核苷酸水平，为DNA复制、转录和翻译提供原料和能量，加速细胞周期G1/S转换，最终促进细胞增殖。

蛋白质精氨酸甲基转移酶1（protein arginine methyltransferase 1, PRMT1）是一种催化蛋白质精氨酸残基甲基化的表观遗传调控酶，通过甲基化组蛋白和非组蛋白调控基因表达、细胞周期及DNA修复等生物学过程，在多种肿瘤中表达异常，与肿瘤生长、转移、耐药和不良预后等密切相关。Antal等[44]研究发现，在胰腺导管腺癌细胞中，HNRNPF通过结合

并稳定PRMT1 mRNA而维持PRMT1的高活性，从而促进肿瘤细胞增殖。

6 HNRNPF调控肿瘤细胞的侵袭转移

研究[45]发现，在肿瘤干细胞（cancer stem cell, CSC）中，HNRNPF通过与lncRNA Mir100hg结合，促进其核-质转运并形成外泌体，最终增强非CSC的肿瘤细胞的侵袭转移能力。

肿瘤的侵袭转移与上皮-间充质转化（epithelial-mesenchymal transition, EMT）密切相关。EMT是上皮细胞通过特定程序转化为具有间质特性细胞的过程。肿瘤细胞通过EMT获得的间质特性使其更容易进入血管和淋巴管，进而发生远处转移[46-47]。HNRNPF通过与EMT相关基因如Snail、Slug和Twist的mRNA 3'非翻译区结合，增强mRNA的稳定性和翻译效率，上调这些分子的表达，进而促进EMT和肿瘤转移[48-49]。

成纤维细胞生长因子受体2（fibroblast growth factor receptor 2, FGFR2）是一种跨膜受体酪氨酸激酶，属于受体酪氨酸激酶家族，通过结合成纤维细胞生长因子激活下游信号通路，调控细胞增殖、分化和迁移等过程[50-52]。在食管鳞状细胞癌中，HNRNPF通过与lncRNA UCA1结合调控FGFR2的可变剪接，促进FGFR2Ⅲb亚型向FGFR2Ⅲc亚型转换，后者通过激活PI3K/AKT信号通路促进EMT，从而促进食管鳞状细胞癌的侵袭和转移[53]。此外，HNRNPF还可以通过稳定促瘤趋化因子CCL13的mRNA而促进口腔鳞状癌细胞迁移[33]或通过其RRM2结构域结合LINC01189的5′非翻译区端促进胃癌细胞的迁移和侵袭[54]。

然而也有研究发现HNRNPF可抑制肿瘤细胞侵袭和转移。HNRNPF通过与circ_0057582结合，参与选择性剪接调控并降低转录共激活因子YAP的表达，导致下游靶基因SRY-Box转录因子9（SOX9）的表达下调，从而抑制乳腺癌细胞的迁移和侵袭[55]。CD44是一种非激酶细胞表面跨膜糖蛋白，属于细胞黏附分子家族，是透明质酸的主要细胞表面受体，广泛参与细胞间及细胞与细胞外基质的黏附和通讯。CD44可通过激活PI3K/AKT/mTOR和Wnt等信号通路，诱导EMT并增强肿瘤细胞的增殖、侵袭和转移能力[56-59]。HNRNPF通过结合CD44 pre-mRNA的G-四链体结构促进CD44剪接变异体的产生，从而抑制EMT进程[60-61]。

丙酮酸激酶（pyruvate kinase, PK）是糖酵解途径的限速酶，由PKLR和PKM两种基因编码[62]。PKM经选择性剪接产生两种同工酶：PKM1和PKM2[63]。肿瘤细胞中高表达PKM2，有利于细胞进行有氧糖酵解而快速获取能量，促进肿瘤生长和侵袭[64-66]。此外，PKM2也是一种RNA结合蛋白，与G-四链体结构有高度亲和力[67]。研究[68]表明，HNRNPF通过与PKM2竞争结合EMT相关分子的G-四链体结构，抑制相关基因的表达，进而抑制乳腺癌EMT进程。

7 HNRNPF与肿瘤靶向治疗

HNRNPF在多种肿瘤中异常高表达，通过调控转录和选择性剪接等过程参与肿瘤的发生发展。在套细胞淋巴瘤（mantle-cell lymphoma, MCL）中，HNRNPF高表达与患者不良预后有关，提示HNRNPF可能成为MCL治疗的潜在靶点[69]。外泌体装载着蛋白质、脂质、核酸等多种生物活性分子，广泛参与细胞间通讯、疾病发展、免疫调节等过程。CSC中的HNRNPF可促进外泌体向非CSC肿瘤细胞转运，进而增强肺癌细胞的侵袭转移[45]，这为转移性肺癌提供了新的治疗靶点。

前述研究[17]表明，HNRNPF参与LTFe介导的LTF转录激活及铁死亡调控，提示LTFe-HNRNPF-LTF调控轴可能具有潜在的前列腺癌治疗价值。

Jiang等[70]研究发现，HNRNPF可通过与p21 mRNA结合维持其稳定性。而USP30-AS1通过干扰HNRNPF与p21 mRNA的结合导致p21表达下调，最终促进乳腺癌进展，因而针对HNRNPF与USP30-AS1的相互作用进行干预，可能为乳腺癌治疗提供新思路。醉茄素A（withaferin A, WA）是一种从醉茄中分离到的甾体内酯，具有抗炎和抗肿瘤等功效。研究[12]发现，在三阴性乳腺癌（triple-negative breast cancer, TNBC）细胞中，WA可与HNRNPF共价结合，提示HNRNPF是WA发挥抗TNBC的重要靶点，为TNBC的治疗提供了新途径。

8 总结与展望

HNRNPF通过参与转录、pre-mRNA的选择性剪接等过程调控肿瘤免疫微环境、肿瘤细胞增殖、迁移以及侵袭（图1），揭示HNRNPF作为肿瘤治疗和预后评估的潜在价值，针对HNRNPF或许会成为肿瘤治疗的一个新策略，开发HNRNPF的小分子抑制剂或单克隆抗体可能作为一种有效治疗途径。

利益冲突声明：所有作者均声明无利益冲突。

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