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非编码RNA与先天免疫信号调控*

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【摘要】 先天免疫对消除和控制感染至关重要，但不受控制的免疫反应可损伤宿主组织。机体免疫稳态的调节是一个精确的、复杂的过程，其中，非编码RNA是多种生物过程中的重要调控因子。目前研究表明微小RNA、长链非编码RNA通过调控先天免疫途径中的基因表达参与抗病毒反应、肿瘤免疫及自身免疫性疾病。通常情况下，微小RNA通过与mRNA的3′端非翻译区结合，在转录后水平调节基因表达，而长链非编码RNA则作为微小RNA的内源竞争RNA，抑制微小RNA与信使RNA的结合，发挥免疫调控作用。本综述总结了非编码RNA在先天免疫中的调节作用及其机制，为先天免疫的调节及免疫相关疾病的研究提供参考。同时，我们也展望了该领域未来的研究方向，包括新型非编码RNA的表达与成熟调控机制，以及非编码RNA在进化中的保守性等。

【关键词】 先天免疫 非编码RNA 微小RNA 长链非编码RNA

Non-Coding RNA and Innate Immune Signal Regulation

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【Abstract】 The innate immune system is critical to the elimination and control of infections. However, uncontrolled immune responses can cause indirect host-mediated tissue damage. The regulation of immune homeostasis is a complex but finely regulated process. ncRNAs have been increasingly identified as important regulators of a variety of biological processes. Recent research findings suggest that microRNAs and long non-coding RNAs participate in antiviral responses, tumor immunity, and autoimmune diseases by regulating gene expression in the innate immune pathways. MicroRNAs regulate gene expression at the post-transcriptional level by binding to the 3′ untranslated regions of mRNA, while long non-coding RNAs act as endogenous competing RNAs for microRNAs, inhibiting the binding of microRNAs and mRNAs. In this review, we summarized the regulatory role of non-coding RNAs in innate immunity and its mechanism to provide references for research in the regulation of innate immunity and immune-related diseases. In addition, we also reported discussions on the future research directions in the field, including the expression and maturation regulation mechanism of new non-coding RNAs, and the conservation of non-coding RNAs in evolution.

【Key words】 Innate immune ncRNA miRNA lncRNA

非编码RNA（non-coding RNA, ncRNA）是一种独特的RNA转录本，占人类基因组RNA的90%以上，除少数具有开放阅读框，因而具有编码潜能以外，通常不编码蛋白质，而是作为发育、增殖、转录、转录后修饰、凋亡、细胞代谢等多种生物过程的重要调控因子[1-3]。ncRNA包括微小RNA（microRNA, miRNA）、小干扰RNA（small interfering RNA, siRNA）、PIWI-interacting RNA（piRNA）、转运RNA衍生小RNA（tRNA-derived small RNA, tsRNA）、核小RNA（small nuclear RNA, snRNA）、核仁小RNA（small nucleolar RNA, snoRNA）、长链非编码RNA（long non-coding RNA, lncRNA）、环状RNA（circular RNA, circRNA）、假基因等[1, 4-5]，其中，miRNA、lncRNA、circRNA均有参与先天免疫的调节[6-8]。

先天免疫是最普遍、作用最迅速的免疫类型，能够识别并杀死多种病原体。先天免疫系统通过先天免疫细胞表面的模式识别受体（pattern recognition receptors, PRR）识别病原体相关分子模式（pathogen-associated molecular pattern, PAMP）和宿主损伤相关分子模式（damage-associated molecular pattern, DAMP），从而触发炎症和招募免疫细胞来消除病原微生物和对自身有伤害的分子[9]。本文总结了近年来在ncRNA的特点功能、生物合成以及先天免疫信号传导领域的新发现，重点总结了ncRNA对先天免疫信号蛋白表达和功能调控的新机制，并对未来相关领域的研究进行了展望。

1 ncRNA的特点、功能及其生物合成

miRNA是短ncRNA，约为22～23个核苷酸，其编码基因由RNA多聚酶Ⅱ转录，通过与mRNA 3′端非翻译区（3′ untranslated region, 3′UTR）之间的结合调控mRNA的表达，超过60%的编码基因是miRNA的潜在调控靶点[1, 10]。

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lncRNA是长度超过200个核苷酸的非编码RNA, 其生物发生过程与mRNA类似。lncRNA在细胞周期调节、染色质修饰、mRNA翻译等多种生物过程中发挥重要作用[11]。circRNA属于lncRNA, 主要由外显子或者内含子序列产生, 是一种单链环状RNA分子, 可以作为竞争性内源性RNA与miRNA结合, 调节转录或影响亲本基因表达[12]。在哺乳动物中, piRNA是一种长度约为21 ~ 35个核苷酸的小RNA, 由长单链转录本加工而成, 这些转录本的基因组位点聚集在整个基因组中, 并由RNA多聚酶Ⅱ转录。人类基因组中大约有20 000个piRNA, 主要表达于性腺细胞。piRNA通过两种方式沉默转座子: ①引导PIWI蛋白与新生转座子转录本结合, 并在目标转座子的启动子处产生抑制性染色质状态以抑制转座子的转录; ②将PIWI复合物引导至转座子的mRNA, 直接切割转录本[1, 13]。tsRNA来源于核酸酶对tRNA的酶切, 通常长度为18 ~ 40个核苷酸[14], 在调节翻译、维持mRNA的稳定性、基因沉默、逆转录等过程中发挥重要作用[15]。见图1。目前, miRNA和lncRNA对靶基因表达调控的分子机制已有较为深入的研究, 但piRNA在性腺细胞高表达的原因, 以及tsRNA分子的成熟机制仍有待进一步研究。

2　先天免疫中的PRR及其信号通路

目前已知的PRR家族包括Toll样受体(toll-like receptor, TLR)、C型凝集素样受体(C-type lectin receptor, CLR)、核苷酸结合寡聚化结构域(nucleotide-binding oligomerization domain, NOD)样受体(NOD-like receptor, NLR)、视黄酸诱导基因蛋白Ⅰ(retinoic acid-inducible gene Ⅰ, RIG-Ⅰ)样受体(RIG-Ⅰ-like receptor, RLR)、黑色素瘤缺乏因子2 (absent in melanoma 2, AIM2)样受体(AIM2-like receptor, ALR)、2′-5′寡聚腺苷酸合成酶(2′-5′oligoadenylates synthesis, OAS)样受体(OAS-like receptor, OLR)[16-17]。TLR是一个跨膜蛋白家族, 在树突状细胞、巨噬细胞、上皮细胞等细胞中表达[18]。TLR识别PAMP后, 招募下游分子, 诱导核因子-κB (nuclearfactor-kappaB, NF-κB) 、干扰素(interferon, IFN)调节因子(interferon regulatory factor, IRF)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的活化, 启动先天性免疫反应[19-20]。根据下游分子的不同, TLR信号通路有两种, 分别是髓样分化因子88(myeloid differentiation factor 88, MyD88)依赖途径和IFN-β TIR结构域衔接蛋白(TIR-domain-containing adaptor inducing interferon-β, TRIF)依赖途径。其中, MyD88依赖途径主要诱导炎性细胞因子的转录, TRIF依赖途径是TLR3和TLR4所特有的, 当TLR3和TLR4受到配体的刺激时, 会引起TRIF或TRIF相关接头分子(TRIF-related adaptor molecule, TRAM)的募集, TRIF和肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6)的相互作用导致IKKi/TANK结合激酶1(TANK-binding kinase,

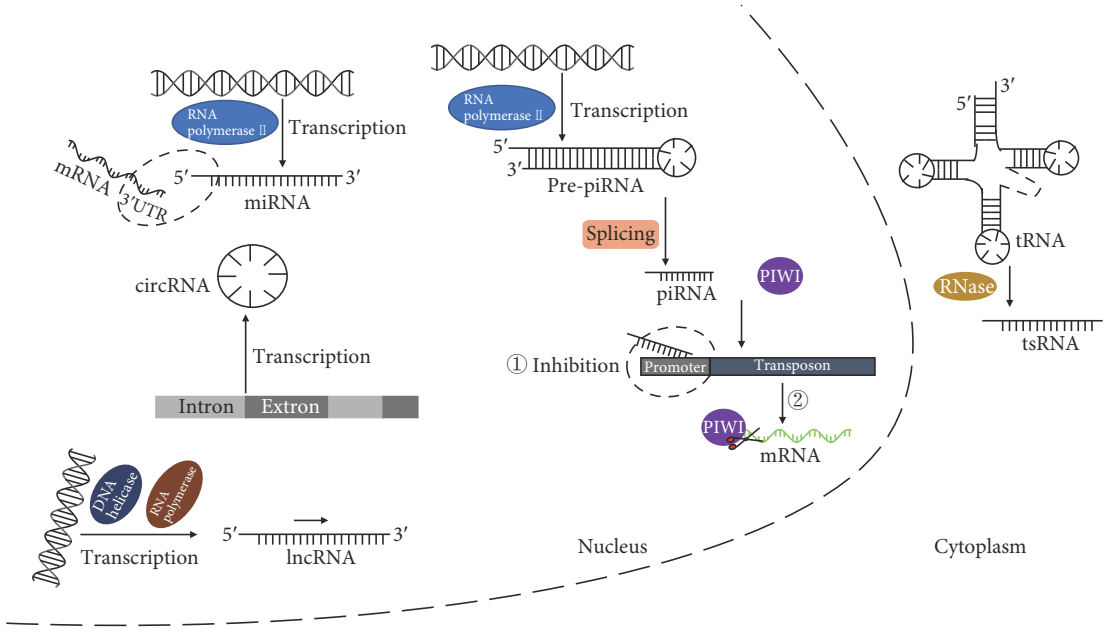

图 1　非编码RNA的生物合成

Fig 1　Biosynthesis of non-coding RNA

miRNA: MicroRNA; mRNA: Messenger RNA; circRNA: Circular RNA; lncRNA: Long non-coding RNA; piRNA: PIWI-interacting RNA; tRNA: Transfer RNA; tsRNA: Transfer RNA-derived small RNA.

TBK1)对受体相互作用蛋白-1(receptor-interacting protein, RIP-1)的泛素化。RIP-1激活转化生长因子β(transforming growth factor beta, TGF-β)活化激酶1(TGF-β-activated kinase 1, TAK1)复合物。TRIF和TRAF3的相互作用,募集TBK1和IKKi,导致干扰素调节因子3(IRF3)磷酸化形成二聚体,与细胞核中的IFN-β启动子结合,诱导干扰素表达[18]。CLR是钙依赖的碳水化合物结合蛋白,大多数CLR是跨膜蛋白,具有一个或多个碳水化合物识别结构域(carbohydrate-recognition domain, CRD)或C型凝集素样结构域(C-type lectin-like domain, CTLD),从而识别病原体表面的碳水化合物[21]。NLR是存在于细胞质中的受体,当其受到刺激时,引起NF-κB信号的激活和基因表达的改变,导致炎症复合体的形成。RLR是细胞质内RNA的感受器,是检测RNA病毒的主要PRR[22],当其与病毒RNA结合后,向线粒体抗病毒信号蛋白(mitochondrial antiviral signaling, MAVS)发出信号,以诱导IRF3和IRF7介导的Ⅰ型IFN反应[23]。ALR是细胞质中的DNA感受器,其检测细胞内的DNA后,通过内质网相关适配器干扰素基因刺激因子(stimulator of interferon genes, STING),触发STING依赖性干扰素刺激基因(interferon-stimulated genes, ISG)通路的激活[24]。OLR是一种细胞质中的核酸感受器,包括OAS蛋白和环GMP-AMP合酶(cyclic GMP-AMP synthase, cGAS),被细胞质中的双链核酸激活后,产生第二信使分子,如cGAMP,结合并激活STING,启动下游先天免疫反应[17, 25]。尽管目前对STING和MAVS等先天免疫下游信号传导途径已有较多研究,但对于先天免疫信号的起始,尤其是不同核酸感受器对不同核酸的特异性识别机制仍有待进一步研究。

先天免疫通路的各环节在转录和转录后水平受到严格的调控,其中,越来越多的研究表明ncRNA在先天免疫的调节中发挥重要作用。ncRNA可以通过多种机制调控先天免疫反应中的IRF、TRIF、RIG-I、MAVS、cGAS、STING等多种成分,从而在机体抗病毒免疫、自身免疫性疾病、肿瘤免疫等多种生理及病理过程中发挥作用(表1)。

3 ncRNA调控先天免疫反应的具体机制

3.1 miRNA对先天免疫的调节

3.1.1 miRNA对IRF的调节 IRF是一类转录因子,IRF蛋白都有一个保守的氨基末端DNA结合域(DNA-binding domain, DBD),可识别IFN基因的启动子,调节IFN的表

表 1 ncRNA调控先天免疫的机制

Table 1 Mechanism of ncRNA in regulating innate immunity

Components of innate immunity	Regulation mechanism of ncRNA
IRF	① miRNA: Directly binds to the 3′UTR of *IRF* mRNA and inhibits its expression[26]; indirectly inhibits phosphorylation of IRF[27]; inhibits the expression of upstream molecules of IRF, thereby inhibiting IRF[28]. ② lncRNA: Competitively binds to miRNA to inhibit the binding of miRNA to target gene, thereby blocking miRNA function[29]; competes with IRF3 to bind to the IFN-β promoter, interfering with the binding of IRF3 and IFN-β[30]; binds to TBK1 kinase ubiquitination adaptor OPTN and stabilizes OPTN, promoting TLR-TBK1-dependent IRF3 phosphorylation[31].
TRIF	① miRNA: Directly binds to the 3′UTR of *TRIF* mRNA and inhibits its expression[32]. ② circRNA: Interacts with miRNA as a competitive endogenous RNA of *TRIF* mRNA[32].
RIG-Ⅰ	① miRNA: Inhibits the expression of RIG-Ⅰ ubiquitination regulator TRIM25, thereby inhibiting the ubiquitination of RIG-Ⅰ[33]; targets the 3′UTR of RIG-Ⅰ encoding gene DDX58 to inhibit the expression of RIG-Ⅰ[34]; functions as ligand of RIG-Ⅰ, thereby contributing to immune enhancement[35]. ② lncRNA: Competitively binds to the CTD of RIG-Ⅰ with viral RNA and limits its protein conformational changes, leaving RIG-Ⅰ in an inactive state[36]; eliminates SFPQ's transcription inhibitory effect on RIG-Ⅰ[37].
MAVS	① miRNA: Directly binds to the 3′UTR of MAVS mRNA and inhibits its expression[38]; indirectly regulates MAVS by targeting mitochondrial transporter[39]. ② lncRNA: Competitively binds to miRNA, thereby blocking miRNA function[40].
cGAS	① miRNA: Directly binds to the 3′UTR of cGAS mRNA and inhibits its expression[41]; suppresses the mRNA level of cGAS by acting on epigenetic factors that maintain the expression of cGAS[42]. ② lncRNA: Indirectly regulates the cGAS pathway by participating in the assembly of the HDP-RNP[3].
STING	① miRNA: Directly binds to the 3′UTR of STING mRNA and inhibits its expression[43]. ② lncRNA: Indirectly regulates STING transcription through CREB[44].

ncRNA: Non-coding RNA; IRF: Interferon regulatory factor; miRNA: MicroRNA; 3′UTR: 3′ untranslated regions; lncRNA: Long non-coding RNA; IFN-β: Interferon-β; TBK1: TANK-bindingkinase; OPTN: Optineurin; TLR: Toll-like receptor; TRIF: TIR-domain-containing adaptor inducing interferon-β; circRNA: Circular RNA; RIG-Ⅰ: Retinoic acid-inducible gene Ⅰ; TRIM25: Tripartite motif-containing protein 25; CTD: C-terminal domain; SFPQ: Splicing factor proline-and glutamine-rich protein; MAVS: Mitochondrial antiviral signaling; cGAS: Cyclic GMP-AMP synthase; HDP-RNP: HEXIM1-DNA-PK-paraspeckle components-ribonu-cleoprotein complex; STING: Stimulator of interferon genes; CREB: cAMP response element-binding protein.

达[45]。研究表明, miRNA-23b、pol-miR-731、miR-146a均可直接作用于IRF mRNA的3′UTR, 降低mRNA水平, 抑制Ⅰ型IFN介导的免疫应答, 在病毒感染中, miRNA-23b、pol-miR-731表达上调, 抑制抗病毒反应[26, 46], 系统性红斑狼疮患者体内miR-146a表达下降, 与疾病的临床活动性相关[28]。miR-217-5p与核苷酸寡聚化结构域1(NOD1)的3′UTR结合抑制NOD1的表达, 间接抑制IRF3[29]。除了通过其经典的转录后调控功能发挥免疫调节作用, miRNA也可间接调节IRF, Nc886通过RIG-Ⅰ/MAVS途径间接抑制IRF3的磷酸化, 但其具体机制尚不明确[27]。见图2。因此, miRNA可通过直接或间接作用调节IRF的表达或活性, 参与机体的抗病毒反应或者先天免疫疾病的发展, 但Nc886通过RIG-Ⅰ/MAVS途径间接抑制IRF3的磷酸化的机制有待进一步研究。

3.1.2　miRNA对IFN-β TRIF的调节　IFN-β TRIF主要存在于TLR3通路中, TLR3可以直接与TRIF结合[47], 引起TBK1对IRF3的激活[48]。TLR3-TRIF通路在机体对许多病毒的先天免疫反应中发挥作用, 包括流感病毒、呼吸道合胞病毒、单纯疱疹病毒2和小鼠巨细胞病毒[49], 而miRNA可通过调节TLR3-TRIF通路调节机体抗病毒反应。miR-15a-5p可与*TRIF* mRNA的3′UTR的互补序列结合, 抑制TRIF的表达, 而源自Deltex E3泛素连接酶1(Dtx1)基因的circDtx1(一种circRNA)是TRIF的一种内源竞争RNA(competing endogenous RNA, ceRNA), 与miR-15a-5p结合并调节其表达和活性, 减弱其对TRIF的抑制作用[32]。由此可见, miRNA对TRIF的调节受到内源竞争circRNA的干扰, circRNA-miRNA-mRNA组成复杂的调控网络, 共同发挥调节先天免疫的作用。

3.1.3　miRNA对RIG-Ⅰ的调节　RIG-Ⅰ由*DDX*58编码, 主要包含两个N端半胱天冬酶激活和募集结构域(caspase activation and recruitment domain, CARD)和一个C端RNA解旋酶结构域[50], 主要检测细胞质中的双链5′–三磷酸RNA(5′-triphosphate RNA, 3pRNA)[51], 识别病毒的RNA后, RIG-Ⅰ的CARD结构域被E3连接酶TRIM25泛素化而激活, 与位于线粒体外膜上的衔接蛋白MAVS相互作用, 从而激活下游转录因子IRF3和NF-κB, 诱导Ⅰ型干扰素和促炎细胞因子的产生[50]。小鼠和人类的*DDX*58基因的3′UTR存在两个miRNA-218的结合位点, miRNA-218可直接抑制RIG-Ⅰ的转录, 从而抑制Ⅰ型干扰素的产生并促进病毒免疫逃逸[34]。miRNA-202-5p可在转录后水平抑制TRIM25的表达, 抑制RIG-Ⅰ的泛素化, 使其处于非活性状态[33]。但是, 一些miRNA被认为是RIG-Ⅰ的激动剂, 有助于增强免疫反应[52], 在前列腺癌细胞中, miR-139作为RIG-Ⅰ配体激活RIG-Ⅰ, 诱导IFN-β反应[35]。因此, miRNA通过在转录水平和转录后水平调节RIG-Ⅰ的表达水平和活性, 抑制或促进先天免疫反应。

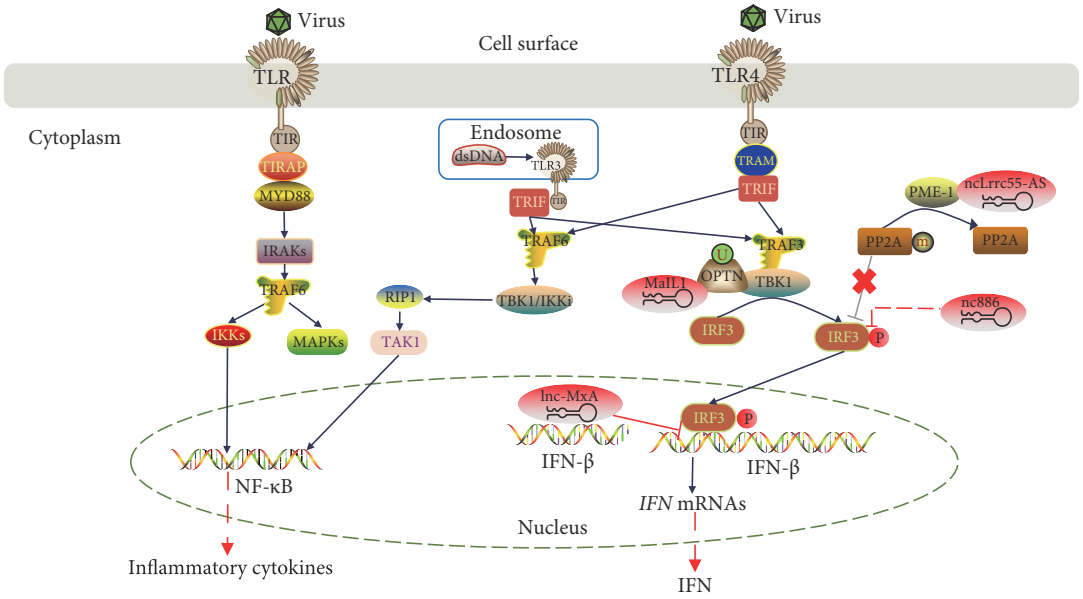

图 2　ncRNA调控IRF3

Fig 2　The regulatory mechanism of ncRNA on IRF3

TLR: Toll-like receptor; TIR: Toll/IL-1R; TIRAP: TIR domain containing adaptor protein; IRAKs: IL-1 receptor associated kinase; TRAF: Tumor necrosis factor receptor-associated factor; IKKs: Inhibitor of NF-κB kinase complex; MAPKs: Mitogen-activated protein kinases; TBK1: TANK-binding kinase 1; IKKi: Inducible IκB Kinase; RIP1: Receptor-interacting protein 1; TAK1: Transforming growth factor β-activated kinase 1; TRAM: TRIF-related adaptor molecule; TRIF: TIR-domain-containing adaptor protein inducing IFN-β; OPTN: Optineurin; IRF: Interferon regulatory factor; PP2A: Protein phosphatase 2A; IFN: Interferon.

3.1.4 miRNA对MAVS的调节 MAVS定位于线粒体外膜上,包含一个N端CARD结构域、一个脯氨酸富集区和一个C端跨膜结构域[22]。MAVS在线粒体介导的先天免疫信号通路中发挥关键作用[53]。MAVS的活性和有效性受其泛素化和去泛素化,磷酸化和去磷酸化的严格调控[22, 54]。miRNA可通过直接或间接调控MAVS的表达调节先天免疫反应。miR-3 570、miR-122、miR-125a和miR-125b、miR-22、miR-3470b与MAVS的3′UTR具有潜在互补序列,在转录后水平抑制MAVS表达,从而抑制MAVS介导的NF-κB和IRF3信号传导,抑制抗病毒反应,促进病毒的复制[38, 40, 55-58]。而miR-302b靶向线粒体转运体SLC25A12,间接调节MAVS介导的先天免疫[39]。但是,circRNA circPIKfyve作为MAVS的竞争性内源性RNA,通过吸附miR-21-3p,增强先天免疫反应。因此,miRNA对MAVS的调节同样受到circRNA的干扰。

3.1.5 miRNA对cGAS/STING信号通路的调节 双链DNA介导的cGAS的激活可催化ATP和GTP合成cGAMP,cGAMP结合并激活下游分子STING,STING二聚体招募TBK1,磷酸化并激活IRF3,最终导致Ⅰ型干扰素的表达[59]。*cGAS*和*STING*的mRNA 3′UTR存在某些miRNA的潜在结合位点[43, 60],miRNA通过与mRNA直接结合或者通过间接作用调节cGAS/STING的表达,发挥免疫抑制作用。YU等[41]研究发现miR-23a/b可以与cGAS 的mRNA的3′UTR直接结合,抑制cGAS的表达,抑制cGAS介导的先天免疫反应。miR-24[61]、miR-210[43]、miR-24-3p[60]通过靶向作用于STING的3′UTR区,调节STING的表达,从而抑制STING介导的信号通路。在缺氧条件下,miR-25和miR-93发挥间接调节作用,通过作用于维持cGAS表达的表观遗传因子NCOA3,导致*cGAS* mRNA水平下调,帮助缺氧肿瘤细胞逃避免疫反应[42]。而在硬骨鱼的抗病毒免疫反应中circSamd4a则可以通过海绵作用吸附miR-29a-3p,增强STING介导的NF-κB/IRF3信号通路[62],但是这种调节机制是否存在于其他物种体内尚不明确。

3.2 lncRNA对先天免疫的调节

3.2.1 lncRNA对IRF的调节 lncRNA可以通过海绵作用吸附miRNA,从而发挥调节作用,干扰宿主的免疫信号通路[29],也可以直接与先天免疫通路的成分结合,调节先天免疫反应。研究发现,NOD1抗菌和抗病毒相关 lncRNA NARL可竞争性结合miR-217-5p,抑制其表达和活性,发挥免疫增强作用[29],同样,ncRNA MaIL1与TBK1激酶泛素化适配器OPTN结合并稳定OPTN,促进TLR-TBK1依赖的IRF3磷酸化,发挥免疫增强作用[31](图2)。ncLrrc55-AS与磷酸酯酶甲基酯酶1(pectin methyl esterase1, PME-1)结合,促进 PME-1介导的蛋白磷酸酶PP2A(IRF3信号的抑制剂)去甲基化和失活,增强IRF3磷酸化和信号传导[63](图2)。相反,lnc-MxA直接与IFN-β启动子结合,干扰IRF3、NF-κB亚单位p65与IFN-β的结合,抑制IFN-β的转录,从而发挥免疫抑制作用[30](图2)。由此可见,不同的lncRNA可通过不同的机制调节IRF,从而发挥免疫抑制或免疫增强作用。

3.2.2 lncRNA对RIG-Ⅰ的调节 lncRNA可通过调节RIG-Ⅰ介导的信号通路在肿瘤免疫、病毒感染等疾病中发挥免疫抑制或者免疫增强作用。RNA病毒感染鼠巨噬细胞后期,lnc-Lsm3b与病毒RNA竞争性结合RIG-Ⅰ的CTD,限制其蛋白构象变化,使RIG-Ⅰ处于非活性状态,从而抑制IFN Ⅰ的产生[36]。然而由于lncRNA表达的物种特异性,在人类基因组并未找到lnc-Lsm3b同源基因[64]。在人类lncRNA中,lncATV在病毒感染后表达上调,对RIG-Ⅰ介导的抗病毒先天免疫发挥负向调控作用[64]。汉坦病毒感染后,lncRNA NEAT1的转录增加,NEAT1通过将富含脯氨酸和谷氨酰胺的剪切因子SFPQ重新定位到细胞核中的亚结构小体paraspeckles,消除SFPQ对RIG-Ⅰ、DDX60分子的转录抑制效应,从而促进IFN-β介导的先天免疫[37]。所以,lncRNA对RIG-Ⅰ的调节可能存在物种特异性,在不同的物种中可能存在不同的机制。

3.2.3 lncRNA对MAVS的调节 lncRNA可作为miRNA的内源竞争RNA(ceRNA)或者通过干扰线粒体稳态,抑制MAVS的活化,调节先天免疫。MAVS抗病毒相关lncRNA(MARL)作为miR-122的内源竞争RNA,直接与miR-122结合,抑制其活性及表达水平,以促进MAVS蛋白表达,从而抑制病毒的复制并促进抗病毒反应[40]。然而lncRNA调节MAVS的研究相对较少,是否存在其他lncRNA通过干扰miRNA和MAVS的结合来调控先天免疫反应,以及是否存在通过调节MAVS从而抑制先天免疫的lncRNA,有待进一步研究。

3.2.4 lncRNA对cGAS/STING信号通路的调节 cGAS/STING信号通路刺激Ⅰ型干扰素和炎症细胞因子的表达,在DNA诱导的先天免疫中发挥重要作用。研究表明,HDP-RNP复合物可调控DNA刺激的先天免疫反应中cGAMP的合成,从而影响cGAMP介导的*IFN-β* mRNA水平,而lncRNA NEAT1是HDP-RNP组装所必需的[3],因此NEAT1可间接调节cGAS通路。lncRNA *MALAT1*基因敲除抑制高氧诱导的肺上皮细胞中STING的表达及其转录启动子活性,机制研究发现,*MALAT1*沉默后,cAMP反应元件结合蛋白(cAMP response element-binding protein, CREB)的mRNA表达水平和结合STING启动子的能力下

降, 从而抑制STING的转录, 因此MALAT1通过MALAT1-CREB信号通路促进STING的转录[44]。circRNA属于lncRNA, XIA等[65]发现了一种circRNA cia-cGAS, 在稳态条件下结合到cGAS, 阻断其合成酶活性, 抑制cGAS介导的造血干细胞中Ⅰ型IFN的产生, 从而维持机体的稳态。以上研究表明, lncRNA在cGAS/STING信号通路中可通过不同的机制发挥正向及负向调节作用, lncRNA对cGAS/STING信号通路的调节是一个复杂的过程。

4　总结及展望

先天免疫反应在宿主防御功能及启动适应性免疫中发挥重要作用, 免疫稳态的维持依赖于精确的调控机制[8], 越来越多的研究表明ncRNA参与先天免疫反应的调节。病毒感染过程中, 诱导宿主基因表达的改变, 包括ncRNA的改变。自身免疫性疾病患者体内, 某些ncRNA表达水平的变化也与疾病的发展相关[28]。其中, miRNA和lncRNA在先天免疫中的调节作用已经有广泛的研究。一般情况下, miRNA与mRNA的3′UTR直接结合, 调节先天免疫通路中相关蛋白的表达, 而lncRNA通常作为内源竞争RNA, 阻止miRNA和mRNA的结合, 发挥调控先天免疫的作用。然而, 也有部分lncRNA可以直接与先天免疫通路的成分结合[30, 36]或者通过调节线粒体发挥调节先天免疫的作用, 而且, lncRNA的表达存在物种特异性, 一些保守的lncRNA在加工、定位和功能上也不保守, 使得lncRNA的研究更加复杂[64]。另外, 也有研究表明circRNA也参与先天免疫的调节[32], 参与免疫相关疾病的发生[6], circRNA-miRNA-mRNA组成复杂的调控网络, 共同调节先天免疫[66]。因此ncRNA可以通过多种机制调控先天免疫反应, 其复杂的调控网络有待进一步研究, 从而为先天免疫相关疾病的诊断和治疗提供新的思路。

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利益冲突　所有作者均声明不存在利益冲突

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