# microRNA 在固有免疫中的作用研究进展

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**摘 要** MicroRNA(miRNA)是一类短小非编码 RNA,能够调节机体内 mRNA 的转录表达水平。目前,固有免疫在免疫系统中的作用逐渐成为学者们研究的热点,而 miRNA 在固有免疫应答过程中,能够对多种细胞的应答水平具有显著的调节作用,影响、参与全身各器官炎症反应过程,对免疫状态的调节有重要的意义。本文对 microRNA 在炎症的固有免疫阶段的调节活动的研究进行综述,以期对后续研究提供理论参考。

**关键词** microRNA;固有免疫;炎症;进展

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# Advances of microRNA activity in innate immunity

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**Abstract** MicroRNA (miRNA), sharing the character of regulating the transcriptional level and expression level of mRNAs, is one kind of small non-coded RNAs. At present, innate immune has become one of the hot topics for researchers, and miRNAs as a sort of bioactive substance greatly take part in the whole regulation progress. In detailed, miRNAs can influence the immune state of immune cells during innate immune period and further regulate inflammatory conditions in whole body. By systematically summarizing miRNA function during innate immunity, this present review may provide a reference for peer researchers.

**Key words** microRNA; innate immune; inflammation; advances

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固有免疫(innate immunity)是机体在种系发育和进化过程中形成的天然免疫防御功能,即出生后就已具备的非特异性防御功能,也称为非特异性免疫(non-specific immunity)。固有免疫是宿主快速识别病原菌感染的第一道防线,也是机体适应性免疫的基础。在固有免疫应答过程中,多种免疫细胞参与炎症发展过程。吞噬细胞表面相应的模式识别受体(pattern recognition receptors,PRRs)识别

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各种病原体相关分子模式(pathogen associated molecular patterns,PAMP),PAMP 激活 PRRs 同时发送信号给 Toll 样受体,Toll 样受体(Toll-like receptor,TLR)在接受到信号后,通过 Toll 样受体信号通路向细胞核内传递基因调节信号,得到信号后,基因的表达会对表面受体表达、多种杀菌机制的激活、可溶性急性炎症反应介质的释放以及补体系统的激活产生效应[1]。肥大细胞和树突状细胞在炎症过程中分泌多种与炎症相关的细胞因子、炎性介质,促进炎症的发生,并趋化粒细胞向炎症区域富集。自然杀伤细胞可以直接杀伤被感染的细胞,同时能够通过表达细胞因子来参与免疫反应。

传统上研究者们认为,中枢神经系统与外周系统是相对独立的系统,在炎症过程中,也仅能通过血-脑脊液屏障筛选后的小分子物质进行交流,很多中枢炎症与外周炎症之间的相似性和相关性并不能得到清晰的解释。随着硬脑膜中淋巴导管的发现[2],为中枢神经系统与外周神经系统的炎症联系奠定了解剖学基础,使炎症状态下外周系统和中枢系统的一些同步性现象得到了解释。

在过去的研究中,研究者们一直在寻找能够反映出疾病发展进程,并且在疾病的治疗过程中具有临床指示意义的小分子生物标识物质。但是在过去的研究中,此类物质的寻找始终不能达到研究者们的预期,成为理想的生物标识物质[3]。近年来,随着对 microRNA 研究的深入,研究者们发现其可能会成为一种理想的治疗靶点。microRNA(miRNA)是一类长度为 18 ~ 25 nt 的、非编码的小分子 RNA,它们来自含有茎环结构的细胞内 RNA,具有 RNA 沉默和转录后调节基因表达的功能。目前研究认为,miRNA 影响 mRNA 翻译的机制可能有3 种:(1)在翻译过程前将 mRNA 链剪切成两段;(2)通过减短 mRNA 的 poly(A)端从而影响 mRNA 的稳定性;(3)降低核糖体翻译 mRNA 的效率以调节基因的表达情况。miRNA 通过以上一种或几种过程来对 mRNA 的翻译过程进行干预,产生 RNA 沉默和对基因表达产生调控作用[4-5]。

## 1　miRNA 在固有免疫中的调节作用

### 1.1　miRNA 对巨噬细胞的调节作用

巨噬细胞(macrophages,Mφ)是固有免疫过程中主要的效应细胞,通过吞噬病原体、释放炎性细胞因子、辅助其他免疫细胞发挥免疫效应等方式参与固有免疫应答。病原体通过皮肤屏障进入到机体内部后,其表面的 PAMP 迅速被 Mφ 表面的 PRRs 所识别。在 PRRs 被激活的同时,一个 TLR 同时被激活,然后通过启动一系列激酶调节的磷酸化反应,最终使 NF-κB 从其抑制因子中释放出来并调节细胞核内的基因表达。Mφ 释放出的炎性介质还能够激活嗜中性粒细胞,辅助其他 Mφ 进行吞噬和攻击病原体的功能。Mφ 将载有炎性介质的炎性小泡释放到组织间隙,小泡中的内容物释放出来后,与血管内皮细胞结合,引起血管中的中性粒细胞黏附至血管壁上,同时增加血管通透性,使中性粒细胞趋化游离出血管。此外,Mφ 能够启动自身内的活性氧损伤系统和活性氮损伤系统,在细胞质内产生过氧化物阴离子($O_2^-$)、过氧化氢($H_2O_2$)、游离羟基(·OH)、氮氧化物等具有活性的氧中间产物和有活性的氮中间产物,对已经吞噬的病原体进行杀伤和消化。miRNA 通过调控以上途径来影响固有免疫应答的水平[6]。

Naqvid 等[7] 报道,miR-24、miR-30b、miR142-3p 的过表达能够显著抑制单核 Mφ 对大肠埃希菌和金色葡萄球菌的吞噬作用,其中,miR142-3p 直接抑制与吞噬作用相关的蛋白激酶 C-α(PKC-α)的表达。同时,3 种 miRNA 显著降低下游 TNF-α、IL-6 和 IL-12-p40 等激活炎症的细胞因子的分泌。

Taganov 等[8] 报道,miR-146a 能上调 Mφ 对于细菌脂多糖的敏感性,负反馈影响 TLR 通路中肿瘤坏死因子相关因子 6(TRAF6)和白细胞介素 1 受体相关激酶 1(IRAK1)的表达水平,对于口腔疱疹病毒所引起的 1 型干扰素在 Mφ 中的表达也具有负调节作用[9]。miR-21 在免疫前期出现上调,能够触发与 TLR7/TLR8 相关的免疫应答,促进炎症发展[10],在固有免疫阶段的中后期,miR-21 的浓度出现回落,此时主要作用于程序性细胞死亡因子 4(PDCD4)编码基因,增加 Mφ 对 LPS 的敏感性,抑制 LPS 所介导的 NF-κB 的激活和白细胞介素 6(IL-6)的表达,但同时能够提高 IL-10 的表达,促进免疫系统的稳态和恢复[11]。miR-155 对炎症发展具有促进和抑制两方面的调节作用:一方面,miR-155 能够激活 TLR4[12]、TLR2[13]、TLR3[14] 和 TLR9[15] 的活性,并在下游延长 TNF-α 转录子的半

衰期[15-17];另一方面,miR-155 能够抑制细胞因子信号转导抑制因子 1(SOCS1)和 SHIP1 蛋白酪氨酸磷酸酶等负调控因子的表达[13,18-19]。miR-147 被 TLR2、TLR3、TLR4 的信号所诱导,防止在炎症过度激烈[20]。在 Mφ 和小胶质细胞中,MiR-9 可以被 LPS 接触后所诱导,并且通过负调节 NF-κB,来调节 NF-κB1 转录子[21]。Let-7i 和 miR-125b 在由细菌感染引起的固有免疫阶段中,可以增强固有免疫反映的能力[15,17,22-23]。miR-101 可以通过抑制 miR-101/MKP-1/MAPK 通路,抑制下游 iNOS、TNF-α、ILL-1β、IL-6 等炎症介质的分泌[24]。miR-92a 能抑制 TLR 所介导途径中 MKK4 的表达,从而抑制下游 JNK/c-Jun 信号通路和该信号通路上 TNF-α、IL-6 等炎症介质的表达[25]。

此外,作为另一条杀菌途径,对于已被吞噬的病原体,活性氧起到重要的损伤作用。Ranjan 等[26]研究发现,miR-451 的缺失会引起 Mφ 内 ROS 活性和数量的降低,机制可能为 miR-451(或 miR-451 的前体物 pre-miR-451)干扰了 Ago2 的翻译过程(图 1)。

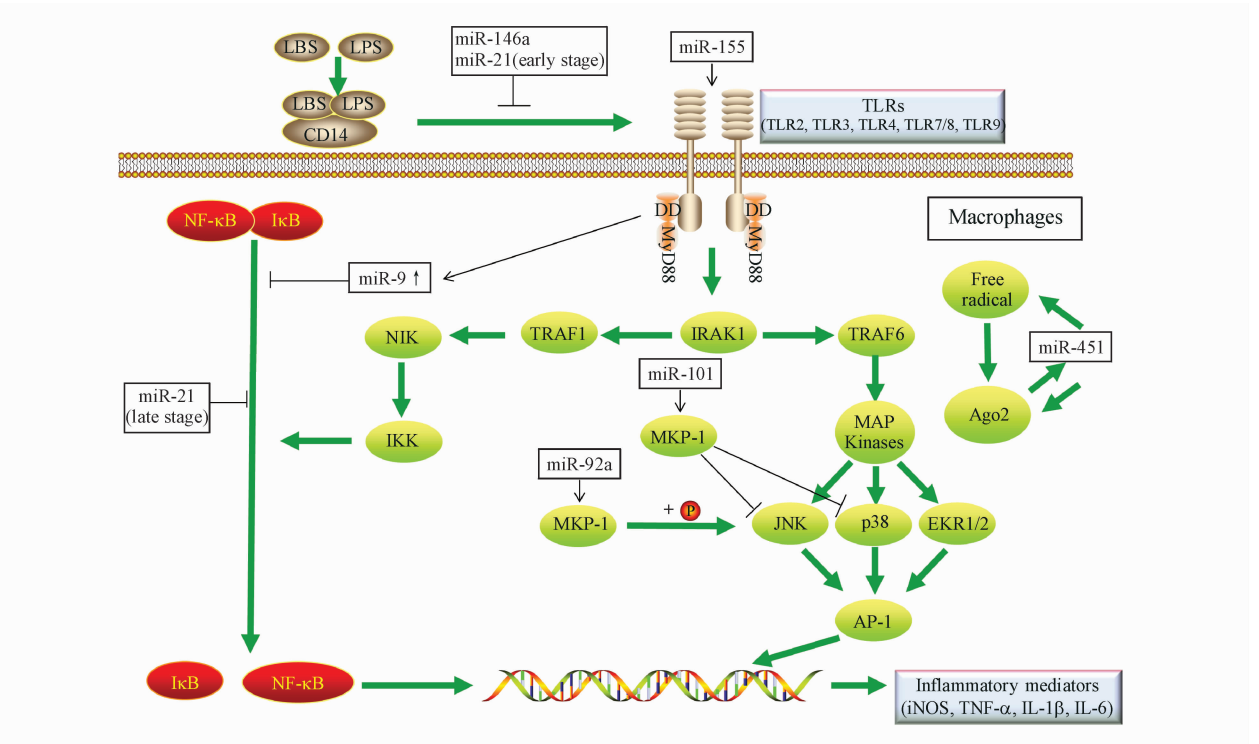


**Figure 1** Regulation activities of miRNAs in macrophages

### 1.2 miRNA 对小胶质细胞的调节作用

小神经胶质细胞是一种属于单核吞噬细胞系统中的骨髓源细胞,在脑内炎症的过程中发挥着重要的作用。小胶质细胞在中枢神经系统内分布广泛,在脑内各区均有分布。小胶质细胞在形态学、免疫表型和生物学功能上与单核/巨噬细胞系相关,是脑内固有的免疫效应细胞,被认为是中枢神经系统内的主要免疫效应器,具有免疫监视作用,能对中枢神经系统损伤做出级联反应[27]。

局部缺血是引起脑部炎症的主要因素之一,多数情况下对脑部会造成不可逆的损害。大量研究发现,中枢缺血损伤后,小胶质细胞中的 miRNA 被激活,调节中枢缺血时的炎症状态。Kong 等[28]报道,在原代大鼠小胶质细胞中,通过氧剥夺和葡萄糖剥夺的处理模仿局部缺血损伤时小胶质细胞的免疫状态。小胶质细胞造模激活后,用定量聚合酶链反应(qRCR)的检测,发现大脑中 miR-9、miR-124、miR-132、miR-134 及 miR-138 的表达均发生了改变,并且表达的变化呈现出时间依赖性。此外,小胶质细胞中 Let-7a 基因的敲除,能够抑制 p38-MAPK 和 JNK 通路的激活,减少凋亡和炎症的反应程度,呈现出中枢缺血时神经保护作用[29]。

此外,miRNA 还通过调节众多与炎症相关的信号通路和与炎症信号传到相关的节点,从而对小胶质细胞的状态进行调节(表 1)。

### 1.3　miRNA 对肥大细胞的调节作用

肥大细胞(mast cell)在固有免疫应答中主要扮演调节者的角色,通过分泌细胞因子来参与固有免疫的应答。肥大细胞所释放含有花生四烯酸、组胺、多种白细胞介素等内容物的炎症颗粒,这些内容物可进一步激活脂肪环化酶和环氧合酶途径,产生白三烯、前列腺素、血栓素等炎性因子,同时,可以改变血管通透性、趋化嗜中性粒细胞、激活 Mφ 的活性和调节急性期蛋白的分泌[30]。miRNA 对于肥大细胞的调节作用主要集中在影响其细胞因子的分泌(表 1)。

Yamada 等[30]发现,在对人源肥大细胞系的实验中,通过抑制 Dicer 酶的活性,使 miRNA 的数量减少,此时肥大细胞脱粒现象也减少,所以推测肥大细胞的脱粒活动与 miRNA 的调节有关。在进一步的研究中发现,miR142-3p 过表达可以增强 FcεRI 所介导的肥大细胞脱粒现象,并且对 Dicer 静默作用而产生的脱颗粒减少现象有一定的拮抗作用。在从 miR142-3p 缺乏小鼠中获得的骨髓分化肥大细胞实验中,也得到了相似的结果。Yang 等[31]报道,miR-363 也有增强 FcεRI 的作用。miR-26a 和 miR-26b 的分泌能够影响环氧合酶 2(COX-2)的活性,调节分泌细胞因子和脱粒的水平[32]。miR26a 和 miR-26b 最关键的靶点为 COX-2,同时可以作用于 HDAC3、MCP1、TGase Ⅱ 的表达过程,减少炎症期间 FcεRI 和 Lyn 之间的相互作用。在 miR26a 抑制剂和 miR26b 抑制剂以及 miR26a 类似物和 miR26b 类似物的实验中也得到了相似的结果。

### 1.4　miRNA 对树突状细胞的调节作用

树突状细胞(dendritic cell,DC)是固有免疫过程和特异性免疫过程的桥梁细胞。miRNA 通过含量水平的高低来调节 DC 的状态,影响炎症的过程(表 1)。

miR-155 能够诱导 TLR 激活,促进 IL-1β、TNFα 和 TNFβ 等细胞因子的生成,参与氧化低密度脂蛋白和低密度脂蛋白的代谢过程[33]。通过调节 TLR 的活性,miR-155 也影响了下游 CD40 和 CD86 的表达。人源单核细胞来源的树突状细胞(moDC)中的 miR-155 能调节 PU.1 的 mRNA 表达水平。研究发现,在 moDC 成熟的过程中,miR-155 表达水平的升高会降低转录子 PU.1 的水平,并引起树突状细胞表面 2 型跨膜凝集素受体(DC-SIGN)的 mRNA 的降解[34]。Ceppi 等[35]发现,在 LPS 激活的 moDC 中,miR-155 的含量上升,导致炎症过程中 IL-1α、IL-1β、IL-6、TNF-α 以及 IL-23 等细胞因子基因表达的上调。相似地,Let-7i 和 miR-126 含量水平的升高、miR-107a 含量水平的降低对炎症过程起也到正调节作用[36-38]。相反地,miR-29a、miR-146a、miR-148 含量水平的上升和 miR-142 含量水平的下降有抑制炎症的作用[39-44]。

### 1.5　miRNA 对 NK 细胞的调节作用

NK 细胞是参与固有免疫应答中又一种重要的细胞。它可不依赖抗原提呈细胞的呈递和补体系统的介导,直接杀伤靶细胞;此外,NK 细胞亦可通过释放细胞因子,参与免疫功能的调节。对于已经被病毒所感染的细胞,NK 细胞能够通过穿孔素(perforin,Prf1)/颗粒酶(granzyme B,GzmB)和(或)通过 Fas 调节的途径,导致由激活的 caspase 蛋白酶系列调节并产生核 DNA 片段的细胞程序性凋亡。同时,NK 细胞所释放的 IFN-γ 可以调节 Mφ 和中性粒细胞免疫细胞。近期研究发现,NK 细胞的功能与 miRNA 的调节密切相关(表 1)。

Fang 等[45]在研究中发现了一种新的在 NK 细胞中表达的 miRNA——miR-362-5p。进一步研究发现,miR-362-5p 的作用靶点为 NF-κB 通路上的负调控子肿瘤抑制因子(CYLD)。miR-362-5p 的过表达能增强 CYLD 所调控的下游 IFN-γ、Prf1、GzmB、CD107a 的表达,增强 NK 细胞的细胞毒作用。

Ma 等[46]发现,miR-30c 可以通过上调 NKG2D 的表达水平来提高 NK 细胞的细胞毒作用。通过直接作用于转录因子同源框包含子 1 提高细胞内肿瘤坏死因子 α 的表达,使细胞内 miR-30c-1 的表达过量,构建出具有很强细胞毒性的 NKL 细胞系。发现过度表达 miR-30c 的 NKL 细胞系能够明显增强 NKL 细胞对 SMMC-7721 细胞的细胞毒性,并且能够明显上调 FasL 的表达。相反,miR-1245 能够负向调节 NKG2D 的表达,从而调节 NK 细胞的细胞毒性[47]。

Prf1 和 GzmB 是 NK 细胞发挥细胞毒性的重要介质,Kim 等[48]发现 miR-27a 能够静默 Prf1 和 GzmB 的表达,负向调节 NK 细胞的细胞毒性。在敲除 miR-27a 后,NK 细胞的细胞毒性急剧增加,

能显著降低移植瘤在体内的生长速率。此外,miR-150通过调节Prf1影响NK细胞的细胞毒性。

### 1.6 miRNA对嗜酸性粒细胞的调节作用

嗜酸性粒细胞是一种多功能性的粒细胞。研究认为[49],嗜酸性粒细胞主要作用对象以寄生虫为主,主要通过分泌碱性蛋白来破坏寄生虫的膜结构,达到杀灭病原体的目的。miRNA在IL-5Rα、CCR3等碱性蛋白的表达过程中具有重要的调节作用(表1)。

Yang等[50]研究发现,在炎症发生的4~14 d中,与IL-5Rα、CCR3相关的转录因子克隆表达明显增加。在应用IPA软件和miRanda数据库进行miRNA和特殊转录子进行匹配后发现,所选择的68个miRNA均不能直接调节粒细胞主要碱性蛋白(major basic protein,MBP)或者嗜酸性粒细胞相关的核糖核酸酶。相比之下,有7个miRNA与IL-5Rα链的调节相关,其中2个表现为正向调节(miR-362-5p,miR-1896),5个显示为负向调节(miR-7b,miR-181c,miR-467e,miR-486,miR-669b)。与CCR3表达相关的miRNA有10个,其中miR-193b,miR-292-5p,miR-1896等3个为正向调节,miR-7b,miR-378,miR-421,miR-467a,miR-467b,miR-467e,miR-486等7个为负向调节。其中,miR-7b,miR-467e,miR-486,miR-1896与IL-5Rα、CCR3的表达均有关联。

## 2 miRNA与疾病

miRNA作为一类精确的小分子生物标志物,作用靶点多且精确,同时具有较好的流动性和传递性,能够在机体组织和体液中穿梭[50-54],其中包括血清、血浆、眼泪、尿液、羊水、胃液等。在穿梭的过程中,miRNA能够携带重要的生物信号,调节机体的状态。基于miRNA的这个特点,并且得益于miRNA检测方法的进步[55],对miRNA检测有助于临床中对疾病的预测、诊断以及治疗等工作的进行[56-58]。目前,miRNA对于各类疾病过程中炎症过程的诊断和治疗方面已有较多的应用,其中,在肿瘤和脑卒中方面的运用已较为成熟。

### 2.1 miRNA与肿瘤过程中炎症调控

肿瘤miRNA(oncogenic miRNAs,oncomiRs)是一类在肿瘤的病理过程中过度表达的具有病理性质的miRNA。肿瘤的病理过程中,部分miRNA能够参与肿瘤状态下的炎症反应的调节,影响相关炎症因子的表达。因此,检测肿瘤进程中特定的miRNAs表达,将有助于对肿瘤过程中炎症状态的诊断和评价。

在结肠癌的发展进程中,miR-21的含量显著升高[59],并且,miR-21和IL-6的含量水平呈现出正相关的关系[60]。这提示miR-21可能是通过调节IL-6等细胞因子来调节结肠癌进程中的炎症状态的。Iliopoulos等[61]也证实miR-21对结肠癌期间的炎症反应存在正反馈调节的作用。此外,Strillacci等[62]报道,在结肠癌的过程中,miR-101会出现显著的下调,并且导致COX-2的过表达,从而导致急性炎症的发生。相似地,miRNA也可以通过调节与炎症相关的细胞因子影响肺癌病理过程中炎症的状态[63],同时也能阻止肿瘤细胞的浸润、迁徙、转移[64]。

### 2.2 miRNA与脑卒中过程中炎症调控

脑卒中是一种具有高致死率的急性中枢炎症反应。疾病发生过程中,局部缺血和再灌注均能造成不可逆的炎症损伤,并且导致脑内局部细胞死亡和血-脑脊液屏障的紊乱[65]。在传统诊断中,脑卒中发病过程具有发病急、不易监测等特点,不能提前得到有效诊断和预防。但随着miRNA在临床诊断方面的应用,为脑卒中的早期诊断提供了可能。

Wang等[66]发现,相比于MRI诊断阴性的患者,在磁共振成象诊断呈现阳性的脑卒中早期患者血清中,hsa-miR-106b-5P和hsa-miR-4306的含量显著性增高,hsa-miR-320d的含量显著性降低,提示这3种miRNA可能作为新的生物标志物在急性脑卒中进行早期检测。Liu等[67]报道,在急性缺血性脑卒中的发生过程中,参与调节与中枢炎症相关的基质金属蛋白酶(matrix metalloproteinase-9,MMP-9)和C反应蛋白的3种miRNA(miR-124、miR-9、miR-219),在血浆中的含量水平较正常对照人群均有显著的下降。提示这3种miRNA将可能作为潜在的治疗靶点,用于对脑卒中损害程度进行改善。

## 3 小结与展望

固有免疫是机体抵御外来病原体的第一道防线,其作用的重要性逐渐被人们认识[1]。随着研

究的深入,miRNA 在固有免疫应答过程中的调节作用逐渐被阐释。以上研究表明,miRNA 主要是通过调节炎症相关细胞因子表达释放、影响固有免疫细胞特定表面受体的表达以及影响细胞内关键酶表达来参与调控固有免疫应答过程的。因此,寻找 miRNA 调节固有免疫的相关机制,对于准确调控固有免疫具有积极的意义。

中枢炎症网络和外周炎症网络并不是孤立存在的。研究者们已经证实,巨噬细胞和树突状细胞能够通过血-脑脊液屏障,进入中枢系统中参与免疫反应[68]。同时,miRNA 也可能作为中枢-外周炎症网络中的信号物质存在。小胶质细胞和巨噬细胞同源于单核细胞,具有相似的免疫学特性。成熟的巨噬细胞广泛分布于肺泡、胸腔、脾脏、肝脏、肾小球等外周各器官中,是外周免疫最重要的免疫细胞之一,在外周固有免疫应答过程中有重要的调节作用;小胶质细胞主要聚集于中枢神经系统内,是中枢神经系统中重要的免疫细胞,在中枢炎症过程中发挥重要的免疫作用。在固有免疫应答的过程中,miR-101、miR-125b、miR-155、miR-21、miR-9、miR-92a 等 miRNA 在对于小胶质细胞与巨噬细胞具有相似的调节作用,作用于相同或者相似的炎症靶点,对相同的炎症通路进行调节。而 miRNA 作为具有生物活性的小分子物质,能够自由穿过血-脑脊液屏障,所以可以猜测,在中枢-外周的炎症网络中,miRNA 可能是构建次网络的物质基础之一,为中枢炎症状态和外周炎症状态的交流提供了信息传递的物质基础[69]。

在疾病的治疗过程中,机体对药物的耐受性是疾病无法得到及时治疗和有效治疗的一大阻碍。而部分具有多重调节功能的 miRNA 具有成为治疗此类疾病的有效候选靶点。部分 miRNA(如 miR-21)具有既有关于炎症反应,又在肿瘤的发生过程中其重要调节作用的特性[55]。对于部分耐药的肿瘤,此类 miRNA 具有较好的诊断和治疗价值。Lauren 等[70]总结报道,因为基于调整细胞周期和调节代谢过程,miRNA 能够对部分耐药的肺肿瘤细胞的生长和代谢过程进行抑制,作为新的治疗靶点对肿瘤进行治疗。

此外,miRNA 对于固有免疫的调控具有重要的意义,除了上述调控位点和功能以外,尚有一些固有免疫过程中经典的调控途径未见 miRNA 调控的相关报道。ROS 途径是机体内涉及到的又一种重要的抵御病原微生物的免疫途径。ROS 的生成受到多种酶系的调控,如 Mφ、嗜酸性粒细胞内 ROS 的产生需要关键酶黄细胞色素 b558 的参与,而其编码基因是否能作为 miRNA 的调控靶标,miRNA 是否能通过影响免疫细胞中 ROS 的生成来增强或者减弱固有免疫细胞的活性,有待进一步深入研究。相似的,补体系统在固有免疫应答过程中具有重要的意义,虽然之前的报道中有关于 miRNA 对补体系统 H 因子、正五聚蛋白 3(Pentraxin 3)等补体系统成分的调节作用[71-73],但是关于 miRNA 能否系统地通过调节补体系统影响固有免疫的过程,需要进一步深入的研究。此外,之前的研究发现,肝脏在固有免疫的急性期所分泌的补体反应蛋白[59]、甘露糖结合蛋白[74]、$\alpha_1$-酸糖蛋白[75]、血清淀粉 P 物质[76]等能够增强机体抵抗力,减少组织损伤并且促进炎症损伤的修复,同时肝脏中 miRNA 的含量在整个固有免疫过程中亦有明显的变化[77]。那么,在固有免疫阶段,miRNA 是否参与这些蛋白的表达调控以及肝脏是否能通过这些蛋白的分泌而参与固有免疫应答过程的问题,尚有待进一步深入的研究。

**Table 1**　miRNAs in different cells relating with innate immune

| Cell | miRNA | Reported involvement/function | Reference |
|---|---|---|---|
| Microglia | let-7a | Ischaemia | [29] |
| | miR-9 | Ischaemia, MCPIP1 and NF-κBsignal pathway | [28,78 - 80] |
| | miR-17 | NADPH oxidases and reactive oxygen species production | [81] |
| | miR-21 | Ischaemia | [79] |
| | miR-22 | Purinergicsignal pathway | [82] |
| | miR-29b | Aging, TNF, IP3 and NF-κB signal pathway | [84] |
| | miR-32 | TRAF3 signal pathway | [84 - 85] |
| | miR-34a | NF-κB signal pathway and TREM2-regulated | [86 - 88] |
| | | Phagocytosis activity | |
| | | p53 signal pathway | |

(Continued)

| Cell | miRNA | Reported involvement/function | Reference |
|---|---|---|---|
| | miR-92a | JNK/c-Jun through targeting of MKK4 | [89] |
| | miR-124 | Ischaemia | [79] |
| | miR-124a | CEBPA-SPI1 (PU.1) signal pathway, cell activation, cell quiescence | [90 -91] |
| | miR-125b | Purinergic signal pathway, STAT3 signal pathway | [82] |
| | miR-132 | Ischaemia | [79] |
| | miR-134 | Ischaemia | [79] |
| | miR-138 | Ischaemia | [79] |
| | MiR-142 | Viral infections, SIRT1 regulation | [79,92] |
| | miR-145 | Contribute to alternative activation, IL4/STAT6 signal pathway, p53 signal pathway | [93] |
| | miR-146a | Promoting and resolving inflammation, tumor suppression, NF-κB and JAK-STAT | [94 -95] |
| | miR-146b | Purinergicsignal pathway | [82] |
| | miR-155 | Contribute to classical activation state, SOCS1 activity | [96] |
| | miR-181a | Ischaemia | [97] |
| | miR-195 | Autophagy | [98] |
| | miR-200b | c-Jun/MAPK signal pathway | [99] |
| | miR-221 | Ischaemia | [79] |
| | miR-222 | Ischaemia | [79] |
| | miR-365 | NF-κBsignal pathway, IL6/STAT3 signal pathway | [82] |
| | miR-424 | Cell cycle regulation and pro-inflammatory pathways | [86 -88] |
| | miR-689 | Canonical pro-inflammatory pathway | [93] |
| | miR-711 | Canonical pro-inflammatory pathway | [93] |
| Macrophage | let-7i | Toll-like receptor | [21] |
| | miR-101 | MKP-1/MAPK signal pathway | [24] |
| | miR-125b | Toll-like receptor | [15,17,22 -23] |
| | miR142-3p | decrease TNF-α production, inhibit phagocytosis | [7] |
| | miR-146 | Target TRAF6, IRAK1 and IRAK2, NF-κB signal pathway | [8 -9] |
| | miR-147 | TLR2, TLR3, TLR4 | 20] |
| | miR-155 | TLR2, TLR3, TLR4, TLR9, TNF-α, SOCS1, SHIP1 | [12 -19] |
| | miR-21 | TLR7/TLR8, PDCD4 | [9 -11] |
| | miR-24 | decrease TNF-α production, inhibit phagocytosis | [7] |
| | miR-30b | decrease TNF-α production, inhibit phagocytosis | [7] |
| | miR-92a | Toll-like receptor | [25] |
| | miRNA-451 | Ago2 translation | [26] |
| Mast cell | miR142-3p | FcεRI gene related with degranulation | [30] |
| | miR-363 | FcεRI gene related with degranulation | [31] |
| | miR-26a | COX-2, degranulation, cytokine production, HDAC3, MCP1, Tgase Ⅱ | [32] |
| | miR-26b | COX-2, degranulation, cytokine production, HDAC3, MCP1, Tgase Ⅱ | [32] |
| Dendritic cell | miR-155 | Target Arg2, regulate expression of IL-1β, IL-6, IL-23, TNF-α, TNF-β and PU.1, and degrade the mRNA of DC-SIGN receptor | [33 -35] |
| | let-7i | CD80 and CD86 | [21] |
| | miR-29a | Induces cell cycle arrest through the down-regulation of p42.3 | [39 -44] |
| | miR-107a | Pro-inflammatory cytokine production | [36 -38] |
| | miR-126 | Negatively worked on kinase mTOR | [36 -38] |
| | miR-142 | Pro-inflammatory cytokine production and T-cell activation | [39 -44] |
| | miR-146a | Target IL-1 receptor-associated kinase 1 to block TLR-induced NF-κB | [39 -44] |
| | miR-148a | Calcium/calmodulin-dependent | [39 -44] |
| | miR-148b | Protein kinase IIα | [39 -44] |
| NK cell | miR-27a | Silence gene of Prf1 and GzmB to decrease cytotoxicity of NK cell | [48] |
| | miR-30c-1 | Target at NKG2D to improve cytotoxicity | [46] |
| | miR-150 | Target at Prf1 to influence the cytotoxicity of NK cell | [48] |
| | miR-362-5p | Target at CYLD to influence expression of IFN-γ, Prf1, GzmB2 and CD107a | [45] |
| | miR-1245 | Target at NKG2D to decrease cytotoxicity | [47] |

(Continued)

| Cell | miRNA | Reported involvement/function | Reference |
|---|---|---|---|
| Eosinophilic granulocyte | miR-7b | Down-regulation of IL-5α<br>Down-regulation of CCR | [50] |
| | miR-181c | Down-regulation of IL-5α | [50] |
| | miR-193b | Up-regulation of CCR | [50] |
| | miR-292-5p | Up-regulation of CCR | [50] |
| | miR-362-5p | Up-regulation of IL-5α | [50] |
| | miR-378 | Down-regulation of CCR | [50] |
| | miR-421 | Down-regulation of CCR | [50] |
| | miR-467a | Down-regulation of CCR | [50] |
| | miR-467b | Down-regulation of CCR | [50] |
| | miR-467e | Down-regulation of IL-5α | [50] |
| | miR-486 | Down-regulation of IL-5α<br>Down-regulation of CCR | [50] |
| | miR-669b | Down-regulation of IL-5α | [50] |
| | miR-1896 | Up-regulation of IL-5α<br>Up-regulation of CCR | [50] |

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