综述

刘星，博士，中国科学院上海免疫与感染研究所研究员、博士生导师，国家重点研发计划蛋白质机器专项青年项目首席。一直从事病原体感染引起的机体免疫应答调控机制研究，探索病原微生物致病机理以及宿主细胞抵御病原体入侵的关键免疫规律，旨在为相关感染性疾病如脓毒症、自身免疫性疾病的精准治疗提供新的药物靶点和治疗策略。已发表高水平SCI学术论文40余篇，累计影响因子>900；他引9 000余次；近五年关键研究成果以通讯或共同通讯作者身份发表于*Nature*、*Science*、*Immunity*、*Nat Immunol*、*Proc Natl Acad Sci USA*、*Nat Rev Drug Discov*、*Ann Rev Immunol*等知名学术期刊。刘星博士曾获中国细胞生物学学会青年科学家奖、上海市青年科技启明星、哈佛大学杰出华人生命医学学术奖、美国免疫学会青年科学家奖等荣誉。

RNA与炎性免疫反应

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摘要：RNA是构成生命的基础性大分子，既能作为遗传信息的中间载体调控蛋白质的表达，也能作为信号分子参与调节生物体中各种生理过程以及机体对外界刺激的响应。在机体免疫系统中，RNA扮演的角色十分重要，编码RNA调控多种免疫功能相关蛋白的表达，非编码RNA能够影响免疫通路信号传递，同时RNA能作为配体激活特定受体并起始炎性免疫反应。本文以RNA在免疫与炎症反应中发挥的作用为主题，讨论不同类型RNA及其代谢过程调控和影响机体稳态与病原感染过程中各种免疫信号的机制，同时介绍RNA作为配体激活的免疫反应以及RNA相关的炎症反应和自身免疫疾病。

关键词：核糖核酸；炎症；免疫反应；自身免疫疾病

RNA and inflammatory immune response

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Abstract: RNA, a fundamental macromolecule essential for life, not only regulates protein expression as an intermediary carrier of genetic information but also functions as a signal molecule involved in various physiological and pathological processes and responses to external stimuli. RNA plays a crucial role in the immune system, with coding RNA controlling the expression of numerous proteins related to immune function and non-coding RNA affecting signal transduction in immune pathways. RNA also acts as a ligand to activate specific receptors and initiate immune responses. This review focuses on the role of RNA in immune and

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inflammatory responses, discussing the regulatory mechanisms of different types of RNA and their metabolic processes in various immune signals during physiological homeostasis and pathogenic infection. We also highlight the immune responses directly activated by RNA, as well as RNA-related inflammatory responses and autoimmune diseases.

Key Words：RNA; inflammation; immune response; auto-immune diseases

核糖核酸(ribonucleic acid，RNA)是生物体中非常重要的大分子，根据结构和功能分为编码RNA和非编码RNA(non-coding RNA，ncRNA)。编码RNA主要指信使RNA(messenger RNA，mRNA)，在机体中占比超过90%，ncRNA包括核糖体RNA(ribosomal RNA，rRNA)、转运RNA(transfer RNA，tRNA)、核小RNA(small nuclear RNA，snRNA)、核仁小RNA(small nucleolar RNA，snoRNA)、微RNA(microRNA，miRNA)和长非编码RNA(long non-coding RNA，lncRNA)等。蛋白质翻译过程中，rRNA参与组成的核糖体以mRNA为模板，通过tRNA转运氨基酸引导肽链组装。非编码RNA从基因组转录后不作为模板合成蛋白质，但同样在越来越多生理过程中展现新的重要作用。目前生物体内相当比例RNA的功能尚未明确，发掘RNA新的功能机制有助于促进对生物体内生理和病理过程的理解，并为RNA相关疾病提供更多的治疗策略。

炎性免疫应答是机体在病原感染或组织损伤后的生理性免疫反应，机体通过炎性免疫应答释放危险信号引导自身进入自我保护状态，促进病原的清除和损伤组织的更新。当免疫系统紊乱时，炎性免疫应答的抑制不利于机体清除入侵的病原体及组织修复，而炎症反应的过度激活会诱发炎性疾病。

RNA是免疫系统的重要组成部分，炎性反应往往伴随着免疫信号通路中关键蛋白的mRNA水平上调。同时，RNA作为多种感受器的配体，能够通过激活核因子-κB(nuclear factor kappa-B，NF-κB)信号通路和细胞焦亡等途径引起炎症反应。因此，RNA的代谢与稳态在机体生理过程和病理过程中具有举足轻重的作用。

1 RNA代谢

在经典的中心法则理论中，蛋白质是各项生命活动的主要执行分子，RNA通过控制蛋白质的翻译调控各项生理过程。实际上整个RNA代谢过程，包括RNA的转录合成、剪接、修饰和降解过程对多种生理及病理过程都具有重要的调控作用。

1.1 RNA转录合成

真核生物绝大多数RNA的转录由DNA依赖的RNA聚合酶Ⅰ、Ⅱ、Ⅲ完成[1]。其中，RNA聚合酶Ⅰ专职合成rRNA，RNA聚合酶Ⅱ合成mRNA和ncRNA，RNA聚合酶Ⅲ合成tRNA、snRNA以及5S rRNA等小片段RNA[2]。RNA聚合酶Ⅰ在核仁起始rRNA的合成，RNA聚合酶Ⅱ主要在细胞核内行使功能，并在新的研究中被发现在核仁外周参与调控rRNA的生物合成[3,4]。RNA聚合酶Ⅲ除在核内发挥转录功能外，还在胞质内参与调控天然免疫反应，其能检测胞质内的DNA类似物poly(dA:dT)并将其转录成RNA，进而激活视黄酸诱导基因蛋白-Ⅰ(retinoic acid inducible gene protein Ⅰ，RIG-Ⅰ)依赖的信号通路，诱导1型干扰素(type Ⅰ interferon，type Ⅰ IFN)的产生[5,6]。不同基因转录过程在多种转录因子的协同调控下影响生物过程。例如，中性粒细胞在不同发育阶段、激活状态和组织微环境下体现出不同的基因表达模式[7]。在实验性自身免疫性脑脊髓炎小鼠模型中，转录因子干扰素调节因子8(interferon regulatory factor 8，*IRF8*)敲除小鼠相较于野生型小鼠显著抵抗实验诱导的自身免疫反应[8]。DNA拓扑异构酶1(DNA topoisomerase 1，TOP1)正向调控RNA聚合酶Ⅱ介导的转录，而*TOP1*缺失能够帮助小鼠抵抗病原感染引起的致死炎症[9]。

1.2 RNA剪接

mRNA在转录合成后通过选择性剪接去除内含子，并连接外显子形成连续编码蛋白质的成熟序列。细胞核内的剪接体通过识别内含子末端的保

守序列从而精确调控剪接过程，在不同组织和不同发育时期，同一基因转录合成的mRNA通过选择性剪接途径翻译产生差异化的蛋白质亚型(isoform)以适应不同功能需要，使基因表达具有丰富的多样性。因此，RNA的选择性剪接影响蛋白质的结构、定位、功能以及与其他生物大分子的互作，对机体组织分化、器官发育和系统功能具有重要生理意义。

此外，多种疾病与mRNA选择性剪接相关。RNA剪接方式改变或异常可导致编码蛋白质序列或结构的改变，从而影响蛋白质的正常功能，引起细胞、器官病理性反应。已有研究显示，RNA选择性剪接异常引起多种肿瘤相关基因表达显著上调，促进肿瘤发展，同时与肌萎缩性侧索硬化症、阿兹海默症(Alzheimer's disease，AD)等神经性疾病和系统性红斑狼疮(systemic lupus erythematosus，SLE)、类风湿性关节炎等常见自身免疫病有关[10-12]。例如，神经细胞中的异质性核糖核蛋白A1(hnRNP A1)功能紊乱可导致RNA剪接过程的变化，引起多发性硬化症(multiple sclerosis，MS)中的神经变性[13]。在胰腺导管腺癌中，丝氨酸/精氨酸富集剪接因子1(serine/arginine-rich splicing factor 1，SRSF1)通过选择性剪接调控mRNA稳定性，上调白介素-1(interleukin-1，IL-1)和丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)信号，加速胰腺炎及肿瘤的发生[14]。干扰素α(interferon α，IFNα)促进胰岛B细胞中人白细胞抗原Ⅰ类分子(human leucocyte antigen Ⅰ，HLA-Ⅰ)、抗原呈递相关基因和趋化因子的表达，同时通过选择性剪接影响胰岛B细胞新抗原的产生，这些过程受到核苷酸结合寡聚结构域(nucleotide-binding oligomerization domain，NOD)样受体家族半胱-天冬氨酸蛋白酶募集结构域(caspase recruitment domain，CARD)相关蛋白5(NOD-like receptor family CARD domain containing 5，NLRC5)的调控，在1型糖尿病中发挥重要作用[15]。调控RNA剪接的DExD-框解旋酶39B(DExD-box helicase 39B，DDX39B)发生突变能够使白介素7受体(interleukin-7 receptor，IL-7R) mRNA剪接产生可溶的IL-7R(soluble form of IL-7R，sIL-7R)，增加MS疾病风险[16]。DDX39B同时调控转录因子叉头框蛋白P3(forkhead box protein P3，FOXP3)的mRNA剪接，进而控制调节性T细胞功能与发育[17]。在白血病发生过程中，异柠檬酸脱氢酶(isocitrate dehydrogenase，IDH)、SRSF2和整合因子复合物亚基3(integrator complex subunit 3，INTS3)的mRNA剪接异常会促进髓系肿瘤的发生[18]。

1.3 RNA修饰

常见的RNA修饰包括甲基化、乙酰化、尿苷化和腺苷转换肌苷编辑等。动态变化的RNA修饰影响RNA加工、翻译和降解等多种生物过程，对RNA行使生物功能非常关键。

N6-腺苷酸甲基化(N6-methyladenosine，m6A)是RNA中最丰富的修饰，调控许多生物过程中的基因表达[19]。绝大多数m6A修饰发生在rRNA上，而mRNA的m6A修饰主要发生在3′非翻译区(untranslated regions，UTR)和终止密码子区域[20]。甲基转移酶样蛋白3(methyltransferase-like 3，METTL3)和METTL14组成异二聚体介导mRNA转录后的添加m6A修饰[21-23]。锌指含CCHC结构域蛋白4(zinc finger CCHC-type containing 4，ZCCHC4)和METTL5主要在rRNA上产生m6A修饰，另外，METTL16负责snRNA上的m6A甲基化[24-26]。脂肪量和肥胖相关蛋白(fat mass and obesity-associated protein，FTO)和ALKB同源蛋白5(alkB homolog 5，ALKBH5)则是主要的mRNA去甲基化酶[27,28]。RNA的去甲基化过程在系统发育和肿瘤发展过程中具有重要作用[29-31]。YTH(YT521-B homology)家族蛋白是读取m6A修饰的重要成员[32]。其中，含YTH结构域蛋白1(YTH domain containing 1，YTHDC1)在核内读取m6A修饰以调控mRNA选择性剪接与出核等过程[33,34]。YTHDC2主要在睾丸中表达，识别m6A修饰并影响蛋白质翻译，YTHDC2失活会导致精子产生过程的缺陷[35]。YTH结构域家族蛋白1和3(YTH domain family protein 1/3，YTHDF1/3)在胞质读取m6A修饰后，引导真核转录3(eukaryotic translation initiation factor 3，eIF3)复合物开始翻译过程[36,37]。而YTHDF2/3读取m6A修饰介导mRNA降解[37,38]。除YTH家族外，胰岛素样生长因子2 mRNA结合蛋白1、2和3(insulin like growth factor 2 mRNA binding protein 1/2/3，IGF2BP1/2/3)与脆性X智力低下蛋白(fragile X mental retardation

protein，FMRP)读取m6A修饰并提高mRNA的稳定性[39,40]。此外，RNA上其他位置的RNA甲基化修饰还发挥了不同的功能，如5-胞嘧啶甲基化(5-methylcytosine，m5C)修饰调控tRNA和rRNA的结构和稳定性，1-腺苷酸甲基化(1-methyladenosine，m1A)修饰影响RNA的碱基配对，7-鸟苷酸甲基化(7-methylguanosine，m7G)修饰调控mRNA的加帽过程[41-44]。

RNA修饰可通过调控免疫细胞中炎症信号相关基因的表达，影响病理和感染过程中的免疫反应[45-48]。研究者比对SLE患者和健康人体内的RNA修饰发现，患者总体m5C和4-胞嘧啶乙酰化(N4-acetyldeoxycytosine，ac4C)比健康人修饰水平有所降低，但是患者的白细胞分化抗原4阳性(cluster of differentiation 4^+，$CD4^+$) T细胞中，mRNA上翻译起始位点的m5C修饰增多，编码序列上ac4C修饰增多，并且可以观察到多种炎症因子和干扰素等炎症反应基因表达水平显著上调[49,50]。巨噬细胞在病毒感染过程中会通过降低去甲基化酶ALKBH5的表达而增强m6A修饰，降低病毒复制需要的亚甲基丁二酸相关酶的表达量，从代谢上发挥不依赖IFN通路的抗病毒作用[51]。树突状细胞(dendritic cell，DC)中，METTL3在CD40、CD80和Toll样受体4(Toll-like receptor 4，TLR4)信号通路中的接头蛋白TIRAP(TIR domain-containing adaptor protein)的mRNA上添加m6A修饰以增强相应基因的表达，并促进NF-κB信号通路的活化[52]。YTHDF1能够读取m6A修饰以增强溶酶体内组织蛋白酶的表达，该基因缺陷会导致组织蛋白酶表达降低，并显著提高DC细胞交叉提呈肿瘤抗原和对$CD8^+$ T细胞的交叉致敏的能力[53]。在肿瘤浸润的自然杀伤细胞(natural killer cell，NK cell)中，METTL3表达量显著下降，METTL3或YTHDF2的缺失阻断m6A调控的免疫信号，严重影响NK细胞的功能，被炎症因子、肿瘤或巨细胞病毒感染活化的NK细胞中YTHDF2显著上调，显示了m6A修饰在NK细胞抗肿瘤和抗病毒过程中的重要作用[54,55]。

病毒来源RNA上的修饰同样调控宿主病原相互作用。在巨噬细胞中，人类免疫缺陷病毒-1(human immunodeficiency virus-1，HIV-1)来源的RNA能够通过m6A修饰逃逸RIG-Ⅰ的识别[56]。水疱性口炎病毒(vesicular stomatitis virus，VSV)借助宿主细胞内的METTL3进行m6A修饰并减少双链RNA(double-stranded RNA，dsRNA)的产生，从而规避RIG-Ⅰ和黑色素瘤分化基因5(melanoma differentiation gene 5，MDA5)介导的抗病毒反应[57]。

1.4 RNA降解

成熟的mRNA在去除5′加帽结构和3′poly(A)结构后暴露两端并进入降解过程。RNA脱帽酶1和2x(decapping enzyme 1/2x，DCP1/2x)形成复合物后去除mRNA的5′加帽结构，由5′-3′核酸外切酶1(exoribonuclease-1，XRN1)识别RNA裸露的末端并开始降解过程[58]。poly(A)特异性核酸酶[poly(A) specific ribonuclease，PAN] 2和3形成的复合物以及碳分解代谢物阻遏蛋白4(carbon catabolite repressed 4，CCR4)和不含TATA框转录因子抑制蛋白(negative on TATA-less，NOT)形成的复合物开始去腺苷酸化过程，以截短poly(A)尾状结构，为RNA外切体开始沿3′-5′方向降解RNA提供空间[59]。此外，核酸内切酶也可以直接剪切RNA并触发双向降解过程[60]。

RNA的降解过程会影响免疫细胞中炎症基因的表达和相关通路的激活水平。在巨噬细胞中，TLRs受体识别对应配体后，激活NF-κB信号通路，上调多种炎症因子的表达水平，同时被诱导上调的RNA酶Zc3h12a通过介导炎症因子IL-6的mRNA降解控制免疫反应，避免免疫紊乱[61]。*Zc3h12a*缺失的巨噬细胞在TLR配体刺激后分泌的IL-6和IL-12b比野生型细胞显著提高，心肌细胞中*Zc3h12a*的缺失同样上调IL-6表达量并引起严重心肌病[61,62]。此外，*Zc3h12a*缺失小鼠会发生严重贫血，血清免疫球蛋白和自身抗体显著上调，并表现出过度炎症反应导致的自身免疫病症状[61]。与之对应的NF-κB激活因子1(nuclear factor NF-kappa-B activator 1，ACT1)结合CXC蛋白趋化因子1(C-X-C motif chemokine ligand 1，CXCL1) mRNA的3′UTR发挥稳定作用，抑制mRNA降解过程，增强mRNA翻译和IL-17介导的皮肤炎症和气道炎症[63]。

2 NcRNA

2.1 miRNA

miRNA是长度约为22 nt的转录产物，多数

miRNA由非编码转录本或内含子产生[64,65]。在经典miRNA合成途径中，由RNA聚合酶Ⅱ在细胞核内合成的初级miRNA被Drosha-DiGeorge氏综合征相关蛋白8复合物(Drosha-DiGeorge syndrome critical region 8，Drosha-DGCR8)切割成为前体，然后被输出蛋白Exportin-5运送到胞质内[66-71]。前体miRNA经过RNA内切酶Dicer切去环状结构并脱去随从链后介导形成沉默复合物(RNA-induced silencing complex，RISC)[72-74]。RISC在miRNA的引导下靶向目标RNA，经过含三核苷酸重复序列接头蛋白6(trinucleotide repeat containing adaptor 6，TNRC6)招募胞质poly(A)结合蛋白1[poly(A) binding protein cytoplasmic 1，PABPC1]蛋白到目标mRNA上[75,76]。在PAN2-PAN3和CCR4-NOT复合物的作用下，mRNA转录受到抑制，稳定性下降并触发降解过程，该过程被称为RNA干扰(RNA interference，RNAi)[77-79]。在免疫细胞发育、分化、发挥功能的过程中，miRNA具有重要调控作用[80-85]。如TLR信号通路可调控部分miRNA的表达水平，同时miRNA能够靶向TLR通路中的关键组分[86]。除RNAi之外，miRNA能够诱导免疫细胞分泌多种炎症因子，并且减轻自身免疫性糖尿病模型小鼠的症状[87]。

miRNA参与维持机体的发育和系统的稳定运行，miRNA缺陷与多种自身免疫疾病和肿瘤免疫相关。这些疾病常伴随DNA高度甲基化、IFN通路高度活化、炎症因子高度表达等特征。风湿性疾病是典型的慢性炎症失调疾病，包括类风湿性关节炎、骨关节炎和骨质疏松等，miRNA调控这些疾病患者体内免疫细胞和肌肉骨骼细胞中的多种生物进程[88]。多种miRNA在风湿性疾病中分别发挥抗炎和促炎的功能，miRNA表达的变化会影响炎症反应和关节疼痛[89-92]。SLE、MS等疾病也与特定miRNA的异常表达有关[93-95]。miRNA还参与调控免疫系统在病理或病原感染过程中的免疫反应。在过敏原引起的哮喘中，miR-24和miR-27抑制T细胞的敏感性，这些miRNA的缺失会导致免疫系统高度活化及组织病变[96]。在假单胞菌感染角膜的过程中，miR-183/96/182的表达水平下降显著提高了宿主清除病原的能力[97]。

2.2 lncRNA

lncRNA主要通过RNA聚合酶Ⅱ转录产生，也可由内含子加工后产生[98]。绝大多数lncRNA在表达上受到严格调控，部分lncRNA具有小片段编码区域，其编码的小肽段发挥特有的生理调控作用。lncRNA在肌肉、大脑等多种组织器官中广泛存在，在多种细胞如神经细胞和免疫细胞中普遍表达，在胞质和细胞核内都有分布，不同lncRNA在时间和空间上具有高度特异性[99-103]。lncRNA在维持染色质构造中具有重要作用，参与调控RNA剪接、降解和蛋白质翻译等过程[104-106]。

在免疫系统中，lncRNA参与维持机体正常功能，能够动态调控宿主在病理条件下的炎症反应。在训练免疫中，免疫相关基因启动子上的组蛋白(histone) H3第四位赖氨酸三甲基化(H3K4me3)的水平与该基因表达水平呈正相关[107]。一系列lncRNA通过增强H3K4me3修饰促进炎症反应[108,109]。在机体发生炎症反应时，多种lncRNA的表达发生变化。例如，lncRNA *GAPLINC*在炎症反应中迅速下调，*GAPLINC*缺失会提高NF-κB通路本底激活水平，显著增强炎症基因的表达并帮助小鼠抵抗脂多糖(lipopolysaccharide，LPS)诱导的休克[110]。LPS诱导表达的lncRNA *Mirt2*减弱肿瘤坏死因子受体关联因子6(tumor necrosis factor receptor-associated factor 6，TRAF6)的K63泛素化，抑制NF-κB和MAPK信号通路的活化和炎症因子的释放，并作为免疫负调控因子在内毒素血症小鼠模型中具有显著保护作用[111]。巨噬细胞中的lncRNA *lincRNA-EPS*通过调控核小体的定位抑制免疫反应相关基因的表达，当细胞受到病原来源的配体刺激后其表达下调，促进TLR4依赖的炎症反应[112]。

大量lncRNA在炎症相关疾病中发挥重要功能。lncRNA *PSMB8-AS1*诱导单核细胞和巨噬细胞对内皮细胞的黏附，促进血管炎症反应和动脉粥样硬化，而另一lncRNA *MALAT1*表达降低时具有类似的生理作用[113,114]。人血管平滑肌细胞中特定表达的lncRNA *INKILN*在细胞分化后下调，并在炎性刺激后依赖NF-κB通路上调。人动脉粥样硬化和腹主动脉瘤中*INKILN*的表达显著上调，并进一步提高促炎基因的表达水平，*INKILN*缺失则有效抑制炎症反应[115]。lncRNA *Neat1*在巨噬细胞中辅助NOD样受体家族热蛋白结构域相关蛋白3(NOD-like receptor family pyrin domain-containing protein

3，NLRP3)、NLRC4和黑色素瘤缺乏因子2(absent in melanoma 2，AIM2)炎症小体的激活，同时增强caspase-1的活性。小鼠中敲除*Neat1*显著降低了NLRP3和NLRC4活化引起的机体炎症反应，因此*Neat1*可作为炎症小体过度激活相关疾病的治疗靶点[116]。在结肠炎中，lncRNA *NAIL*通过抑制p38激酶和NF-κB亚基p65的共同负调控因子蛋白磷酸酶1D(protein phosphatase 1D，PPM1D)，促进骨髓细胞分化成巨噬细胞并向炎症区域聚集[117]。lncRNA缺陷也会导致机体炎症反应失调。结肠组织髓细胞中的lncRNA *HOXA11os*与线粒体中电子传递链复合体Ⅰ结合并维持其活性，*HOXA11os*缺陷会导致线粒体功能障碍，诱导胞内活性氧(reactive oxygen species，ROS)水平上调，加速结肠炎进程[118]。自身免疫病中的lncRNA具有显著的疾病调控作用。lncRNA *MIR155HG*编码的微肽能够调节DC细胞向T细胞提呈抗原的过程，减缓DC细胞活化介导的银屑病样皮肤炎症和中枢神经系统中的自身免疫反应[119]。

3 RNA模式识别受体

RNA在多种生物功能中起着至关重要的作用，为了维持正常的生理过程，宿主自身RNA代谢受到严格调控。同时，来自入侵病原体(如RNA病毒)的外来RNA会引发免疫反应。细胞内具有一系列负责识别RNA的模式识别受体(pattern recognition receptors，PRRs)。RNA识别过程异常会导致免疫缺陷或自身免疫性疾病。

3.1 NOD样受体

胞质内的NOD样受体(NOD-like receptors，NLRs)负责识别分布在胞质内的病原相关分子模式(pathogen-associated molecular patterns，PAMPs)和损伤相关分子模式(damage-associated molecular patterns，DAMPs)。近年来，NLRs识别的配体不断被报道，NLRs激活的免疫反应在感染性疾病和自身免疫性疾病中发挥重要作用。

NLRP1炎症小体最早被发现能够调控巨噬细胞对炭疽杆菌致死毒素的易感性[120]。在之后的研究中，研究者发现，正链RNA病毒——塞姆利基森林病毒(Semliki forest virus，SFV)能够激活NLRP1炎症小体[121]。SFV在胞质复制过程中产生的dsRNA或者直接向胞内递送的长dsRNA都能够与NLRP1的富含亮氨酸的重复序列(leucine-rich repeat，LRR)结构域结合并导致NLRP1活化[121]。有趣的是，dsRNA仅能活化人源皮肤细胞系中的NLRP1，而不能激活啮齿类动物体内同源蛋白NLRP1b，其中的机制还有待深入研究[121]。

dsRNA还能够与NLRP6的多赖氨酸区域结合，这一现象在体外实验和细胞中都得到了证实，被dsRNA激活后的NLRP6发生液-液相分离(lipid-lipid phase separation，LLPS)并激活下游信号通路[122]。NLRP6识别dsRNA的过程在宿主抵抗鼠肝炎病毒和轮状病毒感染过程中发挥关键作用[122]。后续的研究进一步解析了NLRP6在机体中响应dsRNA刺激传导下游信号的机制：NLRP6一方面通过DEAH-框解旋酶15(DEAH-box helicase 15，DHX15)-线粒体抗病毒接头蛋白(mitochondrial antiviral signaling protein，MAVS)依赖的IRF3信号通路产生IFN抑制病毒复制，另一方面通过胱天蛋白募集域的凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a caspase-recruitment domain，ASC)-caspase1-GSDMD(gasdermin D)依赖的细胞焦亡通路造成组织损伤[123]。

与主要表达在小肠近端上皮细胞的NLRP6不同，NLRP9b表达在小肠远端上皮细胞。NLRP9b炎症小体依赖RNA解旋酶DHX9识别dsRNA并诱导细胞焦亡，有效抑制轮状病毒复制[124]。

3.2 Toll样受体

Toll样受体是识别病原入侵产生的PAMPs的重要受体。TLRs具有一个结合特定配体的胞外域、一个帮助锚定在质膜上的跨膜结构域和一个胞质内传导下游信号的Toll/白细胞介素1受体(Toll/IL1 receptor，TIR)结构域。

TLR3在病毒感染过程中识别dsRNA并介导NF-κB信号通路的激活及IFN-Ⅰ的产生[125]。*TLR3*缺失能够阻断病毒dsRNA或poly(I:C)刺激引起的免疫反应[125]。在机体代谢中，TLR3能够识别自身dsRNA结构。在基因转录时，RNA与模板链DNA互补结合，形成DNA-RNA双链杂交体，与非模板链一起产生R-loop结构。Wiskott-Aldrich综合征(Wiskott-Aldrich syndrome，WAS)蛋白(WASp)缺失或突变会导致R-loop增多，引起DNA损伤，同时影响mRNA

剪接，在免疫缺陷和自身免疫疾病中具有重要作用[126]。细胞内R-loop代谢失调后经核酸内切酶G组和F组着色性干皮病偶联因子(xeroderma pigmentosum group G/F，XPG/XPF)切割产生DNA-RNA杂交体并发生积累，同时激活环GMP-AMP合酶(cyclic GMP-AMP synthase，cGAS)和TLR3及下游IRF3信号通路并引起细胞凋亡，引发Aicardi-Goutières综合征(Aicardi-Goutières syndrome，AGS)[127]。

单链RNA(single-stranded RNA，ssRNA)同样能够刺激免疫细胞增加IFN和炎症因子的表达和分泌[128,129]。有报道证明，TLR7能够识别内体中流感病毒的基因组RNA和体外合成的ssRNA[128]。研究人员还发现，鼠源TLR7和人源TLR8负责识别来自HIV-1的富含GU序列的ssRNA，鼠源TLR8却缺少人源TLR8中识别ssRNA关键的五个氨基酸，因而不具备同样的识别功能[129,130]。值得注意的是，RNA上的各种修饰包括m6A、m5C、5-尿嘧啶甲基化(5-methyluridine，m5U)等都能够抑制DC等细胞中TLR3/7/8的活化[131]。部分病毒感染过程中会还产生DNA-RNA杂交体，能够直接激活DC中的TLR9并诱导免疫反应[132]。

TLR3/7/8识别RNA在宿主抗病毒和抗肿瘤过程中发挥着重要作用。由呼吸道上皮细胞中的TLR3和浆细胞样树突状细胞(plasmacytoid dendritic cell，pDC)中的TLR7介导的IFN-Ⅰ免疫反应对于宿主抵御流感病毒或新冠病毒非常关键，IFN-Ⅰ先天性缺陷可能导致病毒在肺部的迅速扩散并引发系统性炎症[133-135]。此外，前列腺细胞能够持续地表达瞬时受体电位阳离子通道亚家族M成员8(transient receptor potential cation channel subfamily M member 8，TRPM8)的RNA，并通过外泌体释放到胞外，进而激活TLR3-NF-κB炎症信号，在前列腺移植肿瘤中招募更多NK细胞浸润，扩大坏死区域，促进抗肿瘤免疫[136]。

3.3 RIG-Ⅰ样受体

RIG-Ⅰ样受体(RIG-Ⅰ-like receptors，RLRs)是一类胞内RNA感受器，包括RIG-Ⅰ、MDA5和遗传学和生理学实验室蛋白2(laboratory of genetics and physiology 2，LGP2)。三个蛋白质都具有相似的解旋酶结构域和C端结构，RIG-Ⅰ和MDA5的N端有两个CARD结构域介导与下游接头蛋白MAVS的相互作用。MAVS进一步激活TANK结合激酶1(TANK-binding kinase 1，TBK1)以及NF-κB信号通路。

最早发现的解旋酶RIG-Ⅰ参与病毒RNA的检测与清除过程，其解旋酶结构域负责感知胞内的dsRNA，而CARD结构域传递信号激活NF-κB和IRF3信号通路[137]。MDA5同样能够在dsRNA进入胞质后促进IFN信号活化。最初的报道中人们发现，猴病毒、人副流感病毒、腮腺炎病毒、仙台病毒和亨德拉病毒的V蛋白能够通过结合MDA5抑制IFN的产生[138]。接下来的研究进一步在小鼠模型上比较了RIG-Ⅰ和MDA5在多种RNA病毒入侵过程中对抗感染反应的调控作用[139]。RIG-Ⅰ和MDA5识别的RNA有所不同，二者分别识别体外转录的RNA和poly(I:C)，另外，RIG-Ⅰ识别副黏病毒、流感病毒和日本脑炎病毒的RNA而MDA5识别小核糖核酸病毒的RNA[139]。LGP2是与RIG-Ⅰ和MDA5同源的解旋酶，LGP2能够结合dsRNA，但由于缺少信号传递的结构域无法激活下游信号。事实上，LGP2在dsRNA识别过程中通过影响RIG-Ⅰ和MDA5扮演双重角色。外源表达LGP2能够从RIG-Ⅰ剥离dsRNA从而阻断仙台病毒和新城疫病毒引起的IFN应答[140]。*LGP2*缺失小鼠中dsRNA对RIG-Ⅰ的激活水平显著提高[141]。与之相反的是，LGP2能够调节MDA5与dsRNA的结合作用并增强MDA5对下游信号的活化[141,142]。

4 RNA与细胞焦亡

细胞焦亡是一种炎性程序性细胞死亡，其主要特征为细胞的裂解，并伴随着大量炎症因子和DAMPs释放到胞外，继续放大炎症反应[143]。GSDM家族蛋白是细胞焦亡的直接执行者，GSDM能够被多种蛋白酶剪切并释放N端片段，靶向细胞膜并形成孔洞导致细胞破裂，使炎症因子和DAMPs经过这些孔洞释放到胞外[144,145]。

胞质内的dsRNA能够直接激活炎症小体NLRP1、NLRP6和NLRP9b介导细胞焦亡[121,122,124]。RNA解旋酶DHX33能结合胞质内的dsRNA并活化NLRP3炎症小体[146]。RNA解旋酶DDX17能够结合胞内逆转座子(retrotransposon)

RNA以激活NLRC4炎症小体[147]。在IFN诱导的抗病毒反应中，RNA酶RNase L剪切病毒和自身RNA使NLRP3与DHX33和MAVS形成复合物激活炎症反应[146]。而Z-DNA结合蛋白1(Z-DNA binding protein 1，ZBP1)识别流感病毒感染产生的Z-RNA导致包括细胞焦亡在内的混合细胞死亡[148]。此外，RNA可在转录水平上调控细胞焦亡。转录因子IRF2通过调控GSDMD的mRNA转录水平控制炎症小体活化GSDMD[149]。转录因子IRF8调控NLRC4接头蛋白——NLR家族凋亡抑制蛋白(NLR family apoptosis inhibitory proteins，NAIPs)的mRNA水平，进而影响NLRC4炎症小体的激活[150]。在多种肿瘤中，与增强子相关的甲基转移酶混合谱系白血病蛋白3/4(mixed lineage leukemia 3/4，MLL3/4)常发生突变而失去抑癌功能。另有研究发现，肿瘤利用MLL3/4抑制$CD8^+$ T细胞的杀伤作用帮助免疫逃逸[151,152]。MLL3/4缺失会导致肿瘤细胞中积累dsRNA，从而激活RIG-Ⅰ和MDA5介导的IFN信号通路，同时上调炎性caspase-1/11和GSDMD的表达，并通过细胞焦亡引起强烈免疫反应[152]。

在肿瘤中，细胞焦亡受到多种RNA的调控。如环状RNA(circular RNA，circRNA) circPDIA3可与GSDME的C端结合，通过抑制锌指DHHC型棕榈酰转移酶3/17(zinc finger DHHC-type palmitoyl transferase 3/17，ZDHHC3/17)介导的棕榈酰化而增强GSDME C端的自抑制作用，最终使结直肠癌细胞对诱导肿瘤细胞焦亡依赖的抗癌药物奥沙利铂产生耐药性[153]。同时，在此过程中circPDIA3通过miR-449a提高X-框结合蛋白1(X-box binding protein 1，XBP1)的表达量，为耐药性增强提供正反馈[153]。

在病原入侵机体时，RNA影响机体中与细胞焦亡相关的抗感染免疫反应。肺炎克雷伯菌感染的肺泡巨噬细胞中，高表达的circCDC42通过抑制cdc42 GTP酶的活性引起pyrin炎症小体的高度活化和细胞焦亡，抑制circCDC42能够降低肺炎克雷伯菌感染小鼠的肺部损伤[154]。lncRNA *LNCGM1082*能够介导蛋白激酶Cδ(protein kinase C-delta，PKCδ)与NLRC4的结合，影响NLRC4炎症小体的活化[155]。寨卡病毒可以通过母婴途径传播，研究发现，寨卡病毒基因组RNA能激活RIG-Ⅰ诱导释放肿瘤坏死因子α(tumor necrosis factor α，TNFα)，随后引起caspase-8和caspase-3依赖的GSDME剪切，造成胎盘细胞焦亡，*GSDME*缺失或TNFα受体拮抗剂处理都能有效减弱病毒感染的怀孕母鼠中胎盘细胞焦亡[156]。RIG-Ⅰ能够在病毒感染后分别通过MAVS-TRAF3-TBK1、MAVS-CARD9-B细胞淋巴瘤因子10(B-cell lymphoma 10，BCL10)、ASC-NLRP3三种途径活化IRF通路、NF-κB通路，引起炎症反应[157]。

此外，多种病理条件下，细胞焦亡受到不同类型RNA的调控。压力条件能够激活免疫细胞中的NLRP3炎症小体并导致细胞焦亡和炎症反应，还会诱导血管生成素介导tRNA生成小RNA(tRNA-derived small RNA，tsRNA)，并将与NLRP3相互作用的X-连锁DEAD-box解旋酶3(DEAD-box helicase 3 X-linked，DDX3X)招募到应激颗粒中，削弱炎症小体的活化[158,159]。炎症反应失控会导致急性肺损伤和急性呼吸窘迫综合征，M2肺泡巨噬细胞分泌的胞外囊泡中的miR-709能够抑制肺泡巨噬细胞中NLRP3导致的细胞焦亡及炎症因子释放[160]。酒精可提高肝细胞中硫氧还蛋白互作蛋白(thioredoxin-interacting protein，TXNIP)的表达，引起NLRP3炎症小体活化，通过caspase-1导致细胞焦亡，miR-148a在肝细胞中的特异表达能够减少细胞死亡并减轻酒精性肝损伤[161]。非酒精性脂肪肝中，NLRP3和NLRP6炎症小体对疾病发展具有推进作用，miR-28a-5p可靶向引起NLRP3降解的E3泛素连接酶膜相关环指蛋白7(membrane-associated RING-CH-type finger，MARCH7)，导致肝脏炎症，lncRNA结合miRNA-28a-5p抑制NLRP3导致的细胞焦亡[162,163]。缺血再灌注引发的炎症和组织损伤伴随着lncRNA-H19表达水平上调，而lncRNA-H19通过miR-21提高程序性细胞死亡因子4(programmed cell death 4，PDCD4)的表达，促进NLRP3/NLRP6导致的小胶质细胞焦亡并导致炎症因子过度释放[164]。同型半胱氨酸是痴呆的重要诱因，而甜菜碱能够发挥还原作用削弱同型半胱氨酸导致的认知障碍。甜菜碱能够降低NLRP3炎症小体各组分及下游GSDMD和炎症因子的表达量，其中NLRP3 mRNA的m6A修饰增强，被YTHDF2

识别而稳定性下降，细胞焦亡被抑制[165]。

5 自身免疫疾病

RNA感受器主要识别病原产生的RNA以激活宿主的抗感染免疫反应。但是越来越多的研究发现，宿主自身的RNA同样能够被RNA感受器识别并激活天然免疫反应。在正常生理过程中，自身RNA识别导致的免疫反应具有重要意义。例如，皮肤损伤后会释放dsRNA并通过TLR3激活IL-6/STAT3信号通路，进而促进皮肤再生[166]。RIG-Ⅰ受体也可识别自身RNA为造血干细胞和祖细胞的生成提供必要的炎症信号[167]。因此，RNA感受器识别自身RNA为宿主正常代谢提供了重要保障。

自身RNA过度积累以及感受器异常则可能导致过度炎症反应，引起自身免疫疾病。有报道发现，神经细胞中胚胎致死异常视觉家族蛋白(embryonic lethal abnormal vision-like，ELAVL)能够增加3′UTR的长度和dsRNA的载量并活化dsRNA识别受体，ELAVL缺陷能够降低细胞对单纯疱疹病毒和寨卡病毒的易感性与自身免疫疾病中的dsRNA水平[168]。太阳紫外辐射会对胞内ncRNA造成损伤，受到损伤的自身RNA被TLR3识别并激活免疫反应，释放TNFα和IL-6等炎症因子[169]。许多circRNA能够形成双链结构抑制dsRNA对蛋白激酶R(protein kinase R，PKR)的激活，生理条件下RNase L能降解抑制性的circRNA，而在SLE病人中circRNA普遍降低，这可能是PKR过度活化的重要原因[170]。RNA酶RNase H2能够解除R-loop结构，维持转录过程稳态，避免DNA损伤和炎症反应，而RNase H2的缺陷可能与AGS病理相关[171]。腺苷脱氨酶RNA编辑酶1(adenosine deaminase acting on RNA 1，ADAR1)可编辑DNA-RNA的错误配对，促进RNase H2清除端粒上的R-loop结构，帮助肿瘤细胞增殖[172]。

RNA修饰代谢异常是多种疾病的潜在诱因。$CD4^+$初始T细胞中的m6A去甲基化酶ALKBH5促进了过继性转移结肠炎的病理发展，而*ALKBH5*缺失在实验性自身免疫脑脊髓炎中提高了IFNγ和CXCL2 mRNA的m6A修饰水平并降低了mRNA的稳定性，从而影响蛋白质表达，进而降低炎症反应造成的神经损伤[173]。自身免疫疾病乳糜泻(Celiac disease)与XPO1(Exportin-1)的5′UTR m6A甲基化提高相关，这一修饰在谷蛋白刺激下进一步提高，并伴随着NF-κB信号激活增强[174]。胞内RNA修饰失调还会促进RNA双链结构的产生。例如，表观遗传上沉默的转座元件在去甲基化后表达上调会导致紊乱的双向转录，产生互补的RNA结构并形成dsRNA。RNA剪接失败导致内含子驻留的RNA也倾向形成易于被dsRNA感受器识别的双链结构。此外，线粒体中的DNA在自然状况下双向转录产生RNA，异常积累的线粒体RNA通过腺嘌呤核苷酸移位酶2(adenine nucleotide translocase 2，ANT2)释放到胞质并通过MDA5引起IFN反应，进而可能引起Sjögren综合征[175-179]。同时，在压力条件下流出到胞外的线粒体dsRNA能活化TLR3并引起炎症反应，该过程可能与骨关节炎相关[180]。RNA结构的改变可能会影响其与相应受体的结合能力。ADAR1能够识别并编辑胞内的Z-RNA，当ADAR1发生突变而无法与Z-RNA结合时，积累的Z-RNA能够通过MDA5-MAVS途径引起强烈的IRF3信号活化和IFN反应并导致AGS[181-185]。实验显示，仅在调节性T细胞中特异性敲除*ADAR1*就能够导致外周调节T细胞的减少，以及致命的自身免疫疾病，特异性敲入*MDA5*的功能获得性突变具有类似的表型[186]。具有RNA识别功能的LGP2在*ADAR1*缺失时促进MDA5产生IFN，PKR和整合应激反应(integrated stress response，ISR)同样在该过程中发挥了关键作用[187,188]。ADAR1能通过编辑Alu元件减少dsRNA的产生，*ADAR1*缺失时，dsRNA可通过活化ZBP1导致细胞凋亡和细胞坏死，而在*ADAR1*和*MAVS*同时敲除的小鼠中，ZBP1活化依然能够引起小鼠早期死亡，且这一过程不依赖MDA5[189]。

许多研究提供的数据表明，多种自身免疫病与RNA感受器的异常有关。RIG-Ⅰ和MDA5的部分突变显著提高了二者与RNA的结合能力，引起AGS、Singleton-Merten综合征和痉挛性肌张力障碍等罕见疾病[190-193]。AD和SLE也可能与有关受体突变导致的RNA识别异常相关。外周血单核细胞等细胞系中MDA5发生A946T突变会增加静息状态以及刺激下产生的IFN-Ⅰ，表达该突变的小鼠能够

在致死的病毒感染中存活，同时表现出显著的自身免疫反应[194]。TLR7功能获得性突变或内体失调导致的TLR7异常激活会导致机体过度识别自身配体引起SLE[195,196]。女性特异性的lncRNA *XIST*是SLE病理过程中激活TLR7信号的重要配体[197]。TLR7信号缺陷能够减少小鼠SLE模型中炎症因子和自身抗体的产生以及减轻宿主对流感病毒的免疫反应[198]。

6 总结

在生物体内，RNA是至关重要的生物大分子，RNA作为遗传信息的载体对蛋白质的翻译发挥了关键性作用。RNA的代谢过程，包括转录合成、选择性剪接、修饰以及降解都参与并调控免疫系统发挥功能的过程。外来入侵的病原体携带的RNA具有一定的特征并被宿主细胞中的RNA感受器识别进而触发免疫信号通路和炎症反应，帮助机体清除病原体。机体自身的RNA同样受到RNA受体的监视，过度的炎症反应能够对机体产生巨大损伤，而免疫抑制同样导致多方面的生理缺陷。除编码RNA外，越来越多的研究证明了ncRNA通过直接参与转录翻译和配体识别之外的途径影响着包括免疫反应在内的多种生命活动。然而大量RNA分子的功能和作用机制至今仍然未知，相关研究仍存在较多空白。因此，进一步探究RNA对机体内各生理和病理过程的调控功能与机制有助于加深对RNA在生物体内作用的认知，同时为RNA相关疾病的治疗提供有力的理论支持。

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