RNA结合蛋白与非编码RNA调节关系的研究进展

倪舒静[1,2] 徐美倩[1,2] 陈辰[1,2] 王玲琳[1,2] 朱婷琰[1,2] 奕天飞[1,2]
吉米丽古丽·艾尼[1,2] 廖奇[1,2]*
([1]宁波大学医学院, 预防医学系, 宁波 315211; [2]宁波大学医学院, 浙江省病理生理重点实验室, 宁波 315211)

摘要 近年来, 越来越多的研究表明, RNA结合蛋白(RNA binding protein, RBP)与多种类型的非编码RNAs(noncoding RNA, ncRNAs)具有互相调节的关系, 且调节机制形式多样。一方面, RBP可以调节ncRNA的生物合成、稳定性和功能; 另一方面, ncRNA也可以影响RBP的功能和结构。同时, RBP和ncRNA的相互作用还在其他靶基因的调节上起着重要的作用, 从而参与众多的生物过程, 如组织发育、代谢性疾病、神经退行性疾病、抗病毒免疫和各种癌症等。该文就RBP与常见类型的ncRNAs, 包括miRNA、lncRNA、circRNA的相互作用方式和调节机制的研究进展作一综述。

关键词 RNA结合蛋白; 非编码RNA; 调节关系; miRNA; 长非编码RNA; circRNA

Progress of Regulatory Relationships between RNA Binding Protein and Non-Coding RNA

NI Shujing[1,2], XU Meiqian[1,2], CHEN Chen[1,2], WANG Linglin[1,2], ZHU Tingyan[1,2], YI Tianfei[1,2], GIMILIGULI·Aini[1,2], LIAO Qi[1,2]*
([1]*Department of Preventative Medicine, Medicine School of Ningbo University, Ningbo 315211, China*; [2]*Zhejiang Key Laboratory of Pathophysiology, Medicine School of Ningbo University, Ningbo 315211, China*)

Abstract In recent years, more and more studies have shown that RBP (RNA binding protein) and various types of ncRNAs (noncoding RNAs) have mutual regulatory relationships. The interactions between RBP and ncRNA have diverse mechanisms. On one hand, RBP can regulate the biosynthesis, stability and function of ncRNA; on the other hand, ncRNA can also affect the function and structure of RBP. At the same time, the interaction between RBP and ncRNAs also plays an important role in the regulation of other target genes, therefore participating in many biological processes, such as tissue development, metabolic diseases, neurodegenerative diseases, antiviral immunity and various kinds of cancers. This review focuses on the research progress of the regulation mechanisms between RBP and several common kinds of ncRNAs, including miRNA, lncRNA, and circRNA.

Keywords RNA binding protein; noncoding RNA; regulatory relationship; miRNA; long noncoding RNA; circRNA

RNA结合蛋白(RNA binding protein, RBP)是一类在RNA调控过程中与RNA结合的蛋白质的总称[1]。目前报道的人类基因组编码的RBP超过800个[2], READDB(http://darwin.soic.iupui.edu/)是一个关于RBP表达和相关疾病信息的数据库, 其中包含的RBP就有1 344个[3]。RBP作为一种反式作

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*通讯作者。Tel: 0574-87600757, E-mail: liaoqi@nbu.edu.cn
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*Corresponding author. Tel: +86-574-87600757, E-mail: liaoqi@nbu.edu.cn
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用因子[4], 与RNA的识别和相互作用主要由特定的RNA结合结构域(RNA binding domain, RBD)介导[5]。RBD是一个具有独特特征的结构, 目前在人类中已找到600多种结构不同的RBD[6], 如异源核RNA k-同源基序(k homology motif, KH)、RNA识别基序(RNA recognition motif, RRM)、锌指结构域(zinc finger domain)等[7]。此外, RBP上还有辅助结构域(auxiliary domain), 该结构域也是介导蛋白质–蛋白质相互作用的结构域。一个或多个RBD结构域与一个或多个辅助域以不同的方式组装在一起, 形成不同的RBP[8]。

RNA与RBP结合形成核糖核蛋白(ribonucleoprotein, RNP)复合物, 在mRNA生命的各个方面发挥功能和作用, 包括翻译调控、mRNA前体剪接、多聚腺苷化、核输出、mRNA定位等[9-10]。因此RNP形成缺陷或受阻将影响疾病的发生和发展。如在神经系统中, 大量基因转录后与特定RBP相互作用而受到调节[11]; 此外, RBP与mRNA的结合对胆固醇代谢、心脏和肌肉发育等生物过程也有很强的调控作用[12-13]。

事实上, RBP不仅能够与mRNA相互作用, 也可以结合ncRNA(non-coding RNA), 如核糖体RNA(ribosomal RNA, rRNA)、转运RNA(transfer RNA, tRNA)、小核仁RNA(small nucleolar RNA, snoRNA)、piwi-RNA(Piwi-interacting RNA)、微小RNA(microRNA, miRNA)、环状RNA(circular RNA, circRNA)和长非编码RNA(long noncoding RNA, lncRNA)等[6]。据报道, 与RBP结合的ncRNA占哺乳动物细胞中所有转录RNA的90%以上, 可见, RBP与ncRNA的结合在生物体中普遍存在[14]。目前已存在一些关于RNA-RBP相互作用关系的网上预测工具和数据库, 如catRAPID(http://s.tartaglialab.com/catrapid/omics)[15]是一个常用的预测RBP和RNA相互作用的工具; ncRNA互作数据库starBase v2.0(http://starbase.sysu.edu.cn/)也收录了RBP-RNA相互作用关系的信息[16]。RBP与ncRNA互作在生命体中起着重要的作用。一方面, RBP与ncRNA的结合可以实现对其他靶mRNA的调节[6], 调控转录后基因表达水平, 有助于前体mRNA加工、成熟、转运、定位和翻译[14]; 另一方面, RBP和ncRNA的相互作用也会影响到参与作用的RBP或ncRNA的表达, 从而影响其功能, 导致多种疾病或癌症的发生发展, 包括神经退行性疾病、代谢性疾病和各种癌症等[7]。本文就近年来在哺乳动物中常见的RBP-ncRNA调节关系的作用方式、功能机制、影响的疾病等的研究进展作一综述。

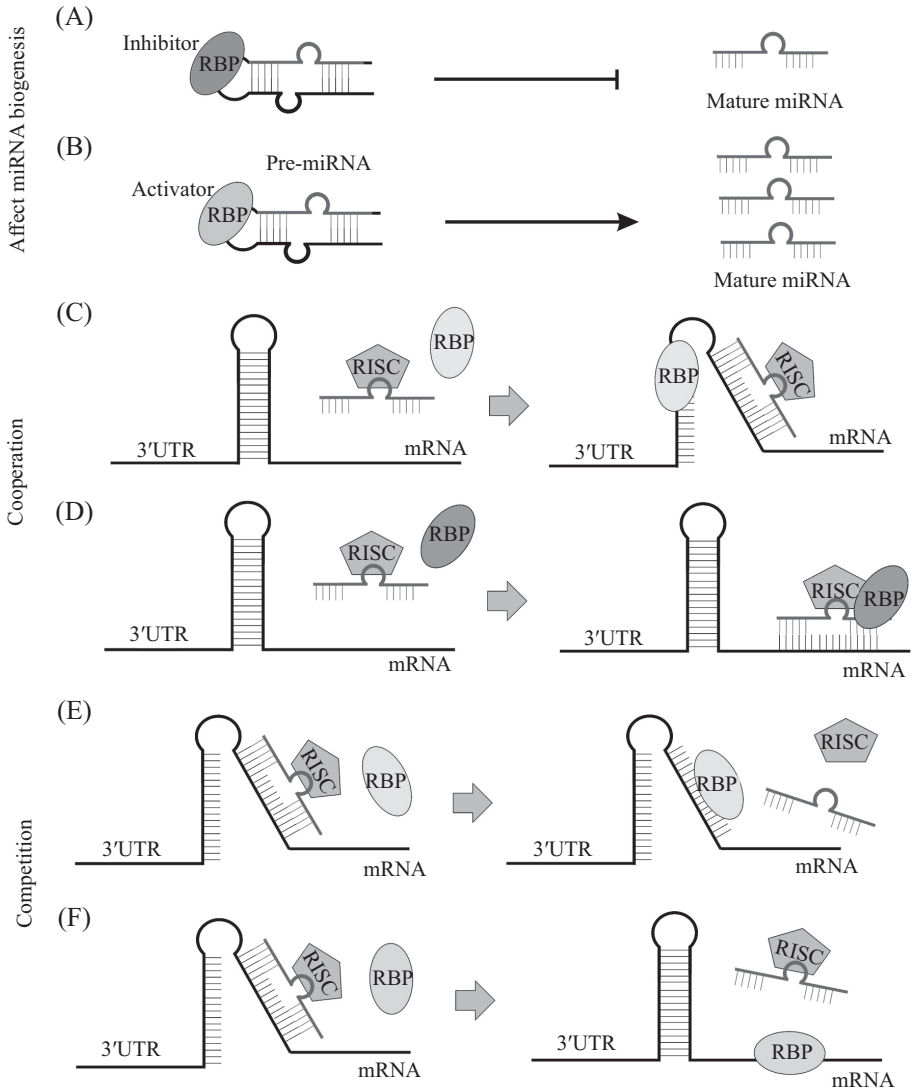
1 RBP与miRNA的相互作用

miRNA是一段长度为21~23个核苷酸的单链RNA[17]。研究表明, miRNA可以调节哺乳动物60%以上基因的表达[18], 控制脊椎动物细胞的增殖、生长、死亡、炎症和发育等[19]。此外, miRNA在行使功能时也受其他分子的调节, 如lncRNAs、转录因子、RBP等, 其中RBP对miRNA的调节起重要的作用。RBP与miRNA的调节关系主要体现在以下3个方面。

首先, 大部分RBP如RNA剪接因子和RNA加工因子, 充当miRNA生物合成的转录后调节因子, 促进或抑制miRNA的生物合成[20-23]。对miRNA生物合成起抑制作用的RBP主要包括: Pumilio RBP、核不均一核糖核蛋白A1(heterogeneous nuclear ribonucleoprotein A1, hnRNPA1)、含三核苷酸重复6C(trinucleotide repeat containing 6C, TNRC6C)/含三核苷酸重复序列蛋白6A(trinucleotide repeat containing adaptor 6A, TNRC6A)蛋白家族的成员等[24](图1A)。例如, 在胚胎干细胞中, RBP Lin-28同源物A(lin-28 homolog A, LIN28A)特异性结合miRNA pri-let-7的末端环区域, 将前体miRNA隔离在细胞质中, 远离核“微处理器”复合物, 从而不能将pri-let-7剪切加工为成熟的let-7[25]; 含有KH结构域的RNA结合蛋白(KH domain containing RNA binding, QKI)的异位表达抑制pri-miR-7向成熟miR-7的加工[26]等。此外, 含有KH基序的RBP KH结构域RNA结合信号转导相关1(KH RNA binding domain containing, signal transduction associated 1, SAM68)定位于染色质体, 与Drosha(drosha ribonuclease III)和Dicer(dicer 1, ribonuclease III)蛋白相互作用, 从而在转录后水平间接抑制miRNA如miR-29b的表达, 进而调节雄性生殖细胞核和细胞质加工事件[27]。对miRNA的生物合成起促进作用的RBP主要包括: RISC装载复合物亚基TARBP2(TARBP2 subunit of RISC loading complex, TRBP2)、DND1(DND microRNA-mediated repression inhibitor 1)、RNA结合基序蛋白38(RNA-binding motif protein 38, RBM38)、不稳定编码区结合蛋白(characterizing the coding region determinant-

binding protein, CRD-BP)等[24](图1B)。如QKI与成熟miR-20a的结合, 可以稳定和维持miR-20a的水平, 并在胶质母细胞瘤中发挥肿瘤抑制作用[28]; RBP SART3(spliceosome associated factor 3, U4/U6 recycling protein)与pre-miR-24a结合, 可以提高miR-34a的表达水平, 从而影响非小细胞肺癌细胞的细胞周期进程[29]。同时, 人类抗原R(human antigen R, HuR)、不均一性核糖核蛋白(heterogeneous nuclear ribonucleoprotein, hnRNP)、核不均一核糖核蛋白A1(heterogeneous nuclear ribonucleoprotein A1, hnRNPA1)和多聚嘧啶区结合蛋(polypyrimidine tract binding protein, PTB)具有双重作用, 即对不同的miRNA可以起抑制作用或促进作用。

其次, RBP可以促进miRNA对靶基因结合位点的识别。RBP通过改变mRNA的二级结构, 暴露miRNA结合位点, 促进miRNA对mRNA的识别。如RBP Pumilio RNA结合家族成员1(Pumilio RNA binding family member 1, PUM1)与*p27* mRNA的3′UTR



A: RBP作为抑制因子, 降低miRNA的生成。B: RBP作为激活因子, 增强miRNA的生成。C: RBP影响mRNA的结构, 使其暴露miRNA结合位点, 促进miRNA对结合位点的识别。D: RBP与miRNA结合, 发生协同作用, 促进miRNA对靶mRNA的结合。E: RBP竞争性结合miRNA在靶mRNA上的结合位点, 从而影响miRNA对靶mRNA的结合。F: RBP在mRNA的miRNA结合位点附近结合, 影响miRNA与靶mRNA的结合。

A: as an inhibitor, RBP reduces the production of miRNA. B: RBP acts as an activator to enhance miRNA production. C: RBP affects the structure of mRNA, exposing miRNA binding sites and promoting miRNA recognition of binding sites. D: RBP interacts with miRNA to promote the binding of miRNA to mRNA target. E: RBP competitively interact with the binding site of miRNA on mRNA, thus affecting the binding of miRNA to mRNA target. F: RBP binds to the region near to the miRNA binding site of mRNA and affects the binding of miRNA to target mRNA.

图1 RBP与miRNA的作用方式

Fig.1 The interaction modes between RBP and miRNA

结合而改变其二级结构，暴露出miR-221/222的结合位点，从而促进miR-221/222对p27的调节，在乳腺癌的细胞增殖和发展中起到重要作用(图1C)[30]。另外，RBP还可以和miRNA协同作用，一起与mRNA结合，调节mRNA的稳定性和翻译(图1D)，如RBP HuR募集miRNA let-7使其与*c-Myc* mRNA的3′UTR结合，从而下调c-Myc的表达[31]；RBP HuD与miR-203a协同作用，共同调节INSM转录抑制因子1(INSM transcriptional repressor 1, *INSM1*) mRNA的表达[32]等。

再次，RBP和miRNA可以竞争性调节mRNA的稳定性[20]。转录物降解是蛋白质丰度调节中普遍存在的重要机制[33]。RBP和miRNA是RNA降解的2个主要调节因子[34]，目前已有几种竞争机制。(1) RBP与mRNA在miRNA重叠位点或临近位点上的结合可能会阻止miRNA与RNA诱导沉默复合体(RNA-induced silencing complex, RISC)的结合，从而促进靶mRNA的稳定性和翻译效率(图1E)。例如，RBP DND1可以与miR-221竞争性结合*Bim*(Bcl-2 interacting mediator of cell death) mRNA的3′UTR，从而稳定Bim的翻译[35]；此外，RBP HuR结合酪氨酸激酶受体2(erb-b2 receptor tyrosine kinase 2, *ERBB2*) mRNA 3′UTR上靠近miR-311-3p靶点的富含U的元件(U-rich element, URE)，与miR-331-3p竞争结合位点，从而阻止miR-331-3p对ERBB2的抑制作用，提高ERBB2的翻译水平[36]。(2) RBP与mRNA在miRNA非重叠位点上的结合可能导致mRNA构象的变化，使其发生RNA寡聚体化，从而影响miRNA与RISC的结合[37](图1F)。除了mRNA，RBP和miRNA也可以共同竞争lncRNA的结合位点，如HuR和lncRNA HOX转录反义RNA(HOX transcript antisense RNA, *HOTAIR*)的表达水平在膀胱癌组织中呈正相关。据报道，HuR与miR-1竞争，结合HOTAIR，增强*HOTAIR* mRNA的稳定性，从而促进膀胱癌的发生发展[38]。

有些miRNA与RBP的作用方式不止一种，且可能互为调节关系。例如，HuR是研究最多的RBP之一，可通过多种机制调节miRNA的功能[39]。一方面，HuR可以影响miRNA的生物合成，从而影响miRNA的表达。如HuR在细胞质中与miR-16结合，导致miR-16表达水平快速下降[40]。另一方面，HuR还可以充当miRNA的“海绵”，通过与miR-21的结合，阻止了miR-21与程序性细胞死亡因子4(programmed cell death 4, PDCD4)的结合，进而降低了miR-21对PDCD4翻译的抑制作用[41]。反过来，miRNA也可以调节HuR的表达水平，如miR-34a、miR-16、miR-125a和miR-519都可以通过影响HuR的稳定性或翻译来调节HuR[42]。另一个RBP，KH型剪接调节蛋白(KH-type splicing regulatory protein, KSRP)，不仅可以作为Drosha和Dicer复合物的组分，调节miRNA的生物发生，如促进pre-miR-206的成熟[43]，而且反过来，miR-206也可以与KH型剪接调节蛋白(KH-type splicing regulatory protein, KSRP) 3′UTR的保守位点结合，抑制KSRP的表达[44]。综上可见，RBP与miRNA的相互作用形式多样、错综复杂，一起调节基因的转录和表达，在各种生物过程中起着重要的作用。

2 RBP与lncRNA的相互作用

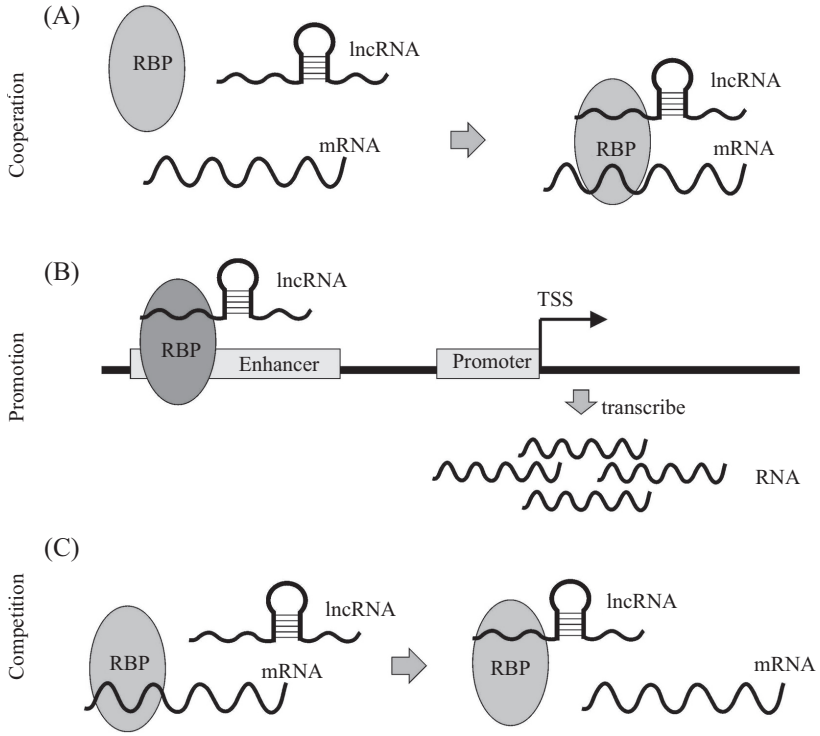
lncRNA一般被定义为超过200个核苷酸，且不编码蛋白质的RNA[45]。类似于mRNA，部分lncRNA转录后，在细胞核中也要进行剪接、成熟，以及细胞质中的输出、编辑、转运和降解[46]。与其他类型的RNA相比，lncRNA由于长度较长，可能由多个结构域或功能域组成，且包含大量的蛋白质结合位点，因此，lncRNA可以为蛋白质的多聚化提供平台[47]。据报道，大部分lncRNA都可以与相应的RBP相互作用[48]，并在各种细胞和生理过程中起着不可替代的作用[49]。例如，核内不均一性核糖核蛋白K(heterogeneous nuclear ribonucleoprotein K, RBP, hnRNPK)与lncRNA相互作用，可以调节其他基因如*p21*的转录，控制mRNA的稳定性和翻译，促进lncRNA核富集，调节基因组结构等[50]。lncRNA与RBP的结合方式和功能主要包含以下几种。

第一，lncRNA与RBP结合后，一起调节其他靶基因。例如，lncRNA尿路上皮癌胚抗原1(urothelial carcinoma associated 1, UCA1)与RBP多嘧啶序列结合蛋白1(polypyrimidine tract binding protein 1, PTBP1)结合，将PTBP1募集到5’-氨基乙酰丙酸合酶2(5’-aminolevulinate synthase 2, *ALAS2*) mRNA上并稳定其表达，从而增强血红素的生物合成，促进红细胞的成熟[51](图2A)；在癌症中，lncRNA肿瘤易感性候选基因9(cancer susceptibility candidate 9, CASC9)与RBP人异质性胞核核糖核蛋白L(heterogeneous nuclear ribonucleoprotein L, hnRNPL)结合，调控一组靶基因如PI3K/Akt信号通路、DNA损伤信号通路中

基因的表达[52]。此外, 在MYCN(MYCN proto-oncogene, bHLH transcription factor)发生扩增的高危神经母细胞瘤患者中, RBP基质蛋白3(matrin 3, MATR3)表达显著上升, 且与患者低生存率相关, MATR3与lncRNA 小核仁RNA宿主基因1(small nucleolar RNA host gene 1, SNHG1)的结合可能调节RNA剪接, 参与细胞周期过程, 从而促进神经母细胞瘤的进展[49]。另外, lncRNA p53诱导的非编码RNA(p53-induced noncoding RNA, PINCR)也可以募集RBP MATR3与p53结合形成复合体结合到*p53*靶基因的增强子区域, 从而调节一系列p53诱导的靶基因[53](图2B)。

第二, lncRNA可以调节RNP复合物中RBP的活性或稳定性, 从而影响RBP与靶mRNA的结合, 抑制或促进mRNA的翻译水平。有些lncRNA直接影响RBP与靶mRNA的结合位点, 即lncRNA可以充当RBP的竞争性内源RNA, 使RBP脱离与靶mRNA的结合, 从而影响靶mRNA的翻译(图2C)。例如, lncRNA OIP5-AS1(OIP5 antisense RNA 1)可以使HuR远离它的靶mRNA, 从而降低这些目标转录物的表达[54]。而有些lncRNA影响RBP活性的机制尚未明确, 不排除可能影响RBP的结构。例如, lncRNA DNA损伤诱导基因7(DNA damage-inducible gene 7, GADD7)与参与mRNA转录、加工和稳定的RBP TAR DNA结合蛋白(TAR DNA binding protein, TDP-43)结合, 从而影响TDP-43与周期素依赖性激酶6(cyclin dependent kinase 6, *CDK6*) mRNA的结合, 并触发*CDK6* mRNA的衰变[55]; 此外, lncRNA H19在小鼠C2C12成肌细胞中与RBP KSRP结合, 导致KSRP介导的靶基因转录本的不稳定[56]。另外, 一种在哺乳动物胎盘中丰富表达的lncRNA DNA损伤激活的非编码RNA(non-coding RNA activated by DNA damage, NORAD), 包含多个高度保守的RBP结合位点, 与多个RBP均具有相互作用, 其与RBP PUM1的结合, 可以降低PUM1的活性, 从而提高靶mRNA的稳定性, 促进靶mRNA的翻译, 尤其是参与有丝分裂进程的mRNA的表达, 进而影响细胞周期[57]。

第三, RBP也可以调节lncRNA的表达水平。例如, RBP胰岛素样生长因子mRNA结合蛋白



A: lncRNA募集RBP至靶mRNA上, 从而促进RBP对靶mRNA的调节。B: RBP与lncRNA结合, 共同作用于靶基因的增强子, 促进其他靶基因的转录。C: lncRNA竞争性地与RBP结合, 从而影响RBP与其靶mRNA的结合。

A: lncRNA recruits RBP to target mRNA, which promotes the regulation of RBP on target mRNA. B: RBP interacts with lncRNA to affect the enhancer of target gene, promoting the transcription of other target genes. C: lncRNA binds to RBP competitively, which affects the binding of RBP to its target mRNA.

图2 RBP与lncRNA的作用方式

Fig.2 The interaction modes between RBP and lncRNA

1(insulin-like growth factor 2 mRNA binding protein 1, IGF2BP1)可以充当衔接蛋白, 募集至细胞质RNA衰变的CCR4-NOT转录复合体亚基1(CCR4-NOT, transcription complex subunit 1, CNOT1), 从而导致lncRNA HULC(hepatocellular carcinoma up-regulated long non-coding RNA)的降解[58]; 此外, 当HOTAIR的泛素化底物的水平较低时, HuR会优先与HOTAIR结合, 并通过募集let-7-Ago2(argonaute RISC catalytic component 2)复合物来降低HOTAIR的稳定性[59]。

另外, RBP和lncRNA的结合还能调节该lncRNA基因组的稳定性。如lncRNA NORAD通过充当RBP Pumilio家族的结合平台来维持其基因组稳定性[60]; RBP hnRNPK可以直接与lncRNA XIST(X-inactive-specific transcript)相互作用, 从而使XIST能够定位于非活性X染色体上[61]。除此之外, lncRNA和RBP的相互作用还可以促进lncRNA的核富集。如RBP hnRNPK可以与含有SIRLOIN(SINE-derived nuclear RNA localization)的lncRNA 结合, 促进lncRNA的核富集[62]。综上所述, RBP和lncRNA有多种调节方式, 它们共同影响众多的生物过程。

3 RBP与circRNA的相互作用

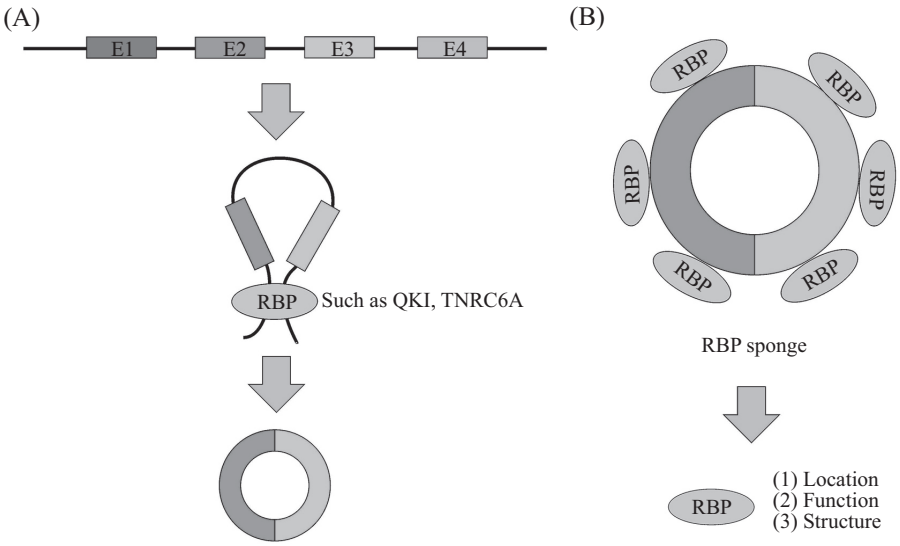
共价闭合的单链circRNA由内含子或外显子组成, 并广泛存在于真核细胞中, 主要来自前体mRNA, 由RNA聚合酶II(RNA polymerase II, Pol II)转录[63]。在人类的poly(A)-RNA中, circRNA可能只占1%[64]。circRNA的表达水平较低, 结构相对稳定, 多数位于胞质内, 常以细胞和组织特异性方式发挥作用。尽管circRNA上的RBP结合位点少于相应线性的mRNA, 但RBP与circRNA的相互作用对circRNA的生物合成和功能都起着重要的调节作用。

circRNA的生物合成存在多种方式, 其中RBP驱动的环化是主要的方式之一。在以RBP驱动的环化机制下, RBP QKI与前体mRNA上环状剪接位点附近的内含子结合, 从而促进circRNA的形成[65](图3A)。除此之外, 双链RNA结合蛋白(double-stranded RNA binding proteins, dsRBP)可通过结合并稳定前体mRNA中内含子互补形成的RNA对子, 来促进circRNA的产生, 例如, dsRNA结合蛋白NF90/NF110直接与mRNA前体中形成的插入重复Alu序列结合以促进circRNA的形成[66]。不仅如此, dsRBP也可以通过使RNA配对不稳定来抑制circRNA的形成, 并在circRNA剪接、加工、折叠、稳定化和定位中发挥作用[65]。例如, RBP含三核苷酸重复序列蛋白6A(trinucleotide repeat containing adaptor 6A, TNRC6A)调节circRNA circ0006916的生物发生, 对细胞生长的调节起着重要的作用[67]。

circRNA还可以作为RBP的“海绵”, 类似于circRNA-miRNA的相互作用方式, 形成RBP-circRNA复合物(图3B)[68]。RBP-circRNA相互作用的原因之一是circRNA的三级结构比线性mRNA序列具有更强的蛋白质结合能力[69]。据报道, RBP-circRNA的相互作用可能影响RBP的结构、功能和亚细胞定位, 从而调节众多的生物过程[70], 如circARSP91与RBP UL16结合蛋白1(UL16 binding protein 1, ULBP1)结合, 上调ULBP1的表达, 从而提高肝癌细胞对NK细胞毒性的敏感性[71-72]。另外, circPABPN1与RBP HuR结合可以抑制HuR与多聚腺苷酸结合蛋白核1基因[poly(A) binding protein nuclear 1, *PABPN1*]mRNA的结合能力, 并抑制其翻译[73]等。

circRNA还能募集RBP至其靶mRNA上, 促进RBP对靶基因的调节。如circMYBL2通过募集RBP PTBP1至FMS样酪氨酸激酶3(fms related receptor tyrosine kinase 3, *FLT3*) mRNA来调节FLT3的翻译, 从而增强其表达[74]; circ0003998与RBP poly(C)结合蛋白1[poly(C)-binding protein 1, PCBP1]结合, 从而促进上皮–间质转化(epithelial-mesenchymal transition, EMT)相关基因如CD44变体6(CD44 variant 6, *CD44v6*)的表达[75]。

circRNA与RBP的相互作用还能影响癌症的发生。一方面, circRNA与RBP可以发生物理结合促进癌症的发生。如circAgo2和HuR发生物理相互作用并被激活, 促进癌细胞的生长、侵袭和转移, 同时促进HuR在靶mRNA 3′UTR上的富集, 从而阻止Ago2与靶基因的结合, 使Ago2/miRNA介导的基因沉默受到抑制, 进而促进肿瘤发生和侵袭性[76]。另一方面, RBP可以通过抑制circRNA的表达来促进癌细胞的增殖, 例如, RBP RBM3的高表达会抑制SCD-circRNA2(硬脂酰基–辅酶A脱氢酶基因3′UTR上来源的circRNA)的表达, 从而促进肝细胞癌(hepatic cell carcinoma, HCC)细胞的增殖[77]。circRNA与RBP在抗病毒免疫中也发挥着重要作用。例如, circARSP91可以通过上调HCC中ULBP1的mRNA和蛋白质水平, 并且通过与*ULBP1*启动子区域相互作用募集RNA聚合酶II来增强*ULBP1*基因的表达, 从



A: RBP与RNA结合, 促进RNA的环化, 生成circRNA。 B: circRNA作为RBP装配的平台, 影响RBP的结构、功能和定位。
A: RBP binds to RNA, promoting the cyclization of RNA and generation of circRNA. B: as a platform for RBP assembly, circRNA affects the structure, function and location of RBP.

图3 RBP与circRNA的作用方式

Fig.3 The interaction modes between RBP and circRNA

而增强NK细胞的细胞毒性[78]。

4 讨论

RBP约占所有蛋白质编码基因的7.5%[6], 主要分为两大类: 经典的RBP, 包含已知的RNA结合基序, 如RRM、KH、双链RNA结合域(dsRNA-binding domain, dsRBD)和锌指, 其结合位点富集在mRNA的UTR区域; 而非经典的RBP, 通常是缺乏确定的RNA结合基序, 其结合位点的富集区域不明确[79]。在细胞中, RNA与RBP结合形成RNP, 从而影响RNA的结构, 并在其生物发生、稳定性、功能、转运和细胞定位中发挥关键作用。真核细胞编码大量的RBP(脊椎动物中有数千个), RBP显著多样性在进化过程中随内含子数量的增加而增加, 并在真核细胞中大量组合, 从而与每种RNA结合产生独特的RNP, 行使特定的功能[80]。

作为维持基因组完整性的重要参与者和协调者, RBP会优先结合成熟的mRNA序列。因此, RBP被普遍认为主要调节mRNA代谢的不同方面, 并决定mRNA的命运[6], 包括mRNA的多腺苷酸化、剪接、定位、稳定化和翻译效率[10,81-82]。尽管目前已确定的1 000多个RBP中, 大约有一半RBP可以根据其靶mRNA进行分组, 但其他RBP可能与多种RNA相互作用, 包括tRNA、核小RNA(small nuclear RNA, snRNA)、snoRNA等[6]。据报道, RBP主要调节ncRNA的生物发生和表达水平[50]。

RBP不仅参与miRNA的生成, 还调节其功能, RBP和miRNA的协同作用还可以影响其他靶基因的翻译[83]。这种协同作用可能是拮抗的, 也可能是促进的[20]。同时, miRNA也可以调节RBP的表达水平, 通过与RBP结合, 影响RBP的稳定性和翻译效率[84]。lncRNA和miRNA一样在转录调控以及转录后调控中起着重要作用[6], 而几乎所有的lncRNA都可以与相应的RBP相互作用[48], 调节RBP的活性。同时, RBP也可以影响lncRNA的表达或功能[58]。另外, circRNA的生物合成也可以通过RBP驱动的环化机制实现[63]。RBP与剪接位点附近的内含子结合, 有助于产生circRNA[85]。RBP还可以与circRNA相互作用, 并在circRNA剪接、加工、折叠、稳定化和定位中发挥重要的作用[65]。此外, circRNA还可以作为RBP的“海绵”。

除了结合RNA之外, RBP还可以与DNA结合, 也就是说, 一些DNA结合蛋白具有结合RNA的能力。HUDSON等[86]在1 267个RNA结合蛋白中定义了407个可以同时与DNA和RNA结合的蛋白, 即双链RNA结合蛋白(double-stranded RNA binding proteins, DRBPs)。对DRBPs进行的功能富集分析表明, 许多DRBPs可能涉及应激的生物过程, 包括DNA损伤反应、细胞凋亡和对极端温度的反应[86]。

综上所述, RBP与多种类型的ncRNA结合, 形式多样, 不仅调节ncRNA的生物合成, 而且影响RBP自身及其靶基因的表达和功能, 从而在众多生物过程中起着重要的作用。

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