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miRNA在结核病中对巨噬细胞免疫反应影响的研究进展

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摘　要

结核分枝杆菌(*Mycobacterium tuberculosis*, Mtb)是结核病(Tuberculosis, TB)的病原菌，侵入人体后巨噬细胞是结核分枝杆菌主要固有免疫细胞，巨噬细胞(Macrophage, Mø)具有高度的异质性和可塑性，在不同的刺激下可极化成M1、M2型巨噬细胞。外泌体作为细胞及器官间通讯的介质，将其内包含的microRNA等信号因子传递到各个细胞或器官影响其功能活动，有研究表明微小RNA (microRNA, miRNA)参与了抑制细胞凋亡、自噬及细胞因子分泌等先天免疫细胞反应，同时miRNA可通过调节巨噬细胞极化趋势，影响结核杆菌的清除效率。本综述描述了结核分枝杆菌感染后外泌体来源的miRNA参与机体免疫反应，包括参与炎症、细胞凋亡、自噬以及调节巨噬细胞极化对结核杆菌影响的研究进展，还阐述了外泌体miRNA作为诊断或治疗结核病的一种新型标志物的潜力性。

关键词

结核病，miRNA，先天免疫细胞反应，M1/M2型巨噬细胞，生物标志物

Research Progress on the Effect of miRNA on the Immune Response of Macrophages in Tuberculosis

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Abstract

Mycobacterium tuberculosis **(Mtb) is the pathogen of tuberculosis (TB). Macrophages are the main innate immune cells of** ***Mycobacterium tuberculosis*** **after invading human body. Macrophages are highly heterogeneous and plastic, and can be polarized into M1 and M2 macrophages under different stimuli. As a communication medium between cells and organs, exosomes transmit signal factors such as microRNA to various cells or organs, which affects their functional activities. Studies have shown that MicroRNA is involved in inhibiting innate immune cell reactions such as apoptosis, autophagy and cytokine secretion, and at the same time, miRNA can affect the clearance efficiency of** ***Mycobacterium tuberculosis*** **by regulating the polarization trend of macrophages. This review describes the progress of research on the role of exosome-derived miRNA in the immune response to** ***Mycobacterium tuberculosis*** **infection, including inflammation, apoptosis, autophagy, and regulation of macrophage polarization on** ***Mycobacterium tuberculosis*****. It also describes the potential of exosomal miRNA as a new marker for the diagnosis or treatment of tuberculosis.**

Keywords

Tuberculosis, miRNA, Innate Immune Cell Response, M1/M2 Macrophages, Biomarker

1. 引言

TB 是由结核分枝杆菌引起的一种可治愈和预防的具有较高传染性的疾病，结核分支杆菌通过飞沫进入机体后引起一系列呼吸道等免疫反应。世界卫生组织在《2021 年全球结核病报告》中指出，我国 2020 年结核病发病率为 59/10 万(2019 年 58/10 万)，成为目前全球第二大结核病高负担国家[1]，在冠状病毒(COVID-19)流行病之前，结核病是单一感染源致死的主要原因，估计 2020 年新增 990 例结核病患者，相当于每 10 万人中有 127 例[2]，对全人类生命健康造成重大威胁。世界上大约四分之一的居民感染了结核分枝杆菌[1]，但只有 5%~10%的感染者患病出现临床症状，发展为活动性结核，但其相关发病机制尚不明确。因此，探索 TB 发病机制为早期诊治提供证据是有需要的。

2. 巨噬细胞

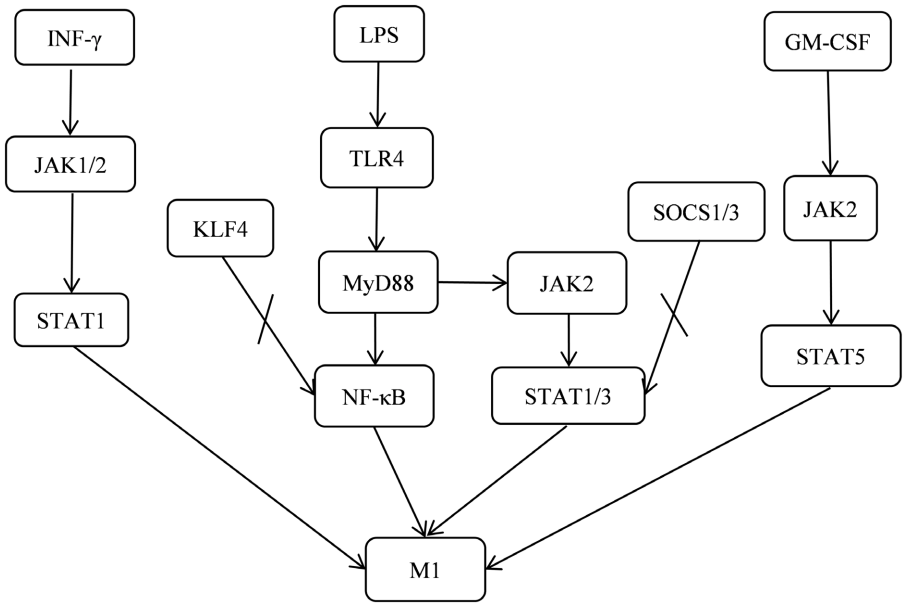
巨噬细胞是结核分枝杆菌的主要宿主细胞，例如肺泡巨噬细胞(AMs)，单核细胞衍生巨噬细胞(MDMs)和间质巨噬细胞(IMs)，在 Mtb 通过呼吸道进入肺泡内时，通常肺泡巨噬细胞(AMs)是首先遇到 Mtb 感染的细胞之一[3]，目前认为巨噬细胞的主要作用有：1) 吞噬病原体、碎片和死亡细胞；2) 抗原处理和呈递；3) 产生不同类型的细胞因子来激活或抑制适应性免疫细胞[4]，通过这些作用，巨噬细胞发挥着其独特的免疫反应，以此来防御病菌。巨噬细胞在体内普遍存在但又有细微差别的免疫细胞群体，不仅有血液中循环的单核细胞，还在大多数器官中可以找到特异性巨噬细胞，例如：肝血窦内的肝巨噬细胞(Kupffer cells)、皮肤中的兰氏细胞(Langerhans cells)、大脑中的小胶质细胞、脾红髓巨噬细胞、肺泡巨噬细胞、脂肪组织巨噬细胞和破骨细胞[5]，不同器官的巨噬细胞在吞噬作用的基础上还发挥着独特的免疫作用。外

周血中单核细胞是巨噬细胞前体，单核细胞/巨噬细胞的活化受到微环境刺激、细胞因子的诱导以及暴露的持续时间等的调节，具体表现为特定的巨噬细胞亚群在感染部位聚集，进而分化为具有特定功能的极化状态，如经典活化巨噬细胞 M1 型和替代活化巨噬细胞 M2 型[3]。巨噬细胞 M1 和 M2 在大多数病理状态下处于动态平衡。

2.1. 巨噬细胞极化机制

M1/M2 巨噬细胞极化的分子机制目前暂不十分明确，但已知主要相关通路有 JAK/STAT [6]、JNK 信号通路[7]、MAPK/NF-κB [8]和 PI3K/Akt 信号通路[9]等。已确定的主要途径之一是 JAK/STAT 途径，JAK-STAT 通路传导主要由 3 部分构成：酪氨酸激酶相关受体、非受体酪氨酸激酶(Janus 激酶，JAKs)和信号传导及转录激活因子(Signal Transducers and Activators of Transcription, STATs)。目前已经确定的 JAKs 有 4 种：JAK1、JAK2、JAK3 和酪氨酸激酶 2 (tyrosine kinase 2, TYK2)，STATs 由 6 个成员构成，即 STAT1-STAT6 [10]。JAK-STAT 基本信号传导过程如下：当信号分子与细胞表面受体结合后，受体分子发生二聚化，促进 JAKs 聚合和磷酸化，激活的 JAKs 可与 STATs 的 SH2 结构域相结合，STATs 磷酸化修饰后激活，启动下游靶基因，进而发挥其细胞生物功能的调控作用。每种细胞因子可通过不同路径诱导巨噬细胞极化，但巨噬细胞极化的途径和调节过程并不是那么简单，更甚至可随环境变化而发生极化转化。

2.2. JAK/STAT 信号通路介导巨噬细胞极化 M1\M2



注：KLF4，Kruppel 样因子 4；SOCS，细胞因子信号抑制物；→，促进；↛，抑制

Figure 1. JAK/STAT signaling pathway mediates M1 polarization of macrophages
图 1. JAK/STAT 信号通路介导巨噬细胞 M1 极化

JAK/STAT 途径中，其中脂多糖(Lipopolysaccharides, LPS)、干扰素-γ (Interferon-γ, IFN-γ)和粒细胞－巨噬细胞集落刺激因子(Granulocyte-macrophage Colony Stimulating Factor, GM-CSF)参与 M1 极化，而白介素-4 (Interleukin-4, IL-4)和 IL-13 主要介导 M2 极化。IFN-γ 与对应受体相结合，可促进 JAK1 与 JAK2 聚合和磷酸化，下一步诱导 STAT1 磷酸化和二聚体形成，促进 M1 极化[11]，分泌促炎因子参与抗感染。

LPS 与巨噬细胞膜上 Toll 样受体(Toll-like Receptors, TLR)结合，下游髓分化因子 88 (Recombinant Myeloid Differentiation Factor 88, MyD88)、含 Toll-白细胞介素 1 (toll-interleukin 1 receptor, TIR)受体结构域衔蛋白发出适当的信号，通过两条途径激活 M1，① 激活 JAK2-STAT1/STAT3 路径[12]；② 激活核转录因子-kappaB (Nuclear Factor-kappaB, NF-κB) [13]；两种途径均可促使 M1 极化(如图 1)。IL-4 激活巨噬细胞中 JAK1/JAK3-STAT6 信号通路，诱导 M2 极化，并参与肌腱骨的愈合[14]。STAT6 主要受 IL-4 和 IL-13 刺激(如图 2)。

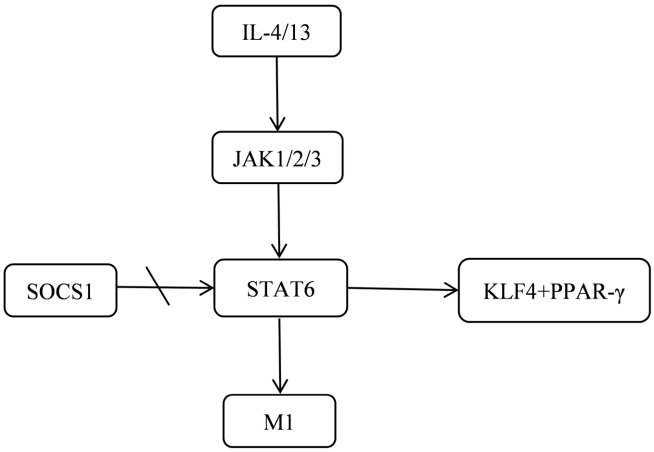


Figure 2. JAK/STAT signaling pathway mediates M2 polarization of macrophages
图 2. JAK/STAT 信号通路介导巨噬细胞 M2 极化

2.3. 促炎性 M1 型巨噬细胞

M1 型巨噬细胞可由单独的 LPS、IFN-γ 或 GM-CSF 刺激巨噬细胞极化而成，极化成 M1 的巨噬细胞可产生活性氧(reactive oxygen species, ROS)和一氧化氮(NO)以及大量的促炎细胞因子如白介素-6 (IL-6)、白介素-12 (IL-12)、IL-23，肿瘤坏死因子-α (Tumor Necrosis Factor, TNF-α)和环氧合酶 2 等，M1 细胞还可分泌大量的趋化因子，如 CCL2、CXCL10、CXCL11 等诱导附近的免疫细胞[15]，M1 展示出吞噬消灭病原菌、促炎和诱导 TH1 免疫反应的能力。M1 极化已被证明有助于宿主控制细菌感染，包括单核细胞增生李斯特菌(*Listeria monocytogenes*)、鼠伤寒沙门氏菌、结核分枝杆菌和衣原体感染[16]。

2.4. 抗炎性 M2 型巨噬细胞

抗炎细胞因子 IL-4、IL-13 和 IL-10 介导巨噬细胞向 M2 型方向极化，该过程又与表面分子 Dectin-1、DC-SIGN、清道夫受体 A 和甘露糖受体 CD206 上调相关，可根据表面分子的表达进行鉴定 M2 型巨噬细胞。M2 型 Mφ 通过释放高水平抗炎细胞因子 IL-10 和转化生长因子(Transforming Growth Factor-β, TGF-β)等，使其具有抗炎、血管生成和 Th2 免疫负性调节特性[3]。通常情况下 M2 极化状态下的特征是不分泌或极少分泌促炎因子，分泌抗炎因子，加强细胞清除能力，促进损伤组织的修复和重塑[16]。认为 M2 型巨噬细胞又可分为四种亚型，即 M2a、M2b、M2c、和 M2d，以及 M4、Mhem 和 Mox [17]。

在感染早期巨噬细胞为了保护机体，通常选择具有灭菌和促炎能力的 M1 型极化，然而结核分枝杆菌拥有着防止 M1 样极化或推动极化向 M2 表型的能力，以此来逃避宿主的免疫反应。巨噬细胞极化在耐多药结核病/广泛耐药结核发病过程中，我们发现 M1 型巨噬细胞表达水平较低，而 M2 型方向极化的巨噬细胞表达量较高，机体免疫反应被抑制，结核分枝杆菌表现为免疫逃逸情况，在宿主细胞内存活[18]。

巨噬细胞主要表现为向 M2 型方向极化不仅存在肺结核等感染性疾病中，还存在于在肺部小细胞肺癌[19]、肝癌[20]、结肠癌[21]中，表现为促进肿瘤的进展。

3. microRNA

miRNA 是可以塑造细胞基因表达模式的小调节 RNA [22]。微小 RNA 是一类小的(≈22 个核苷酸长)单链非编码 RNA，可与靶 mRNA 的 3′非翻译区(3′UTR)互补序列结合，致使 mRNA 降解或翻译抑制，以控制基因表达产生巨大的生物学效应[23]。微小 RNA 在受体细胞中的功能一般可分为两种类型：一种是常规，即通过 RNA 干扰转录水平实现负调节并使靶基因表达水平发生特征性改变；一种是新型，通过与 Toll 样受体结合激活免疫细胞[22]，如 miR-21 和 miR-29a [24]。

3.1. miRNA 来源于外泌体

Pan 和 Johnstone 在研究绵羊网织红细胞成熟过程时首次观察到外泌体，他们称之为囊泡，后来被定义为“外泌体”[25]。外泌体被认为是一种独特的囊泡群体，是自身细胞内的多囊泡体与细胞膜融合后以外分泌的形式释放到细胞外的纳米囊泡[26]，其大小与微泡不同，外泌体定义为 30~100 nm 范围内的脂质双分子层囊泡，该双分子层围绕着高度异质性的物质，该物质是由蛋白质、脂质、核酸和 microRNA 等组成，外泌体已被证明可以将包含的物质传递出细胞，这种特性决定了外泌体能够介导细胞间或者器官间通讯，调节细胞的功能或活动，比如炎症、干细胞维持和组织修复和免疫反应等[27]。

3.2. 外泌体中 microRNA 可作为肺结核生物标志物

外泌体 miRNA 在癌症、心血管疾病、自身免疫性疾病和传染病等疾病中可作为新型生物标志物[28]。外泌体脂质双分子层十分稳定，使包含在内的物质不易被酶降解，保护囊泡内 miRNA 使其相对稳定保存生物学信号，同时外泌体存在生物体各种体液中[22]，被外泌体包裹的 miRNA 可以即准确又稳定的反应疾病信息。在结核病方面，李晓燕等人通过荟萃分析的结果表明，miRNA-155 是可以作为识别活动性结核病的有效生物标志物，并且该生物标志物在儿童中的准确性和有效性是高于成人[29]。Kim J 等人研究发现 miR-199b-3p、miR-6886a-3p、miR-6856-3p、miR-16-5p、miR-374-5p 和 miR-199c-3p，在活动性肺结核(Active Pulmonary Tuberculosis, ATB)患者血液中显著上调，其中特别是 miR-199a-3p 和 miR-6886-3p 可用作检测 TB 感染和区分 ATB 和潜伏期肺结核(latent tuberculosisInfection, LTBI)的生物标志物[30]。Alipoor 等人对结核病患者血清外泌体的 miRNA 谱进行了揭示，表明 miR-484、miR-425 和 miR-96 在结核病中显著上调，并与结核感染水平相关[31]。结核病患者血液中 miR-29a-3p 表达上调被证实是区分活动性结核病和潜伏期肺结核的有价值的候选生物标志物，也是诊断结核病的有效生物标志物[32]。

3.3. MTB 感染后分泌的外泌体 miRNA 作为重要的免疫调节因子

在结核病的进展中外泌体 miRNA 起着关键作用。有研究表明结核分枝杆菌进化出多种机制逃避机体的免疫清除，包括参与控制生物过程的宿主 miRNA 的表达[33]。外泌体 miRNA 表达可以通过诱导先天免疫细胞反应，如调控细胞凋亡、自噬体的形成及成熟和自噬、细胞因子分泌参与结核分枝杆菌的杀伤或逃逸[34] (如表 1)。

miRNA 还可以通过调节转录因子来改变微环境来控制巨噬细胞极化方向，影响促炎和抗炎因子的分泌。在结核分枝杆菌入侵体内后，结核分枝杆菌常通过调整一些系列机制来促使巨噬细胞朝着 M2 方向极化，以此来逃避免疫反应。通常认为 Kruppel 样转录因子(Kruppel-like Factors, KLF)家族中 KLF4 激活促进 M2 极化[56]，KLF6 激活促进 M1 极化作用[57]，有团队观察到 miR-26a 在结核分枝杆菌感染期间下调，引起 KLF4 的上调，通过诱导 M2 极化和抑制结核分枝杆菌向溶酶体的运输而导致 MTB 存活[58]。

Bi J 等人发现，miR-181a 通过直接靶向抑制 KLF6 促进 M2 巨噬细胞极化[59]。在一篇研究中，提出在结核感染后上调的 miR-27a/b 和 miR-135a-5p 分别通过干扰素调节因子 4 (Interferon Regulatory Factor 4, IRF4) 和 STAT6 诱导 M2 极化，相反下调的 miR-155 通过抑制 SOCS1 促进 M1 极化[60]。miRNA 影响巨噬细胞的极化方向在其他疾病中也有体现，如：肺腺癌(Lung Adenocarcinoma, LUAD)-LUAD 细胞通过外泌体 miR-3153 的传递，激活 JNK 信号通路，诱导 M2 型巨噬细胞极化，从而促进 LUAD 的进展[7]；结直肠癌－结直肠癌相关巨噬细胞来源的 miRNA-934 表达上调，通过下调 PTEN 表达和激活 PI2K/AKT 信号通路促进 M2 极化，以此促进结直肠癌肝转移[61]。糖尿病-miR-130b 也通过抑制 PPAR-γ 使其极化偏向 M1 表型，促进糖尿病组织炎症及胰岛素抵抗[62]。这些发现为我们在基因方面控制和消除肺结核提供了新思路，可定向敲除或诱导对应的 miRNA，调控巨噬细胞极化，使其发挥对应的促炎及抗炎作用。

Table 1. miRNA-mediated immunomodulation in tuberculosis
表 1. 结核病中 miRNA 介导免疫调节

miRNAs	Expression	Targets	Biological function	Ref.
miR-33	↑	ATG5、ATG12、LAMP1、LC3B、FOXO3、TFEB、AMPK	抑制自噬途径、溶酶体功能和脂肪酸氧化	[35]
miR-889-5p	↑	TWEAK	抑制自噬体成熟	[36]
miR-432-5p	↑	VPS33A	抑制自噬体－溶酶体融合/抑制自噬体成熟	[37]
miR-23a-5p	↑	TLR2、MyD88、NF-κB	抑制自噬激活	[38]
miR-25	↑	NPC1	自噬障碍	[39]
miR-27a-5p	↓	Ca^{2+}/CACNA2D3	抑制自噬体形成	[40]
miR-106a	↓	ULK1、ATG7、ATG16L	激活自噬	[41]
miR-125a-5p	↑	STAT3	激活自噬	[42]
miR-708-5p	↑	TLR4	降低 IFN-γ、IL-6、IL-1β 和 TNF-α 等促炎因子的分泌	[43]
miR-99b-5p	↑	TNFRSF-4、TNF-α	降低 IL-6，IL-12 和 IL-1β 的产生，发挥抑制炎性作用。	[44]
miR-502-3p	↑	ROCK1	抑制 IL-6，IL-1β 和 TNF-α 的产生	[45]
miR-32-5p	↑	FSTL1	抑制炎性细胞因子 IL-1β，IL-6 和 TNF-α 的积累	[46]
miR-let-7f	↓	TNFAIP7、A20	降低 NF-κB 活性来减少 IL-1β、TNF-α、趋化因子和 NO 的产生	[47]
miR-342-3p	↓	SOCS6	抑制 TNF-α，IL-1，IL-6 等炎症因子和趋化因子-15 的分泌	[48]
miR-223	↑	FOXO3	抑制细胞凋亡	[49]
let-7b-5p	↑	Fas	抑制细胞凋亡	[50]
miR-20b-5p	↓	Mcl-1	抑制凋亡	[51]
miR-27b	↑	p53、Bag2	促进细胞凋亡和细胞杀伤	[52]

Continued

miR-125b-5p	↑	DRAM2	促进凋亡	[53]
miR-125a	↓	Bmf	诱导凋亡	[54]
miR-20a-5p	↓	JNK2	触发巨噬细胞凋亡	[55]

注：miRNA，microRAN；express，表达；targets，靶标；biological function，生物学功能；ref，参考；ATG，自噬相关基因；LAMP，溶酶体相关膜蛋白；LC3，微管相关蛋白 1 轻链；FOXO，叉头盒转录因子 O 类；TFEB，转录因子 EB；AMPK，腺苷单磷酸活化蛋白激酶；TWEAK，TNF 样弱细胞凋亡诱导剂；VPS，液泡蛋白分选；iNOS，一氧化氮合酶；CACNA2D3，钙电压门控通道辅助亚基 $\alpha 2\delta 3$；ULK，丝氨酸/苏氨酸蛋白激酶；STAT，信号换能器和转录激活剂；TNFRSF-4，TNF 受体超家族成员-4；ROCK1，Rho 相关螺旋形成蛋白激酶 1；FSTL1，卵泡抑素样蛋白 1；TNFAIP7，TNFα 诱导蛋白 3；Fas，凋亡相关因子重组蛋白；Mcl，髓样细胞白血病分化蛋白；Bag2，Bcl-2 结合抗凋亡基因 2；DRAM2，DNA 损伤调节自噬调节剂 2；Bmf，Bcl 修饰因子；JNK，Jun N-末端激酶；↑，上调；↓，下调。

4. 结论与展望

结核分枝杆菌入侵人体后，大多数人不会活动性发病，细菌在体内长期潜伏着，然而目前大多数手段对于潜伏期结核诊断困难，且对于早期活动性肺结核诊断也较复杂及漫长，为降低肺结核传播，研究便捷的新型生物标志物迫在眉睫。此时，外泌体 miRNA 不仅可作为肺结核等疾病的诊断生物标志物，还可作为基因治疗的载体。虽然 miRNA 在结核病的发病机制及生物标志物探查方面取得了有目共睹的成果，但仍需要大量的前瞻性研究明确其作为生物标志物的潜力，并为开发新的免疫疗法扫清障碍。

巨噬细胞存在全身各个组织细胞并承担着极为重要角色，巨噬细胞极化方向在一定程度上决定着疾病的进展：恢复或加重。但关于肺结核感染后 miRNA 调节巨噬细胞极化还需要大量的实验性研究明确其可靠性。重塑巨噬细胞极化可能是一种有前途的新型治疗方式。

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