•综　述•

miRNA相关抗结核免疫调控及其潜在治疗靶点的研究进展

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［摘　要］ 微小RNA（microRNA，miRNA）是调控转录后基因表达的一类非编码RNA，具有调控多种细胞生物学过程的功能。越来越多的研究表明，结核分枝杆菌（*Mycobacterium tuberculosis*，Mtb）感染后宿主细胞内多种miRNA发生差异表达，进而通过影响下游通路来调控宿主抗结核（tuberculosis，TB）免疫。文章就Mtb感染后miRNA含量改变对下游因子的调控以及对自噬、凋亡和炎症反应的影响进行综述，认为miRNA是一种有潜力的TB治疗靶点，旨在为miRNA在TB中的深入研究和临床应用提供参考依据。

［关键词］ miRNA；结核病；自噬；凋亡；治疗靶点

［中图分类号］ R52　　［文献标志码］ A　　［文章编号］ 1007-4368（2024）12-1745-11

doi：10.7655/NYDXBNSN240332

Research progress of miRNA-related anti-tuberculosis immune regulation and its potential therapeutic targets

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［**Abstract**］ MicroRNAs（miRNA）are a class of non-coding RNA molecules that regulate gene expression transcriptionally，playing crucial roles in various cellular processes. Increasing investigation indicate that the *Mycobacterium tuberculosis*（Mtb）infection alters the expression of numerous miRNAs in host cells，thereby influencing downstream pathways involved in immune responses against tuberculosis（TB）. This review summarizes how changes in miRNA levels post Mtb infection regulate autophagy，apoptosis，and inflammatory responses. It highlights that miRNAs may serve as potential therapeutic targets for TB，providing insights for further research and clinical applications of miRNA in TB.

［**Key words**］ miRNA；tuberculosis；autophagy；apoptosis；therapeutic target

［J Nanjing Med Univ，2024，44（12）：1745-1754，1762］

结核病（tuberculosis，TB）是由结核分枝杆菌（*Mycobacterium tuberculosis*，Mtb）引起的一种经由呼吸道传播的传染性疾病。根据世界卫生组织发布的《2023年全球结核病报告》，TB是仅次于新型冠状病毒肺炎的全球第二大单一传染病死亡病因[1]。Mtb主要感染肺部，导致典型的肺结核综合征[2]。宿主的免疫功能参与细胞的自噬、凋亡和吞噬溶酶体成熟等生物学过程，对控制Mtb感染至关重要。越来越多的证据表明，微小RNA（microRNA，miRNA）可调控上述大多数生物学过程。miRNA是长度为18~25个核苷酸的小分子RNA，不参与蛋白质的编码，而在细胞增殖分化、信号通路激活、免疫功能调节等生物学过程中充当基因表达的关键控制者[3]。miRNA通过Argonaute（AGO）蛋白形成RNA诱导的基因沉默复合物（RNA-induced silencing complex，RISC）沉默靶mRNA的表达[4]，对靶基因的表达产生负调控作用。

近年来，越来越多的研究发现TB患者和健康人存在miRNA之间的表达差异，进而探究出差异表达的miRNA通过影响下游通路在Mtb感染细胞中导

［基金项目］ 江苏省科技计划专项（BE2023718）；江苏省共建放射医学与辐射防护国家重点实验室开放研究课题（GZK12023015）

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致细胞分子层面的变化（如自噬受损、凋亡受损、促炎细胞因子产生受阻等）。进一步提出miRNA可作为TB的潜在治疗靶点，并通过体内实验进行验证。文章就miRNA相关抗TB免疫调控及其潜在治疗靶点进行综述，旨在为miRNA在TB中的深入研究和临床应用提供参考依据。

1　Mtb感染后miRNA的差异表达调控抗TB免疫

1.1　miRNA对自噬的调控

自噬是胞质内容物被质膜包裹形成自噬体后转运至溶酶体，由溶酶体降解内容物的过程[5]，已被证明可以增强对胞内病原菌的杀伤[6]。通过自噬清除胞内病原体的过程被称为异噬，是宿主对抗多种病原体的先天性防御策略[7]。自噬相关通路在转录后水平受到严格的调控，但在Mtb感染期间，miRNA对自噬的影响在很大程度上是未知的。近几年的一些研究证实Mtb感染期间miRNA的差异表达对自噬存在调控作用（图1）。

1.1.1　miRNA调控自噬相关基因（autophagy related gene，ATG）

几乎所有的ATG蛋白均参与自噬的生物学过程[8]，miRNA可通过靶向ATG的3′非编码区发挥抑制作用，从而对自噬产生影响。在Mtb感染后，miRNA-142-3p在巨噬细胞内的含量下调，其靶基因ATG4c和ATG16L1上调，从而促进了细胞自噬[9]；感染Mtb的巨噬细胞中miRNA-106a显著下调，从而解除其对Unc-51样自噬激活激酶（Unc-51 like autophagy activating kinase 1，ULK1）和ATG7/ATG16L1的抑制，促进自噬[10]。相似地，Mtb感染的巨噬细胞中，miRNA-20a显著下调，导致靶基因ATG7和ATG16L1上调以解除miRNA-20a对自噬的抑制[11]。

目前尚不完全清楚Mtb如何抑制感染细胞的自噬，但miRNA在这一过程中具有重要作用：靶向抑制ATG的miRNA可被Mtb上调，进而抑制自噬，促进Mtb存活。miRNA-144-3p在牛分枝杆菌卡介苗（Bacillus Calmette-Guérin，BCG）感染的巨噬细胞中上调，靶向抑制ATG4a，从而抑制自噬，促进BCG的胞内存活[12]。并且miRNA-144-3p的上调还通过靶向过氧化物酶体增殖物激活受体α（peroxisome proliferator activated receptor alpha，PPARα）和三磷酸腺苷结合盒转运体A1（ATP binding cassette subfamily A member 1，ABCA1）促进巨噬细胞的脂质积累，其对宿主脂质代谢的重编程抑制了Mtb感染引起的自噬[13]。此外，miRNA-155[14]、miRNA-1958[15]均被证实在Mtb感染的细胞中表达上调，并分别通过靶向抑制ATG3和Rheb、ATG5实现对自噬的抑制。

1.1.2　miRNA调控自噬体成熟

自噬体是吞噬泡在ATG蛋白的作用下形成的，其与溶酶体融合，降解胞质内容物，参与胞内病原菌的清除[8]。Mtb可调控相关miRNA的表达以抑制自噬体的成熟，从而抑制自噬、促进TB进展。miRNA 542-3p在Mtb感染的巨噬细胞中表达上调，通过抑制膜泡分拣蛋白11（vacuolar protein sorting 11，VPS11）抑制自噬体的成熟及其与溶酶体的相互作用，从而抑制细胞自噬[16]。与上述研究结果类似，miRNA-423-5p在Mtb感染的巨噬细胞中表达升高并抑制其靶基因VPS33A，从而抑制自噬体-溶酶体融合[17]。Mtb组分Rv1759c可诱导miRNA-25的表达上调，靶向位于溶酶体膜上的细胞内胆固醇转运蛋白C型尼曼-匹克蛋白1（Nimemann-Pick C 1，NPC1），导致溶酶体功能受损，从而抑制自噬溶酶体成熟[18]。此外，毒力蛋白ESAT-6可通过调节miRNA-30a-3p和miRNA-30a-5p的表达水平调控自噬。miRNA-30a-5p的上调会促进感染Mtb的巨噬细胞自噬，而ESAT-6诱导的miRNA-30a-3p通过抑制自噬体和溶酶体的融合从而拮抗miRNA-30a-5p促进自噬的作用[19]。肿瘤坏死因子样弱凋亡诱导因子（tumor necrosis factor-like weak inducer of apoptosis，TWEAK）可通过激活腺苷酸激活蛋白激酶（adenosine 5′-monophosphate-activated protein kinase，AMPK）诱导自噬体成熟。在Mtb感染的巨噬细胞中，miRNA-889上调靶向抑制TWEAK的表达来抑制自噬[20]。研究表明，Mtb具有操纵Ca^{2+}信号以阻止自噬体成熟和自噬体-溶酶体融合的功能，Mtb可诱导巨噬细胞中的miRNA-27a表达上调，miRNA-27a靶向抑制定位内质网的电压依赖型Ca^{2+}通道基因（CACNA203），导致Ca^{2+}信号下调，从而抑制自噬体形成[21]。此外，miRNA-144*在感染的巨噬细胞中上调，靶向抑制DNA损伤调节自噬调节因子2（DNA damage-regulated autophagy modulator protein 2，DRAM2），抑制自噬体的成熟[22]。与上述相反的是，miRNA-215-5p在TB患者中表达下调，可通过间接靶向SNAP29促进自噬体和溶酶体的融合以促进自噬[23]。

1.1.3　miRNA调控其他基因影响自噬

差异表达的miRNA也可靶向其他基因，对自噬产生影响。Mmu-miRNA-25-3p在Mtb感染的巨噬细胞中表达上调，其通过抑制双特异性磷酸酶10（dual-specificity protein phosphatase，DUSP10）的表达促进

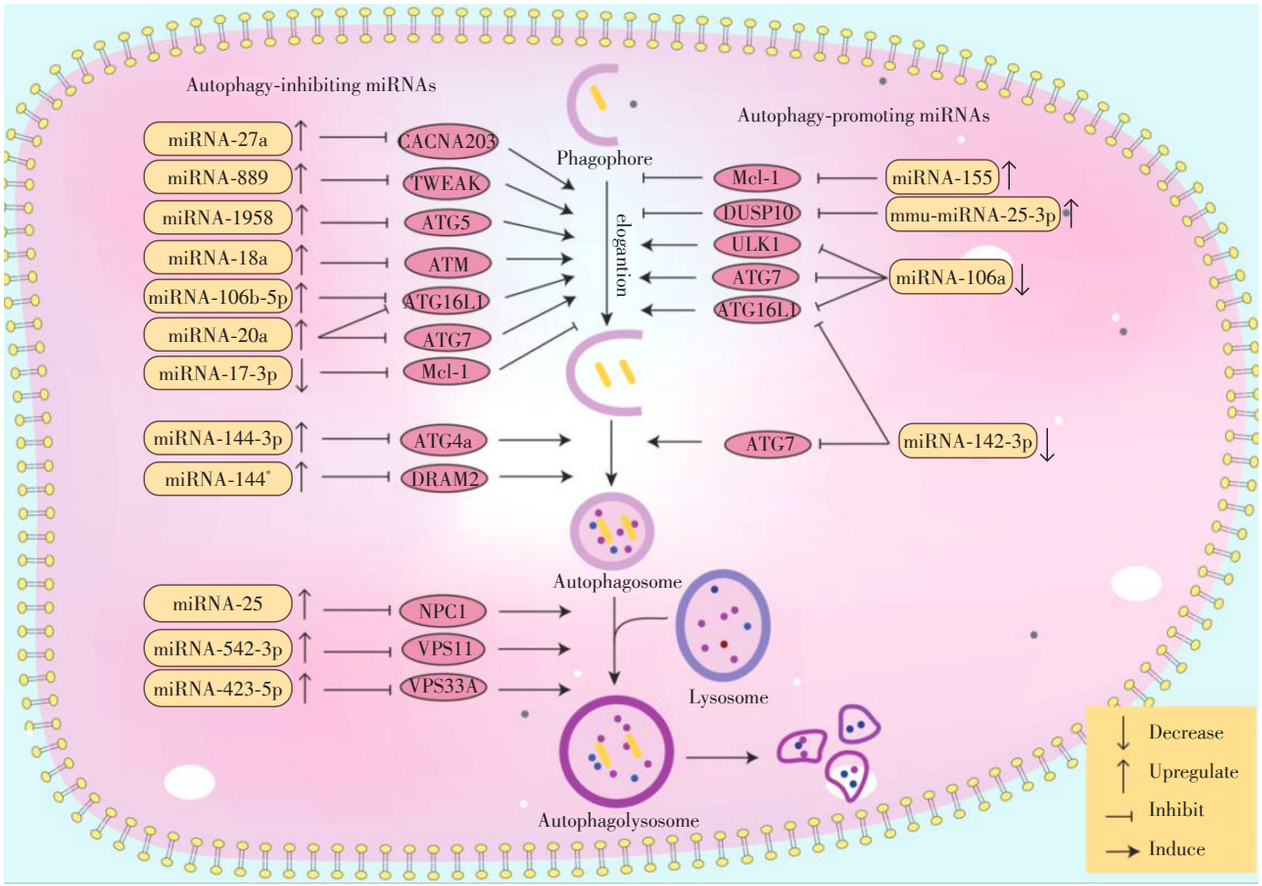

图1　miRNA及其靶基因对自噬的影响

Figure 1　The effect of miRNAs and their target genes on autophagy

ERK1/2蛋白磷酸化，从而增强BCG诱导的巨噬细胞自噬[24]。miRNA-582-5p在感染的巨噬细胞中表达上调，靶向抑制端锚聚合酶2（tankyrase 2，TNKS2），促进自噬[25]。毛细血管扩张性共济失调突变（ataxia telangiectasia mutated，ATM）通路可通过激活LKB1/AMPK/TSC2信号并抑制负调控因子mTORC1以促进自噬。miRNA-18a在感染Mtb的巨噬细胞中上调，并通过下调ATM通路抑制自噬过程[26]。miRNA-17-5p下调后靶向上调了髓样细胞白血病-1（myeloid cell leukemia-1，Mcl-1）和信号转导与转录激活因子3（signal transducer and activator of transcription 3，STAT3），抑制了Mtb诱导的巨噬细胞自噬[27]。Mcl-1属于Bcl-2家族的抗凋亡成员，Bcl-2家族成员除了调节凋亡外，也参与自噬的调控[28]。

总之，自噬对调节Mtb感染的免疫反应和巨噬细胞防御至关重要。部分miRNA在Mtb感染后发生差异表达，影响下游基因调控自噬，进而影响Mtb的胞内清除。

1.2　miRNA对凋亡的调控

细胞凋亡是多种信号共同调控的程序性细胞死亡。小鼠体内实验证实Fas诱导的凋亡途径和Bal-2调节的凋亡途径分别通过清除感染Mtb的巨噬细胞和中性粒细胞在抗结核感染中发挥关键作用[29]。细胞凋亡可阻止胞内病原体的释放和传播，在宿主防御胞内病原体感染中起到关键作用[30]。研究表明，Mtb感染细胞所导致的miRNA差异表达，可通过影响凋亡分子的表达进而调控细胞凋亡（图2）。

1.2.1　miR-155对凋亡调控的双面性

miR-155在H37Rv感染或EsxA刺激的巨噬细胞中持续上调[31]。小鼠在敲除miRNA-155后对Mtb更易感，且其巨噬细胞凋亡被抑制，说明miRNA-155在抗TB免疫中的重要作用[32]。巨噬细胞中的miRNA-155在Mtb或BCG诱导后表达上调，研究表明其上调依赖于Toll样受体（Toll like receptor，TLR）、核因子κB（nuclear factor-kappa B，NF-κB）和Jun氨基末端激酶（Jun N-terminal kinase，JNK）信号通路[31]。miR-155通过靶向叉形头框蛋白O3（forkhead box

O3，FOXO3）抑制单核细胞凋亡[33]。有趣的是，miRNA-155也可通过靶向SOCS1促进巨噬细胞凋亡[34]。miRNA-155在Mtb感染时的双面性可能代表了Mtb在不同类型细胞中的抗感染免疫机制，还有待进一步阐明。

1.2.2　其他差异表达miRNA对凋亡的调控

近年来，已有许多研究证明Mtb感染诱导的miRNA差异表达可遏制细胞凋亡。Mtb诱导巨噬细胞中miRNA-325-3p的过表达，从而靶向抑制E3泛素连接酶LNX1（ligand of numb-protein X1），导致中心体相关表达激酶6（NIMA-related expressed kinase 6，NEK6）的异常积累，进而异常激活STAT3信号，抑制细胞凋亡过程[35]。Mtb感染后，巨噬细胞中miRNA-20b-5p的下调使Mcl-1表达上调以抑制细胞凋亡[36]。miRNA-223在活动性结核病（active tuberculosis，ATB）患者巨噬细胞中大量表达，通过下调FOXO3抑制巨噬细胞凋亡[37]。Mtb也可通过调控miRNA诱导宿主细胞死亡途径的转化，促进自身胞内存活。miRNA-342-3p靶向抑制细胞因子信号抑制因子6（suppressors of cytokine signaling，SOCS6），通过A20介导的K48泛素化和RIPK3降解以及STAT1磷酸化参与Mtb诱导的细胞凋亡和坏死之间的转换。其在感染的细胞中表达下调，促使细胞坏死，Mtb存活[38]。

Mtb感染后miRNA的差异表达可靶向下游基因促进细胞凋亡。miRNA-27b高表达于感染Mtb的巨噬细胞，通过抑制Bcl-2相关抗凋亡基因2（Bcl-2 associated athanogene 2，Bag2）促进了巨噬细胞p53依赖性细胞凋亡[39]。BCG感染巨噬细胞后，miRNA-100-5p的下调靶向促进SMARCA e5的上调，进而通过Caspase-3和Bcl-2促进细胞凋亡[40]。Mtb感染诱导巨噬细胞中的miRNA-20a-5p下调，其靶基因JNK2的表达显著增加，并诱导Bim的表达，随后触发细胞凋亡以促进Mtb清除[41]。miRNA-125b-5p在感染Mtb的巨噬细胞中上调，可通过靶向DRAM2促进细胞凋亡和抑制炎症反应，从而保护巨噬细胞抵抗Mtb感染[42]。

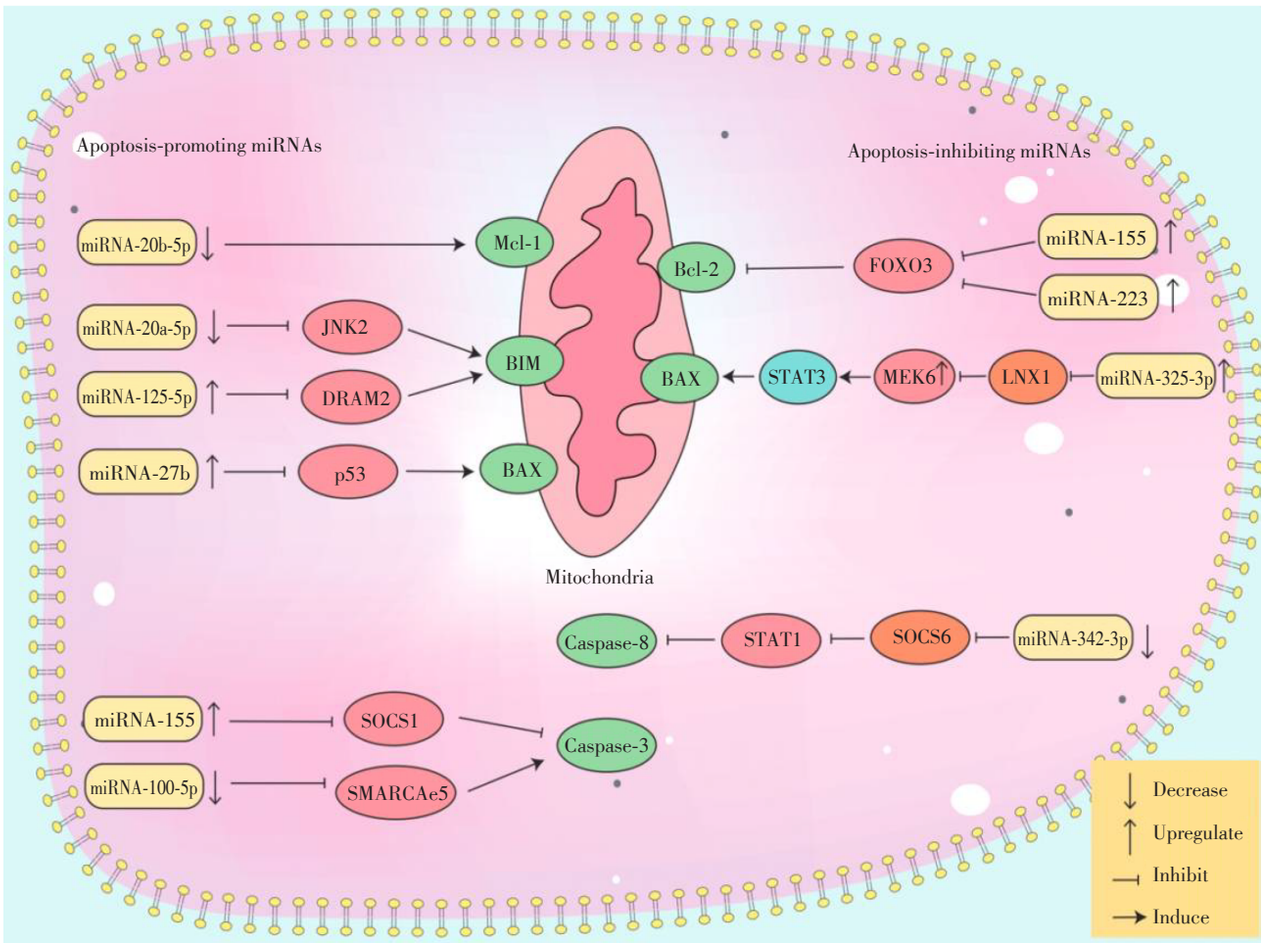

图2　miRNA及其靶基因对凋亡调控因子的影响

Figure 2　The effect of miRNAs and their target genes on apoptosis regulatory factors

综上所述，作为清除胞内菌感染的途径之一，凋亡同自噬一样受到差异表达miRNA的调控，进而影响Mtb的胞内存活。

1.3　miRNA调控促炎细胞因子分泌

炎症是机体对刺激的防御反应，是维持内环境稳定的基本生理过程。当病原体入侵机体后，炎症反应帮助机体清除病原微生物，激发适应性免疫应答[43]，在控制病原体感染中发挥重要作用。

1.3.1　miRNA调控炎症因子分泌

NF-κB通路直接诱导促炎细胞因子如白细胞介素（interleukin，IL）-1、IL-6、肿瘤坏死因子（tumor nerosis factor，TNF）-α等的产生，在先天性和适应性免疫应答中发挥重要作用。诱导NF-κB通路的活化，可显著降低巨噬细胞内的Mtb负荷[44]。Mtb感染后miRNA表达量的改变可通过影响NF-κB通路，促进炎细胞因子的释放（图3）。在Mtb感染的巨噬细胞中，miRNA-20a-3p被诱导上调，并下调其靶基因NF-κB激酶β抑制剂（inhibitor of NF-κB kinase β，IKKβ）的表达，从而抑制NF-κB通路的激活，导致宿主细胞分泌促炎因子以利于Mtb存活[45]。A20是NF-κB信号通路的抑制剂。Mtb可通过抑制miRNA-let-7f的表达，从而上调靶基因A20的表达，抑制促炎因子的分泌[46]。TNF受体相关因子6（TNF receptor associated factor 6，TRAF6）在NF-κB通路中作为信号转导子发挥作用，激活IKKβ对促炎细胞因子做出反应。miRNA-146a[47]和miRNA-125a[48]在感染细胞中表达上调，靶向TRAF6抑制NF-κB信号通路，从而抑制相关促炎因子的分泌。Mtb的毒力组分ESAT-6可抑制miRNA-223-3p的合成，导致其靶基因第10号染色体缺失的磷酸酶和张力蛋白同源基因（phosphatase and tensin homolog deleted on chromosome ten，PTEN）上调，抑制PI3K/AKT/NF-κB通路减少促炎细胞因子的产生[49]。此外，Mtb感染的巨噬细胞中miRNA-502-3p上调，靶向抑制Rho相关卷曲螺旋含蛋白激酶1（Rho associated coiled-coil containing protein kinase 1，ROCK1）以降低促炎细胞因子的表达。并且过表达miRNA-502-3p显著抑制TLR4/NF-κB信号通路相关蛋白的表达，可能协同抑制细胞因子的产生[50]。

与上述相反的是，Mtb感染导致胞内miRNA-340-5p表达显著降低，促进跨膜p24运输蛋白7

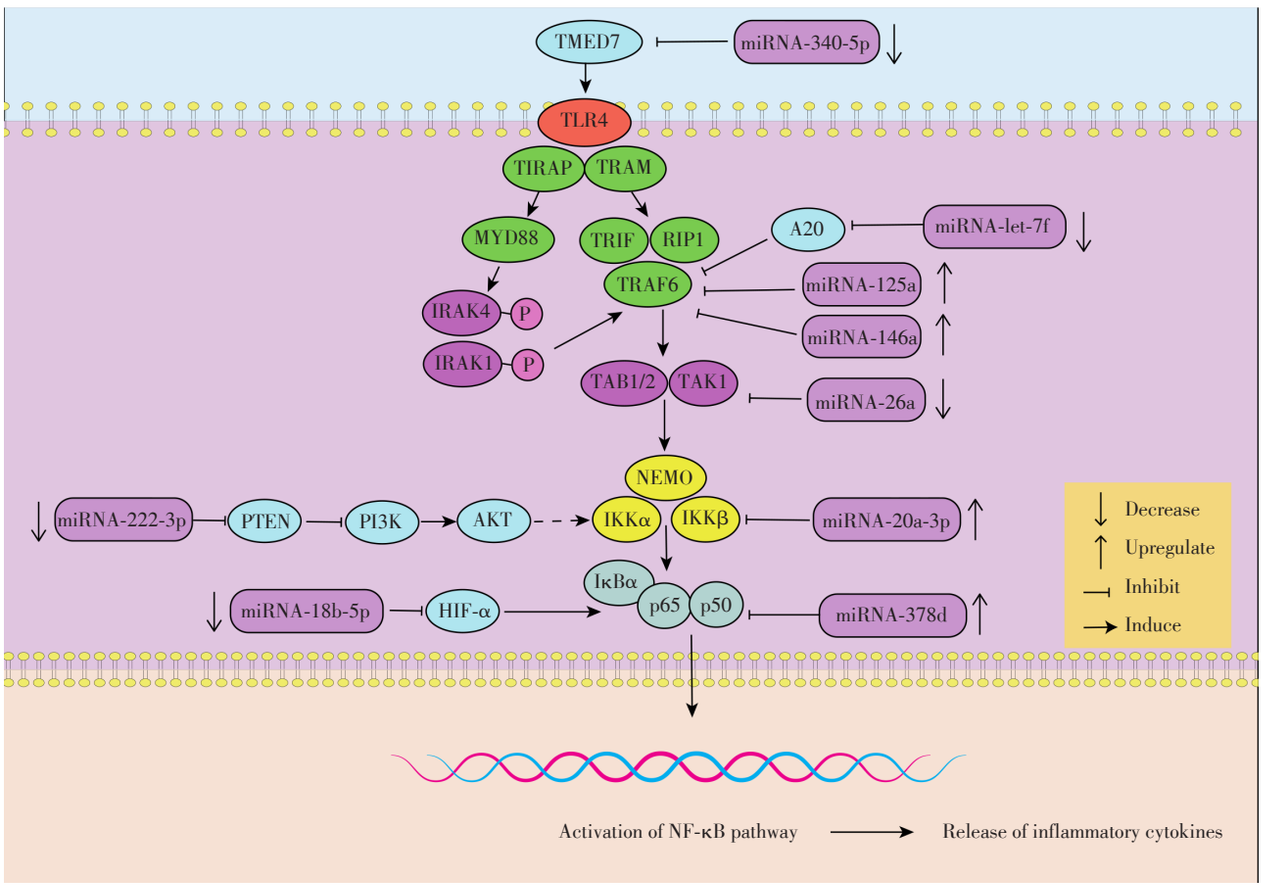

图3　miRNA在感染Mtb后的差异表达及对TLR/NF-κB通路的影响

Figure 3　The differential expression of miRNAs following Mtb infection and their effect on the TLR/NF-κB pathway

(transmembrane p24 trafficking protein 7, TMED7)/NF-κB表达,引起促炎细胞因子的释放[51]。转化生长因子β激活激酶(transforming growth factor β-activated kinase-1, TAK1)是NF-κB通路中的关键酶。miRNA-26a在感染的细胞中下调,进而导致其靶基因TAK1上调,从而激活NF-κB信号通路[52]。在Mtb感染的巨噬细胞中,miRNA-18b-5p表达下调,其靶基因HIF-1α表达增加,MAPK p38和NF-κB p65磷酸化被激活。协同作用导致胞内促炎细胞因子表达上调[53]。最近一项研究证实,Mtb通过NF-κB通路导致miRNA-378d的表达下调,且其下调进一步强化了NF-κB通路的激活,与miRNA-378d靶基因Rab10的上调一起促进促炎细胞因子分泌,抑制胞内Mtb的存活[54]。

TLR可通过MyD88介导信号转导,MyD88诱导IL-1受体相关激酶(IL-1 receptor associated kinase, IRAK)1和IRAK4的募集,进一步募集TRAF6,激活TAK复合体,导致经典的NF-κB通路活化[43]。如前所述,NF-κB通路直接影响促炎细胞因子的产生,部分miRNA可通过直接靶向TLR影响细胞内的炎症反应。miRNA-21-5p的过表达靶向抑制Bcl-2和TLR4,从而抑制促炎细胞因子的产生[55]。在Mtb感染巨噬细胞后,miRNA-708-5p水平上调,其通过靶向抑制TLR4降低相关细胞因子的分泌[56]。miRNA-1178在感染的巨噬细胞中上调,靶向TLR4显著降低了Mtb感染的巨噬细胞中促炎细胞因子的积累[57]。除了上述通路外,miRNA-196b-5p/SOCS3[58]、miRNA-370-3p/卵泡抑素样蛋白1(follistatin like 1, FSTL1)[59]和miRNA-32-5p/FSTL1[60]以及miRNA-206/金属蛋白酶组织抑制因子3(tissue inhibitor of metallopeptidase 3, TIMP3)[61]信号均在Mtb感染的细胞中发挥抑制炎症因子的作用。

1.3.2　miRNA调控活性氧(reactive oxygen species, ROS)水平

人巨噬细胞通过增加过氧化物酶体产生ROS来应对感染,限制胞内的Mtb[62]。Mtb下调巨噬细胞中的miRNA-495,进而上调超氧化物歧化酶2(superoxide dismutase 2, SOD2)的表达,降低ROS水平[63]。miRNA-346-3p在感染的巨噬细胞中下调,靶向RIPK1/RIPK3/MLKL通路,导致ROS释放和Ca^{2+}内流,从而促进Mtb诱导的巨噬细胞坏死[64]。此外,高菌量活动期TB患者外周血单个核细胞中的miRNA-23a-3p表达下调,通过靶向IRF1/SP1促进ROS生成[65]。

总之,miRNA通过调节炎症反应和激活细胞因子,在控制Mtb感染中发挥重要作用。了解其间相互作用的机制可以更好地理解Mtb感染的复杂免疫反应,并进一步探究潜在的治疗方法。

2　miRNA作为潜在的治疗靶点

miRNA表达的生理变化对调节复杂的基因网络和细胞信号至关重要。在TB中,miRNA发生病理性的差异表达,导致下游靶基因信号通路失调,影响患者的免疫功能。因而,逆转病理性表达miRNA可增强患者免疫功能,促进Mtb的清除或减轻炎症损伤。miRNA治疗的总体目标是逆转病理性的miRNA表达变化,即人为上调或增强被病理性抑制的内源性miRNA和下调或阻断驱动疾病进展的miRNA。常用于改变miRNA含量的制剂包括:miRNA模拟剂(miRNA mimic)、携带miRNA编码序列的重组表达载体、miRNA抑制剂(anti-miRNA)和miRNA海绵等。鉴于miRNA治疗剂具有较低的细胞膜通透性,可结合纳米载体、病毒转染、引入化学修饰或与生物分子,进一步通过受体介导的摄取来实现胞内递送[66]。

如前所述,Mtb感染后miRNA含量的改变影响下游分子,进而影响机体抗TB免疫。体外实验中,人为改变相关miRNA的表达可促进抗TB免疫,降低胞内Mtb负荷(表1)。其中,miRNA-155的作用具有争议,报道其上调会促进Mtb的胞内清除,也有研究称其上调会加重感染细胞的细菌负荷。这与前文所述的miRNA-155抗TB作用的双面性相符合[32],miRNA-155在调节宿主对Mtb感染的免疫反应中具有多种作用,其在Mtb感染不同阶段的靶向作用途径亟待进一步探究。

近年来,许多体内实验已证明了miRNA可能成为潜在的TB治疗靶点,相关生物制剂处理的TB小鼠的疾病进展发生显著变化。miRNA-325$^{-/-}$小鼠在感染Mtb后,相比野生型小鼠,肺、脾脏和肝脏的载菌量均显著下调,而miR-325$^{-/-}$小鼠在补充miRNA-325模拟剂后,其器官载菌量显著提升,提示下调TB小鼠的miRNA-325可能有助于缓解TB进展[35]。miRNA-20b可通过靶向NLRP3/Caspase-1/IL-1β通路减轻小鼠的肺部炎症反应,使用miRNA-20b模拟剂处理TB小鼠,其肺部炎症相比对照组明显缓解。相似地,给予miRNA-31激动剂的TB小鼠具有更轻的肺部炎症损伤[67]。而使用miRNA-25抑制剂处理BCG感染的小鼠,相比对照组,有着更低的肺部

细菌负荷和炎症水平[18]，提示下调miRNA-25可以控制TB进展。曾有研究者发现用miRNA-27a拮抗剂处理的TB小鼠，相比对照组有着更低的细菌负荷和肺部炎症水平[21]，以此证明miRNA-27a可以作为TB治疗的靶点。miRNA-337-3p靶向TLR4/MYD88和STAT3，导致维生D受体介导的抗菌反应受损。miRNA-337-3p抑制剂处理的TB小鼠内脏细菌负荷显著下调[68]。此外，miRNA相关制剂除了可以改善TB动物模型的肺部炎症和细菌负荷外，还可改善结核性肺纤维化。miRNA-148a抑制NAPDH氧化酶4和DNA聚合酶相互作用蛋白2表达，miRNA-148a模拟剂处理BCG感染的小鼠后，小鼠胸膜间皮细胞胶原蛋白1A的合成受到抑制，从而延缓结核性胸膜炎的纤维化，证明miRNA-148a可能有助于缓解结核性肺纤维化[69]。

表1 体外实验证实可降低胞内Mtb负荷的miRNA

Table 1 The miRNAs that reduce the intracellular Mtb load confirmed by *in vitro* experiments

Overexpression of miRNAs that reduce intracellular mycobacterial burden	Downregulation of miRNAs that reduce intracellular mycobacterial burden
miRNA-30a-5p[70], miRNA-20b[71], miRNA-27b[39], miRNA-495[63], mmu-miRNA-25-3p[24], miRNA-240-5p[51], miRNA-1249-3p[72]	miRNA-20b-5p[36], miRNA-106a[10], miRNA-579-3p[73], miRNA-30a-3p[70], miRNA-1301-3p, miRNA-5194[74], miRNA-18b[53], miRNA-20a-3p[45], miRNA-142-3p[9], miRNA-502-3p[50], miRNA-21-5p[55], miRNA-542-3p[16], miRNA-100-5p[40], miRNA-20a-5p[41], miRNA-27a[21], miRNA-144-3p[12], miRNA-708-5p[56], miRNA-889[20], miRNA-18a[26], miRNA-25[18], miRNA-4687-5p[75], miRNA-144*[22], miRNA-1958[15], miRNA-125b-5p[42], miRNA-370-3p[76], miRNA-378d[54], miRNA-146a[47], miRNA-325-3p[35], miRNA-1178[57], miRNA-337-3p[68], miRNA-340-5p[51], miRNA-32-5p[60], miRNA-125a[48]

因此，miRNA可以用于增强宿主对Mtb的免疫能力，为TB的治疗提供了一种潜在方法。许多基于miRNA的疗法已经进入临床试验。然而，一种miRNA可靶向多个靶基因，一条基因或一条通路通常受到多个miRNA的调控，从而形成一个复杂的调控网络。改变一种miRNA含量可能会影响多条通路。因而未来还需要进一步的研究来明确miRNA调控网络、miRNA相关药物不良反应、如何使药物有效靶向靶细胞和选择靶向递送药物的材料，从而为基于miRNA的抗TB靶向药物研发提供理论基础。

3 总结与展望

文章总结了miRNA相关抗TB免疫调控及其作为潜在治疗靶点的研究进展；综述了Mtb感染时，miRNA含量改变对下游因子的调控以及对自噬、凋亡和炎症反应等生物学过程的影响；进一步提出miRNA作为免疫调控因子具有作为TB治疗靶点的潜力。

诚然，越来越多的研究揭示了miRNA调控宿主免疫反应的作用机制，其中大部分涉及巨噬细胞和先天性免疫应答，但在关于miRNA在特定免疫细胞群中的表达谱和调控作用知之甚少，缺乏miRNA对适应性免疫应答调控的相关机制。需要进一步明确miRNA在感染性疾病中的作用机制。且miRNA在体内的表达具有周期性，进一步研究miRNA表达谱与TB进展的关系有助于更好地理解TB的发病机制。此外，目前研究主要集中在单个miRNA对细胞分子层面的影响，多个具有不同靶标的miRNA如何影响感染过程中的整体宿主反应还有待研究。并且miRNA作为TB治疗靶点也存在局限。miRNA用作治疗药物尚处于起步阶段，治疗性miRNA如何正确靶向靶细胞是需要攻克的一个难题。鉴于人工智能（artificial intelligence，AI）技术的发展，可利用AI技术设计合理的寡核苷酸载体和转移载体以减少对非靶细胞的影响。值得注意的是，miRNA递送材料的选择和设计也会影响miRNA的功效，今后还需要更多基于miRNA及其相关药物递送系统选择合理性的研究。

总之，miRNA作为免疫调控分子在调节Mtb复制和宿主机体稳态中发挥重要作用，是TB的潜在治疗靶点。明确miRNA在Mtb感染过程中对宿主免疫应答的调控机制，有助于更好地理解TB的发病机制及开发相应的靶向治疗药物。

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[收稿日期] 2024-07-19
（本文编辑：唐　震）

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[收稿日期] 2024-06-26
（本文编辑：陈汐敏）