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hnRNP A1的功能研究进展*

杨宏广　童春梅　邓惠敏**
（华南师范大学生命科学学院，华南师范大学昆虫科学与技术研究所，广东省昆虫发育生物学与应用技术重点实验室，广州 510631）

摘要　核不均一核糖核蛋白（heterogeneous nuclear ribonucleoprotein，hnRNP）是一类多功能RNA结合蛋白家族，能与RNA聚合酶II合成的新生转录本结合，并以复合体形式参与转录本稳定与成熟调控过程. hnRNP A1是hnRNPs家族重要成员，不仅广泛参与癌症与神经系统疾病相关基因的可变剪接调控，还在病毒侵染、细胞衰老及应激恢复中发挥重要作用. 此外，hnRNP A1作为典型的RNA结合蛋白，在转录与可变剪接调控过程中，可通过动态三维结构识别特定序列. 本文总结了hnRNP A1的最新研究进展，以期为进一步探究hnRNP A1在疾病发生中的功能研究提供参考.

关键词　hnRNP A1，hnRNPs蛋白家族，可变剪接
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hnRNPs是一类功能广泛的RNA结合蛋白家族，能与新生转录本结合并形成核糖核蛋白颗粒（ribonucleoprotein particles，RNPs），发挥稳定转录本、剪接调控、多聚腺苷酸化及细胞核输出等功能[1-2]. 作为细胞中最丰富的核蛋白之一，hnRNPs家族成员具有典型的模块结构，其中包括N端（N-terminal region）RNA结合结构域（RNA binding domain，RBD）、C端（C-terminal region）富含甘氨酸序列（又称RGG盒）及其他辅助结构域. 根据功能结构域特点，hnRNPs家族可进一步细分为多个亚族，依次从A到U进行命名[3-4]. hnRNP A1是hnRNPs家族重要成员，在发现之初被鉴定为端粒DNA结合蛋白[5-6]，但随着研究深入，其作为RNA结合蛋白参与转录后调控的功能被更广泛关注，这与其包含多种功能结构域有关. hnRNP A1各功能结构域以组合方式在转录、剪接及核质运输等过程中发挥作用. 此外，hnRNP A1在异染色质形成等方面的功能也相继被发现[7]，具有广泛且灵活的功能特点. 近期研究表明，hnRNP A1不仅能结合染色质高级结构，而且与长链非编码RNA（long noncoding RNA，lncRNA）、微小RNA（microRNA，miRNA）、环状RNA（circular RNA，circRNA）等非编码RNA（non-coding RNA，ncRNA）相互作用参与多种癌细胞恶性增殖和神经系统病变，其中包括脊髓性肌萎缩症（spinal muscular atrophy，SMA）、阿尔茨海默病（Alzheimer's disease，AD）、结肠癌、黑色素瘤及白血病[8-9]. hnRNP A1除直接特异结合靶向序列发挥剪接调控作用外，还能以蛋白质互作方式介导多种疾病相关基因的异常表达，已成为一种重要的临床诊断标记物. 根据hnRNP A1靶向特异序列设计的寡聚核苷酸也在疾病治疗中显现出良好的应用前景[10]. 因此，本文对hnRNP A1蛋白结构特征、结合特异序列及功能研究进展进行了总结.

1　hnRNP A1结构与结合特异序列的研究进展

1.1　结构特征

RNA识别基序（RNA recognition motif，RRM）：hnRNP A1的N端包含2个典型的RRM，能够高亲和力结合DNA与RNA序列（图1a）. 两个RRM高度相似，由4个β折叠和2个位于β1-α1-β2-β3-α2-β4结构中的α螺旋组成（图1b），其中包

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** 通讯联系人.
Tel：020-85210024，E-mail：denghuiminmin@163.com
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括2个高度保守的RNP1和RNP2序列[1, 11]. 高度简并的RNP1和RNP2共有序列分别并列在β3和β1链上，通过碱基间疏水性相互作用与RNA接触[3, 12]. 虽然两个RRM高度相似，但它们与RNA结合的亲和力存在显著差别. 多数情况下，RRM1优先结合RNA并能识别更长的基序，而RRM2结合能力较弱，主要辅助蛋白质与RNA结合. 两个RRM在蛋白质功能行使上也至关重要，RRM间相互作用的破坏或任一结合能力丧失均会影响hnRNP A1抑制剪接的能力[8]. 此外，生化与分子结构研究也表明，RRM不仅能够识别RNA，还参与蛋白质间相互作用. RNP1中两个保守的苯丙氨酸（Phe）残基似乎与结合特定RNA及蛋白质互作有关，并且对调节可变剪接至关重要[13].

RGG盒：由Arg-Gly-Gly重复序列组成，进化上高度保守，并且是RNA结合所必需的（图1a）. hnRNP A1参与人类免疫缺陷病毒1型（human immunodeficiency virus type1，HIV-1）复制与剪接调控表明，截短RGG盒序列对剪接的影响并不显著[14]. hnRNP A1竞争性结合外显子剪接沉默子（exonic splicing silencer，ESS），通过掩盖SR蛋白家族成员SC35结合位点，进而抑制反式转录激活因子（trans-activating factor，Tat）特异识别的3'端剪接位点[14]. 此外，RGG重复序列的精氨酸容易被甲基化酶修饰，影响RNA结合和蛋白质互作能力. hnRNP A1是蛋白质精氨酸甲基转移酶1（protein arginine methyltransferase 1，PRMT1）的非组蛋白靶标，当RGG盒内关键精氨酸残基被不对称二甲基化，将抑制hnRNP A1内部核糖体进入位点反式作用因子（internal ribosome entry site trans-acting factor，ITAF）活性[15]. 另一方面，当RGG盒关键精氨酸残基替换为丙氨酸时，应激颗粒（stress granule，SG）形成受到抑制，表明hnRNP A1也是SG形成所必需的[15]. 值得关注的是，最近报道显示RGG盒有助于UP1结构域结合并破坏RNA和端粒重复序列（the telomere repeats containing RNA，TERRA）形成的环状G-四链体结构[16]，进一步凸显RGG盒在hnRNP A1功能行使中的重要性.

M9序列：部分hnRNPs具有核质间穿梭功能，它们能与前体mRNA（pre-mRNA）形成复合物，协助mRNA完成由细胞核到细胞质的运输过程（图1a）. hnRNP A1是其中一种穿梭蛋白，稳态时主要分布在细胞核内. 当受到特定刺激时，可通过C端M9序列发挥核质穿梭功能[17]. M9序列是一类区别于传统细胞核定位序列（nuclear localization sequence，NLS）的特殊核质穿梭序列，负责穿梭蛋白从细胞核到细胞质的双向运输调控. hnRNP A1转运需要完整的M9序列，核转运蛋白家族的两个转运受体Transportin 1和Transportin 2直接与M9序列相互作用并介导hnRNP A1核输入[18]，而单氨基酸位点突变将破坏蛋白质正常输入与输出过程[19]. 连续截短M9序列也获得相似结果，进一步表明C端M9序列是hnRNP A1正确核定位所必需的[20].

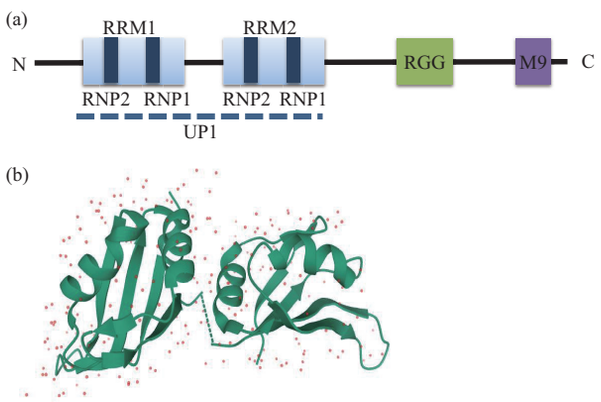

Fig. 1　Schematic diagram of hnRNP A1 structure

图1　hnRNP A1结构示意图

(a) hnRNP A1已知功能位点；(b) hnRNP A1预测三维结构.

1.2　特异序列结合规律

hnRNP A1结合特异序列是两个RRM共同作用的结果. 早期利用SELEX实验技术最先鉴定了hnRNP A1高亲和力结合基序：5'-UAGGGA/U-3'（也称为winner序列）[21]. 两个RRM单独进行SELEX分析结果显示，它们都和5'-UAG-3'核心基序结合，而且核心基序突变将显著降低hnRNP A1抑制体外模型剪接的能力[22-23]. 近年来通过交联免疫沉淀实验（cross-linking immunoprecipitation，CLIP）进一步证实hnRNP A1特异识别含有5'-UAG-3'核心的RNA靶标，其中AG是最普遍的结合基序[24-25]. 除结合核心基序外，hnRNP A1还能与人类淋巴细胞中mRNA不稳定3'非翻译区（3'-untranslated region，3'UTR）的AUUUA重复序列特异性结合，在转录和翻译过程中起反式因子作用[26]. 此外，hnRNP A1还与人类胸苷激酶（human thymidine kinase，HTK）启动子的细胞周期调节元件（cell cycle regulatory unit，CCRU）中

的ATTT序列高亲和力结合，并抑制该基因表达[27]，这也进一步表明hnRNP A1结合具有灵活多变的特点.

端粒末端富含连续鸟嘌呤碱基的核苷酸能形成G-四链体结构并发挥转录阻遏作用. hnRNP A1作为端粒结合蛋白，能与端粒末端TAGGGT重复序列特异性结合，在端粒生物发生和促进端粒酶活性等方面起关键作用[28-29]. 有趣的是，在Kirsten大鼠肉瘤病毒癌基因同源物（Kirsten rat sarcoma viral oncogene homolog，KRAS）中发现，hnRNP A1能结合并打开KRAS的G-四链体结构，进而促进转录[30]. 虽然已有多项研究证实hnRNP A1能与G-四链体结构结合，但这种特殊的相互作用是否发挥普遍的促转录作用还有待确定.

值得注意的是，利用单核苷酸分辨率交联免疫沉淀（individual nucleotide resolution crosslinking immunoprecipitation，iCLIP）生成的共有结合基序显示，hnRNP A1结合位点具有细胞特异性[10]，这暗示已报道hnRNP A1特异结合序列可能具有局限性. 因此，我们归纳了hnRNP A1在基因表达、剪接调控及高级结构结合中的特异序列（表1）[6，10，21-22，26-29，31-44]. 从表1可以看出，早期鉴定的hnRNP A1特异结合序列多来源于HeLa细胞，而细胞生理状态和处理环境酸碱度不同将导致差异. 在整合已鉴定hnRNP A1特异序列基础上，进一步考量特定环境和细胞状态等因素影响，将为设计该蛋白质特异靶向序列提供更全面且有效的参考.

Table 1 hnRNP A1 specific binding sequence

表1 hnRNP A1特异结合序列

时间	材料	主要实验技术	特异结合序列	参考文献
1993	人外周血T淋巴细胞	RNA探针和AU特异结合蛋白测定；单克隆免疫沉淀	AUUUA	［26］
1993	HeLa 细胞	凝胶阻滞分析；双向凝胶电泳；免疫印迹	d（TTAGGG）n r（UUAG/G）	［29］
1995	SVK14和HeLa细胞	迷你基因（minigene）	TAGGGCAGGC	［32］
1997	HeLa S3和DBT细胞	RNA和蛋白质紫外交联；免疫印迹	AGAUUAGAUUUG	［33］
1997	HeLa细胞	转录和剪接测定；免疫沉淀	UAGAGU	［34］
1998	小鼠CB3细胞	端粒重复序列扩增法（TRAP测定）	TAGGGT	［28］
1999	HeLa、SVK14和293细胞	紫外交联免疫沉淀；免疫印迹	UAGGGC	［35］
1999	HeLa细胞	RNA结合测定；体外剪接分析	CUAGACUAGA	［36］
1999	—	蛋白质结晶和X衍射	d（TTAGGG）2	［6］
2000	中国仓鼠成纤维细胞K12	CAT报告质粒分析；凝胶迁移（EMSA）	ATTT	［27］
2001	HeLa和S100细胞	体外剪接分析；紫外交联免疫沉淀；RNA结合测定	GAUUAGUG和UAGUGA	［37］
2002	HeLa、CB3C7和CB3C7-20 细胞	剪接分析；EMSA；RNA亲和层析；免疫印迹	UAGAGU	［38］
2006	大肠杆菌BL21细胞	RNA足迹分析；核磁共振（NMR）；RNA核磁共振与分析；EMSA；体外剪接分析	GAGGAG和UAG	［39］
2009	HeLa细胞	紫外交联；GST-MS2下拉（GST-MS2 pulldowns）；RNA足迹法；EMSA	UAGGGU	［22］
2012	人肾脏表皮细胞 293T	紫外交联免疫沉淀高通量测序；剪接敏感微阵列；转录组测序（RNA-seq）	UAG（G）	［40］
2012	—	NMR；量热滴定（ITC）；圆二色谱	UAGU	［41］
2016	HeLa细胞	单核苷酸分辨率交联免疫沉淀；紫外交联免疫沉淀；表面等离子体共振成像；免疫印迹；mini gene；RNA-seq	UAGG	［10］
2016	—	NMR；小角X射线散射（SEC-SAXS）；尺寸排除色谱；量热滴定	AGUGA	［42］
2017	—	HTS-EQ；ITC；生物膜层干涉；NMR	AGU	［43］
2019	HeLa细胞和人肾脏表皮细胞 293T	紫外交联免疫沉淀结合高通量测序；ITC；NMR	UNAGG or TTAGG	［44］

2　hnRNP A1功能研究

2.1　转录调控

iCLIP分析发现hnRNP A1结合位点富集在3'UTR，这可能反映了该蛋白质某些非剪接功能[10]. 哺乳动物hnRNP A1及其果蝇同源Hrp38可通过直接结合靶基因启动子区调控基因表达. Lau等[27]发现hnRNP A1能高亲和力结合*HTK*启动子的ATTT序列，并抑制该基因表达. 而在果蝇中则发现Hrp38可结合*Nanos* mRNA的3'UTR并抑制翻译[45]. 有趣的是，Hrp38与上皮钙黏素（E-cadherin）mRNA的5'非翻译区（5'-untranslated region，5'UTR）结合却能增强翻译[45]，表明Hrp38发挥促进或抑制作用似乎与结合不同区域有关.

除直接结合靶基因并发挥调控作用外，hnRNP A1多功能辅助结构域也能通过蛋白质间相互作用间接参与调控. 核因子κB（nuclear factor-kappa B，NF-κB）依赖性转录激活通过信号诱导的磷酸化和NF-κB抑制蛋白IκBα（inhibitor of nuclear factor kappa-Bα）降解实现[46]. 体外和体内实验均已证明IκBα和hnRNP A1存在直接相互作用，并由IκBα的C端和hnRNP A1的N端结合结构域介导[47-48]. hnRNP A1通过促进IκBα降解进而增强NF-κB依赖性转录激活.

此外，hnRNPs成员参与外泌体保护mRNA途径的新功能也被发现[49]. 在癌症相关成纤维细胞（cancer-associated fibroblasts，CAFs）中，hnRNP A1与miR-196a相互作用，参与外泌体从CAFs到肿瘤细胞的传递过程[50]. 在小鼠肝细胞Cyp2a5 mRNA的3'UTR发现，71 nt发夹环以hnRNP A1依赖方式，保护mRNA免受RNase降解，进而维持该基因高水平表达[51]. 当结合位点发生缺失，hnRNP A1结合能力降低的同时，Cyp2a5表达也显著降低. 在果蝇中也观察到hnRNPs家族同源基因参与外泌体募集和调控过程. 果蝇Hrp59作为外泌体亚基或Rpr6辅助因子参与外泌体向表达基因的募集过程，可有效降解错误转录或加工产生的RNA分子[49]. hnRNP A1和其他家族成员能够参与外泌体调控新生转录本过程的发现，为进一步探究该蛋白质家族在稳定与降解错误表达转录本中的功能提供基础. 图2展示了hnRNP A1的主要调控功能.

2.2　可变剪接

通过体外鉴定hnRNP A1影响5'端剪接位点，首次获得hnRNPs参与剪接调控的直接证据[52]. 此后陆续发现hnRNPs家族成员广泛参与可变剪接调控. 在5种主要剪接调控方式中，hnRNP A1主要通过协同结合剪接元件并抑制其他剪接因子（如SR蛋白）在相邻位点的结合来调控剪接[1, 22]. 其中，hnRNP A1在5'剪接位点选择中拮抗SF2/ASF和SC35活性，导致远端5'剪接位点激活[53]. Damgaard等[54]对RNA二级结构进行解析后提出Tat剪接受体7（splice acceptor 7，SA7）区域调控模型. 该模型指出，hnRNP A1在SA7剪接调控元件上协同组装，有效掩盖SF2/ASF识别外显子剪接增强子（exonic splicing enhancer，ESE）. 此外，UP1和HIV-1 ISS晶体结构解析进一步证实，hnRNP A1能够结合HIV-1茎环结构保守位点，进而阻断早期剪接体组装[42]. 有趣的是，hnRNPs家族成员能够结合自身pre-mRNA并调节基因表达. 已在hnRNP A1外显子7B附近鉴定出hnRNP A1自身结合峰[10]. hnRNP A1通过结合内含子中心部分保守元件（conserved element，CE）促进外显子7B跳跃，从而调节自身pre-mRNA剪接[34].

hnRNP A1广泛剪接调控功能与多种疾病存在密切关联. 上皮间质转化（epithelial-mesenchymal transition，EMT）中，过表达hnRNP A1将上调CD44v6水平，进而促进肝癌细胞侵袭[2, 55]. 此外，hnRNP A1在运动神经元存活基因（survival motor neuron gene，SMN）外显子7的剪接调节中起决定作用，而该剪接事件与SMA存在密切关联[8]. 最新报道表明，hnRNP A1和hnRNP A2协同参与人乳头瘤病毒16（human papillomavirus type 16，HPV-16）剪接调控，影响E6和E7两种维持恶性肿瘤蛋白的表达平衡[25].

2.3　miRNA/lncRNA/circRNA/hnRNP A1调控网路

miRNA初级转录本（primary microRNA transcripts，pri-miRNAs）先后经过细胞核和细胞质中Drosha和Dicer两种RNase III核酸内切酶剪切加工，最终形成miRNA[56-59]. miRNA通过缩短转录物半衰期和降低mRNA翻译效率两种方式调控真核基因表达[60]. Kooshapur等[61]发现hnRNP A1能结合pri-miR-18a末端并重塑其茎环结构，这有利于Drosha内切酶调节miRNA加工成熟过程. 此外，miRNA-18a能够直接结合hnRNP A1特异位点并抑制其表达，进而诱导结肠癌细胞凋亡[62]. 随

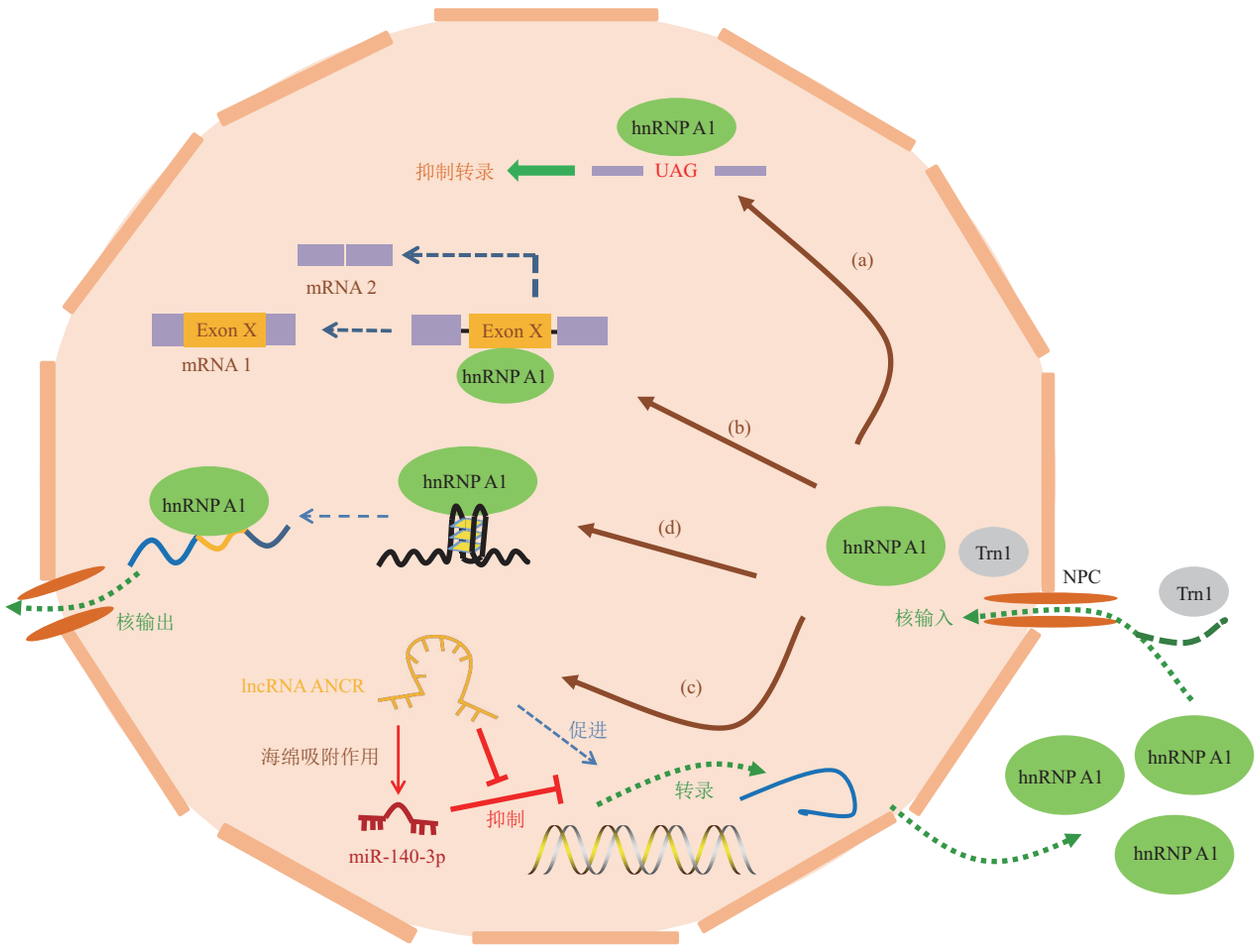

Fig. 2　Schematic diagram of hnRNP A1 function

图2　hnRNP A1功能示意图

（a）转录调控；（b）可变剪接；（c）非编码RNA调控；（d）G-四链体解旋. Trn1：Transportin-1；NPC：核孔复合物（nuclear pore complex）.

后，miRNA和hnRNP A1在多种恶性肿瘤细胞增殖与侵染过程中的调控作用进一步得到确定. hnRNP A1还与大肠癌细胞中细胞周期蛋白依赖性激酶6（cyclin dependent kinase 6，CDK6）相互作用，miRNA-26a和miRNA-584过表达将降低CDK6表达[63]，进而诱导癌细胞凋亡.

另一方面，人体细胞中lncRNA表达水平改变将导致下游基因表达失调，这与细胞异常增殖与病变存在密切关联. CAPERα/TBX3复合体在小鼠细胞衰老中起阻遏作用. lncRNA UCA1能阻断hnRNP A1和CAPERα/ TBX3复合体相互作用并诱导细胞衰老[64]. 值得注意的是，已在多种癌症中发现miRNA与lncRNA除单独调控靶基因表达外，也存在特殊相互作用. lncRNA ANCR（anti-differentiation ncRNA）在多种肿瘤细胞转移中扮演重要角色，能促进癌变细胞的转移和侵袭[65]. 有趣的是，生物信息学分析发现hnRNP A1和ANCR均含有miR-140-3p结合位点. lncRNA ANCR通过抑制miR-140-3p的负调控作用，进而上调hnRNP A1表达来促进原发性肝细胞癌（hepatocellular carcinoma，HCC）细胞和EMT细胞转移和侵袭[65]. 随着多组学技术发展，构建不同物种miRNA/lncRNA/hnRNP A1互作调控网络成为可能，这也将获得更有趣的发现.

circRNAs是一种来源于非规范反式剪接形成的共价闭合环状分子，具有组织和细胞特异性[66-67]. 作为剪接“副产品”，circRNA不仅可以募集剪接因子参与剪接调控，还能与miRNA结合发挥海绵吸附作用调控转录[68-69]. 尽管目前没有证据表明circRNA与hnRNP A1存在直接或间接相互

作用，但结合已报道circRNA、miRNA、lncRNA和hnRNP A1在多种恶性肿瘤和心血管疾病中均发挥重要作用[70-73]，可以预测circRNA/miRNA/lncRNA/hnRNP A1存在复杂的动态调控网络.

2.4　端粒和G–四链体结合

端粒是真核生物染色体末端重要元件，与体细胞正常衰老和死亡存在密切关联. 在正常分裂细胞中，端粒会随着分裂次数增加而不断缩短[74]. 而在敲除hnRNP A1的小鼠细胞中发现其端粒长度较正常细胞短，并在引入外源UP1结构域后端粒长度增加[28]，这暗示hnRNP A1可能在维持端粒长度中发挥重要作用. 此后多项研究表明，hnRNP A1能与端粒末端重复序列形成的G-四链体结构结合，并促进该结构解聚. X射线晶体学研究发现，hnRNP A1与端粒富含鸟嘌呤的突出端结合，这与端粒重复序列和RRM β1、β3链上的疏水残基相互作用有关[3]. hnRNP A1与端粒G-四链体结合的三维结构显示，UP1结合TTAGGG重复序列，RGG盒则增强相邻UP1展开G-四链体结构活性[75-77]. 上述结果表明，UP1和RGG盒可协同展开端粒G-四链体结构.

除端粒外，还发现hnRNP A1与多种癌细胞相关基因启动子区的G-四链体存在特殊相互作用. *KRAS*与胰腺癌细胞侵袭有关，该基因启动子上游包含由G-四链体结构的鸟嘌呤组成的多态性核酸酶超敏元件. UP1高亲和力结合G-四链体结构后将其展开，促进KRAS基因转录[30, 78]. 此外，hnRNP A1直接与受体酪氨酸激酶RON mRNA的5'UTR结合，并通过G-四链体结构激活该基因翻译表达[79]. 在结肠癌细胞中也发现，hnRNP A1通过结合剪接因子TRA2B（transformer 2β）启动子中的G-四链体来调节转录[80]. 近期也有报道，hnRNP A1作为病毒潜伏期相关核抗原（latency-associated nuclear antigen，LANA）调控因子，参与G-四链体解旋进而调控翻译[81]. 综上可以发现，hnRNP A1与多种肿瘤基因形成的G-四链体结构存在特殊相互作用，这可能在开发靶向药物中具有重要应用价值.

2.5　翻译后修饰

hnRNP A1经历多种翻译后修饰，包括磷酸化、甲基化、泛素化、乙酰化及SUMO化等. 翻译后修饰不仅调节蛋白质活性与稳定性，而且在蛋白质定位与功能行使等方面也发挥重要作用[2]. 其中，磷酸化修饰影响hnRNP A1正确核定位和核酸链退火活性[19, 82]. 在细胞应激压力条件下，hnRNP A1 C端被称为“F-peptide”的短序列通过细胞信号通路的磷酸化限制蛋白质核输入[19]. hnRNP A1的N端Ser4/6残基被S6K2激酶磷酸化修饰后，在增强该蛋白质与Bcl-2家族Bcl-xL和X连锁凋亡抑制蛋白（X-linked inhibitor of apoptosis，XIAP）mRNA结合能力的同时，还促进hnRNP A1核输出[2]. 另一方面，精氨酸甲基转移酶PRMT3和PRMT5均可甲基化修饰hnRNP A1精氨酸残基. 其中，PRMT3甲基化修饰R31残基，促进hnRNP A1和三磷酸腺苷结合转运蛋白G超家族成员2（ATP-binding cassette subfamily G member 2，ABCG2）结合，影响细胞耐药性[83]. 而PRMT5则修饰R218和R225残基，通过促进hnRNP A1与内部核糖体进入位点（internal ribosome entry site，IRES）相互作用，增强IRES依赖性翻译[84]. 此外，RGG盒内源性不对称二甲基化则抑制细胞中hnRNP A1 ITAF活性[15].

翻译后修饰还影响hnRNP A1剪接调控功能. 在HCC细胞中，hnRNP A1参与丙酮酸激酶（pyruvate kinase，PK）mRNA剪接调控，促进PKM2特异剪接亚型形成[85]. 当hnRNP A1中4个赖氨酸残基均被去乙酰化酶家族成员SIRT1和SIRT6修饰，将抑制HCC细胞中PKM2剪接亚型形成，进而促进PKM1亚型表达[85]. 另一方面，表皮生长因子（epidermal growth factor，EGF）可诱导E3泛素连接酶衔接子SPSB1募集Elongin B/C-Collin复合体参与hnRNP A1泛素化修饰[86]. 经泛素化修饰的hnRNP A1和SR蛋白激酶共同促进Rac1剪接亚型Rac1b上调表达[86-87].

除常见修饰外，一种特殊的多聚ADP核糖基化（poly(ADP-ribosyl)ation，PARylation）修饰也在hnRNPs参与神经退衰性疾病调控中发挥重要作用[88]. 该修饰可通过多聚ADP核糖聚合酶（poly（ADP-ribose）polymerase，PARP）将多个ADP核糖分子（ADP-ribose molecule，pADPr）连接到目标蛋白质上，进而改变蛋白质功能[89-90]. hnRNP A1高亲和力结合多聚核糖基序，并影响SG募集[15]. 在果蝇中也发现相似的糖基化修饰. pADPr可在体内以非共价方式与hnRNPs家族同源Squid和Hrp38结合，影响多巴脱羧酶（dopa decarboxylase，DDC）可变剪接[91]. 另一方面，果蝇中pADPr和Hrp38的结合会破坏Hrp38和E-钙黏蛋白mRNA的5'UTR相互作用并抑制翻译[45]. 多种翻译后修饰为hnRNP A1和其他

hnRNPs家族成员功能表达提供更加灵活的选择方式.

3 总结与展望

hnRNP A1在转录本稳定、剪接调控和端粒维持等过程中的功能研究已得到大量验证. 而lncRNA/miRNA/circRNA复杂内源性抑制网络模型的提出，也为进一步理解hnRNP A1直接或间接参与该网络调控提供可能. 虽然UP1结晶已经提供hnRNP A1结合特异RNA序列的一般见解，但考虑该蛋白质结合受不同细胞类型、生理状态及酸碱性环境等因素影响，要进一步获得结合特性的全面认识，还需更多数据的支持与完善.

此外，hnRNP A1作为一种重要的剪接因子，参与多种疾病相关基因剪接调控过程. 在已有数据基础上，对hnRNP A1参与多种肿瘤细胞恶性增殖调控的认识不再仅限于转录和剪接调控. 随着研究深入，hnRNP A1与多种非编码RNA和G-四链体结构相互作用，参与胃癌、结肠癌和黑色素瘤细胞恶性增殖调控，也发生从“特殊性”到“一般性”的转变，进一步表明该蛋白质在疾病诊断中的重要性. 此外，随着高通量测序技术的普遍运用，构建hnRNP A1蛋白在多细胞中的动态表达谱有望实现对该蛋白质更全面的认识，同时也将为医疗应用提供有利参考.

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Research Progress in hnRNP A1 Protein*

YANG Hong-Guang, TONG Chun-Mei, DENG Hui-Min**

(*School of Life Sciences, South China Normal University, Institute of Insect Science and Technology, Guangdong Provincial Key Laboratory of Insect Developmental Biology and Applied Technology,Guangzhou* 510631, China)

Abstract Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a family of multifunctional RNA-binding proteins that bind to nascent transcripts synthesized by RNA polymerase II and participate in the regulation of transcript stabilization and maturation in the form of complexes. hnRNP A1 is an important member of this protein family and is not only widely involved in the regulation of alternative splicing of genes related to cancer and neurological diseases, but also plays an important role in viral infection, cellular aging and stress recovery. Besides, as hnRNP A1 is a typical RNA-specific binding protein, the rules of identifying specific sequences through dynamic three-dimensional structures have also been revealed in the regulation of transcription and alternative splicing. This review summarizes the research progress of hnRNP A1 in recent years, providing references for the further exploring its function in disease development.

Key words hnRNP A1, hnRNPs family, alternative splicing

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** Corresponding author.

Tel：86-20-85210024，E-mail：denghuiminmin@163.com

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