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综 述

巨噬细胞极化及其在慢性阻塞性肺疾病中的作用

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摘 要：巨噬细胞具有高度可塑性，在炎症因子的诱导和多种信息分子的调控下可极化为经典活化巨噬细胞(M1)和替代活化巨噬细胞(M2)。慢性肺部炎症反应和肺实质损伤是慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)的主要病理表现。M1促进肺部炎症反应；M2抑制炎症反应，参与肺组织损伤与修复，并吞噬和清除病原微生物和凋亡细胞。靶向干预巨噬细胞极化方向有可能成为COPD治疗的新策略。

关键词：巨噬细胞；巨噬细胞极化；慢性阻塞性肺疾病
中图分类号：R562.2；R563.3；Q471

Macrophages polarization and their role in chronic obstructive pulmonary disease

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Abstract: Macrophages are highly plastic and can be polarized into classical activated macrophages (M1) and alternative activated macrophages (M2) under the induction of inflammatory factors and regulation of a variety of information molecules. Chronic pulmonary inflammation and pulmonary parenchyma injury are the main pathological manifestations of chronic obstructive pulmonary disease (COPD). M1 promotes pulmonary inflammation, whereas M2 inhibits inflammatory response, participates in lung tissue injury and repair, and swallows and removes pathogenic microorganisms and apoptotic cells. Target intervention in the polarization direction of macrophages may be a new strategy for COPD treatment.

Key words: macrophages; macrophages polarization; chronic obstructive pulmonary disease

巨噬细胞来自于骨髓源性的单核细胞、卵黄囊和胎儿单核细胞[1]，它是连接固有免疫和适应性免疫的重要桥梁，是呼吸道及肺部抵御微生物感染的首要防线。巨噬细胞具有高度可塑性，在微环境刺激下发生表型和功能上的适应性改变，即巨噬细胞极化[2]。通常，巨噬细胞极化有两种途径：经典活化途径和替代活化途径[3]。巨噬细胞极化在动脉粥样硬化[4]、哮喘[5]、肥胖[6, 7]等疾病中发挥了重要作用。最近研究证实，巨噬细胞极化在肺部疾病尤其是慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)中起到至关重要的作用[8]。通过调控巨噬细胞极化的方向，使其由促炎的M1型向抗炎的M2型转化，这有可能成为COPD等炎症性肺部疾病治疗的新策略。

1 巨噬细胞的来源

传统观点认为，巨噬细胞来自于骨髓源性的单核细胞。循环中的单核细胞随外周血分布到各个组织，进而分化为成熟的巨噬细胞，发挥免疫、组织修复、代谢平衡、促进组织发育等重要作用[9]。随

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着研究的深入，有学者发现部分组织中存在的巨噬细胞可独立于单核细胞，并且能够维持自我更新[1]。多数小鼠组织中的巨噬细胞来自于胚胎时期的卵黄囊原始巨噬细胞和胎儿单核细胞[1]。因此，巨噬细胞至少有 3 种来源：(1) 来源于卵黄囊，存在于皮肤、肝，胰、脾、脑和肺中；(2) 来自于胎儿单核细胞，如肺部的巨噬细胞、表皮中的朗格汉斯细胞；(3) 骨髓源性巨噬细胞，由单核细胞分化的 $F4/80^+$ 巨噬细胞定居于各器官组织中[1, 10, 11]。

2 巨噬细胞极化

巨噬细胞极化的概念起源于上世纪 90 年代，起初只将 γ- 干扰素 (interferon-γ, IFN-γ) 刺激的巨噬细胞命名为经典活化型巨噬细胞 (即 M1)[12]。后来学者又发现 IFN-γ 刺激的巨噬细胞还能被 Th2 型细胞因子白细胞介素 4 (interleukin 4, IL-4) 和 IL-13 所抑制，而 Th2 型细胞因子刺激的巨噬细胞被命名为替代活化型巨噬细胞 (即 M2)[13]。目前，M1 和 M2 是根据它们的刺激物、分泌的细胞因子、趋化因子、参与调控极化的转录因子及作用等方面进行区分的。

2.1 M1

现代研究证实，Th1 型细胞因子 IFN-γ 单独或联合脂多糖 (lipopolysaccharide, LPS) 或炎性细胞因子如肿瘤坏死因子 α (tumor necrosis factor α, TNF-α) 和粒细胞 - 巨噬细胞集落刺激因子 (granulocyte-macrophage colony stimutaing factor, GM-CSF) 均可刺激 M1 的产生[14]。M1 高表达细胞生物标志物如诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS)、CD86、Toll 样受体 4 (Toll-like receptor 4, TLR4) 和主要组织相容性复合物 -II (major histocompatibility complex II, MHC-II)[15, 16]。M1 可生成高水平的活性氧簇 (reactive oxygen species, ROS) 和 NO，并分泌促炎性细胞因子 TNF-α、IL-1β、IL-6、IL-12 以及 Th1 型趋化因子 (如 CXCL9-11、CCL5 等)[17]，趋化性吸引 Th1 细胞，引发强烈的炎症反应 (图 1)。因而，M1 负责调节 T 细胞抗原表达，促进炎症反应和 Th1 型细胞功能，参与 Th1 型免疫反应，抑制肿瘤生长，具有强烈的杀微生物活性作用，保护宿主免受病原体侵袭[18]。

2.2 M2

M2 一般由 Th2 型细胞因子 (如 IL-4、IL-13) 诱导生成。在某些情况下，IL-4/13 通过自分泌 - 旁分泌方式发出信号，进一步增强 M2 极化[19, 20]。随着研究深入，人们发现 M2 又可进一步细分为三个亚型，即 M2a、M2b 和 M2c。M2a 由 IL-4 和 IL-13 所诱导；免疫复合物和 TLRs 或 IL-1 受体 (IL-1R) 诱导 M2b 生成；IL-10、TGF-β 或糖皮质激素则诱导 M2c 生成[21]。M2 通常高表达甘露糖受体 (mannose receptor，MR，即 CD206)、清道夫受体 (scavenger receptor，SR，即 CD163)、半乳糖模式受体 (galactose-type receptor, GTR)、精氨酸酶 -1 (arginase-1, Arg-1)、FIZZ1 (found in inflammatory zone 1) 和几丁质酶 (chitinase-like secretory lectin, Ym1)。M2 还可大量分泌抗炎细胞因子 IL-10、转化生长因子 -β (transforming growth factor-β, TGF-β) 和一些生物合成酶如基质金属蛋白酶 12 (matrix metalloproteinase 12, MMP-12)[18, 22]，产生 Th2 型趋化因子 (CCL17、CCL22 和 CCL24 等)，趋化吸引 Th2 细胞及其他炎症细胞[19, 23](图 1)。M2 负责调节 Th2 型细胞免疫，抑制炎症反应，促进组织重塑与修复以及血管生成和肿瘤细胞生长[18, 24]。

2.3 巨噬细胞极化的免疫调控机制

核因子 κB (nuclear factor κB, NF-κB) 作为重要的转录因子，参与对巨噬细胞极化的调控。通常情况下，NF-κB 以异二聚体和同源二聚体形式存在于细胞质中，主要指 p50 和 p65，它们分别参与 M2 和 M1 的极化。NF-κB p50 被认为是 M2 表型的关键调节因子[25]，促进 M2 极化，抑制 M1 极化[26]。在动脉粥样硬化模型中，巨噬细胞缺乏 p50，其摄取低密度脂蛋白的能力降低，从而加重炎症损害[27]。研究显示，在寄生虫感染过程中，p50 是促进巨噬细胞向 M2 极化所必需的转录因子[26]。与之相反，NF-κB p65 是 M1 极化的标志。LPS 结合 TLR4 后通过髓样分化因子 88 (myeloid differentiation factor 88, MyD88) 引起下游 NF-κB p65 的激活，促进巨噬细胞向 M1 方向极化[21](图 2)；而中药槲皮素通过抑制 NF-κB p65 的表达，导致上游信号 TLR4/MyD88 失活，从而抑制 LPS 诱导的 M1 极化[28]。

STAT 是另一个控制巨噬细胞极化的重要转录因子，其中，STAT6 是调控 M2 极化的核心转录因子。研究显示，STAT6 调控多种 M2 标志物的表达[29]，且 STAT6 基因敲除可抑制 Th2 型免疫反应，增强 Th1 型免疫反应[30]。IL-4 和 IL-13 与各自的受体结合后，一方面可通过 JAK1/2/3 促进 STAT6 磷酸化，活化后的 STAT6 转而激活了 IRF4，从而触发了 M2 标志物基因 (如 MR、FIZZ1 和 Ym1) 的表达[18, 21]；另一方面，IL-4 和 IL-13 结合受体后激活 PI3K，通

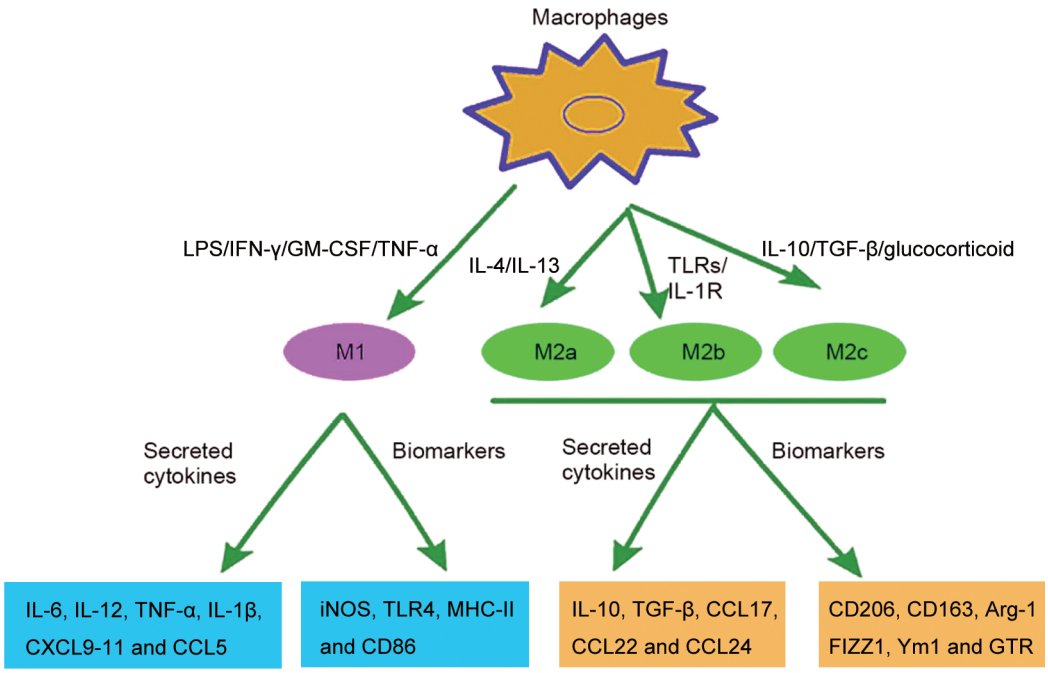

图 1. M1和M2型巨噬细胞极化

Fig. 1. M1 and M2 macrophage polarization. IFN-γ alone or in combination with LPS or inflammatory cytokines, such as TNF-α and GM-CSF, can stimulate M1 macrophages production. M1 can produce high levels of ROS and NO, secrete high levels of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-12, highly express iNOS, CD86, TLR4 and MHC-II, and express Th1 chemokine, such as CXCL9-11 and CCL5. M2 macrophages are usually divided into three subtypes: M2a, M2b and M2c. IL-4 and IL-13 induce M2a subtype; TLRs or IL-1R induces M2b subtype; M2c subtype is induced by IL-10, TGF-β and glucocorticoids. M2 usually expresses CD206, CD163, Arg-1, FIZZ1, GTR and Ym1. In addition, M2 can secrete anti-inflammatory IL-10, TGF-β and some biological synthetases such as MMP-12, and express Th2 chemokines such as CCL17, CCL22 and CCL24. IFN-γ: interferon-γ; LPS: lipopolysaccharide; TNF-α: tumor necrosis factor-α; GM-CSF: granulocyte-macrophage colony stimutaing factor; ROS: reactive oxygen species; NO: nitric oxide; IL-1β: interleukin-1β; iNOS: inducible nitric oxide synthase; TLR4: Toll-like receptor 4; MHC-II: major histocompatibility complex II; CXCL9-11: CXC chemokine ligand 9-11; TLRs: Toll-like receptors; IL-1R: IL-1 receptor; TGF-β: transforming growth factor-β; CD206: mannose receptor; CD163: scavenger receptor; Arg-1: arginase-1; FIZZ1: found in inflammatory zone 1; GTR: galactose-type receptors; Ym1: chitinase-like secretory lectin; MMP-12: matrix metalloproteinase 12; CCL22: CC-chemokine ligand 22.

过 PI3K/PIP3/Akt1 信号转导通路激活 mTOR (存在于雷帕霉素敏感的蛋白复合体中的一种丝氨酸 / 苏氨酸激酶)，上调 M2 标志物的基因表达 [23]。IFN-γ 与其受体结合后引起 JAK1/2 的活化，活化的 JAK1/2 转而激活 STAT3，从而激活下游 NF-κB p65，达到增强 M1 极化的目的。细胞因子信号抑制因子 (suppressor of cytokine signaling, SOCS) 也参与了巨噬细胞极化过程，在 M1 极化过程中，SOCS3 通过与 JAK2 结合以抑制 NF-κB 的活性，从而影响 M1 极化 [21]。而 IL-4/13 刺激后会上调 SOCS1 的表达，进一步促进 M2 极化 [9](图 2)。

表观遗传学调控包括 microRNA (miRNA) 调节、DNA 甲基化和组蛋白修饰。越来越多证据表明，表观遗传学修饰参与巨噬细胞极化过程，部分是通过转录抑制和染色质重塑等机制来发挥作用 [31]。例如，IL-4 可使小鼠巨噬细胞组蛋白去甲基化酶 JMJD3 (Jumonji-domain-containing 3) 表达升高，从而改变染色质修饰，促进 M2 标志基因表达 [32]。JMJD3 可以特异性地结合 NF-κB 依赖基因启动子的转录起始位点，从而抑制 NF-κB 依赖基因的表达 [33, 34]。miR-155 由 LPS 或 I 型 IFN (IFN-α/β) 所诱导 [33]，它能增强 TNF-α 转录的稳定性从而起到促炎作用，而 miR-155 在 M2 中表达量是下降的 [35](图 2)。

3 巨噬细胞极化在COPD中的作用

COPD 是一种慢性阻塞性疾病，其特点是持续

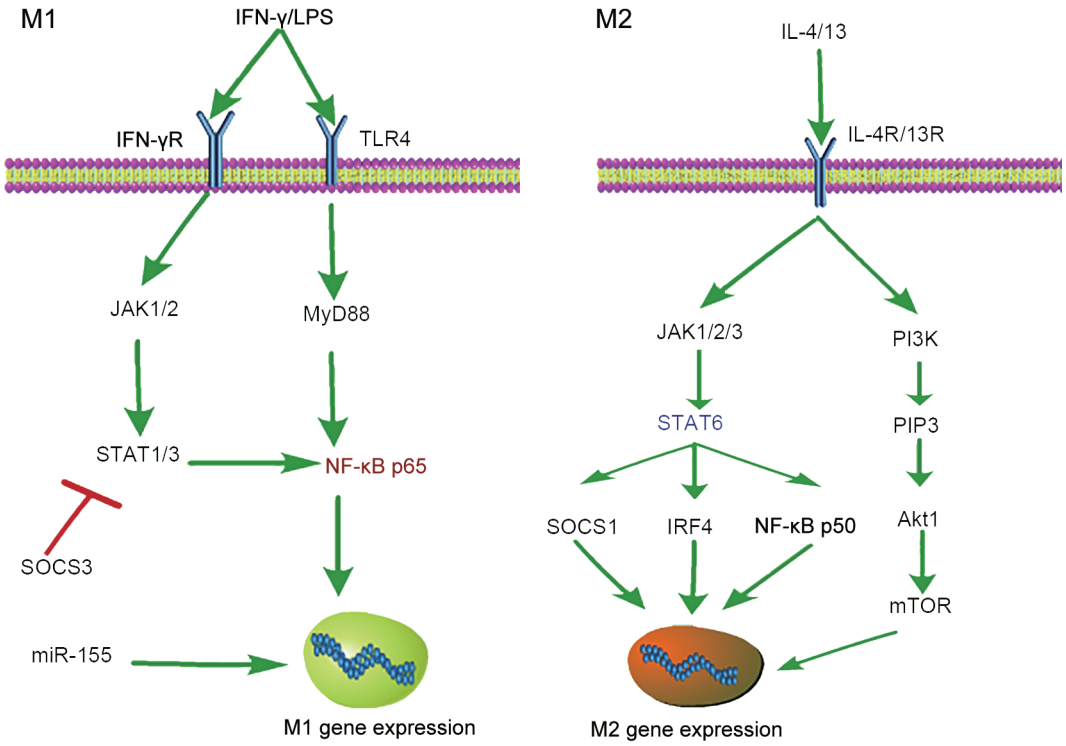

图 2. M1、M2极化的相关转录因子

Fig. 2. M1, M2 polarization-related transcription factors. LPS binding to TLR4 induces activation of downstream NF-κB p65 through MyD88 pathway, thus promoting the polarization of macrophages to M1. While IFN-γ binds to its receptor to activate JAK1/2, which in turn activates STAT1/3. STAT1/3 induces activation of NF-κB p65 to stimulate specific M1 marker genes expression, and this process is inhibited by SOCS3, which can negatively regulate NF-κB by binding to JAK2. In addition, miR-155 is also involved in specific M1 marker genes expression. IL-4 and IL-13 can promote the phosphorylation of STAT6 through JAK1/2/3. Activated STAT6 activates IRF4, which triggers the expression of specific M2 marker genes (such as MR, FIZZ1 and Ym1). In addition, IL-4 and IL-13 up-regulate specific M2 marker genes through (PIP3/PI3K/Akt1/mTOR) pathway. LPS: lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB p65: nuclear factor-κB p65; MyD88: myeloid differentiation factor 88; IFN-γ: interferon-γ; JAK1/2: Janus kinase1/2; STAT1/3: signal transduction and transcriptional activating factor1/3; SOCS3: suppressor of cytokine signaling 3; miR-155: microRNA-155; IL-4: interleukin-4; STAT6: signal transduction and transcriptional activating factor 6; IRF4: interferon regulatory factor 4; MR: mannose receptor; FIZZ1: found in inflammatory zone 1; Ym1: chitinase-like secretory lectin; PIP3: phosphatidylinositol-3 phosphate; PI3K: phosphatidylinositol-3 kinase; Akt1: serine threonine kinase; mTOR: mammalian target of rapamycin.

的、进行性的、不完全可逆的气流受限，并导致肺功能的下降[36]。炎症是 COPD 的核心机制，可累及气道、肺实质和肺血管，但主要影响小气道和肺实质，造成小气道阻塞和肺气肿[22]。吸烟是 COPD 发病的主要原因之一，香烟烟雾会诱导巨噬细胞的激活和数量的增加，活化的巨噬细胞释放趋化因子吸引中性粒细胞、单核细胞和 T 细胞进入肺部，促进炎症反应[37, 38]。而被烟雾诱导活化的巨噬细胞，也即极化后的 M1、M2 参与了 COPD 的发病过程，在炎症反应、组织修复、吞噬能力、肺部微环境的形成中发挥重要作用。

3.1 COPD肺内的巨噬细胞极化

目前对 COPD 肺中巨噬细胞的极化方向存有三种观点：(1) 向 M1 极化。研究显示，在 COPD 患者痰液中促炎性巨噬细胞占主导[37]。M1 还参与肺泡的破坏，导致肺气肿的形成[39]。(2) 向 M2 极化。临床研究显示，香烟烟雾会引起 COPD 患者巨噬细胞向 M2 极化[23]，且在 COPD 患者痰液和支气管肺泡灌洗液中 M2 细胞占单核细胞的比例远高于 M1 所占比例[40]，其数量的增加与 COPD 的严重程度密切相关[41]。Yuan 等通过体外细胞实验观察到，不同浓度的香烟烟雾提取物暴露使小鼠巨噬细胞

M2 标志物 IL-10、TGF-β1 和 TGF-β2 表达上调 [42]。动物实验结果显示，COPD 模型小鼠肺组织中 $CD206^+$ 巨噬细胞 (M2) 数量明显增加 [36]。Lu 等在香烟烟雾诱导的肺气肿模型小鼠中也观察到 M2 增多 [43]。(3) M1 和 M2 同时存在。Vlahos 等 [44] 在 COPD 患者气道中发现 iNOS (M1 标志物) 和 Arg-1 (M2 标志物) 的活性同时升高；Bazzan 等 [45] 在健康者肺组织中发现肺泡巨噬细胞以 M0 (非极化) 状态存在，而随着吸烟和 COPD 的加重，M1、M2 比例逐渐上升，即巨噬细胞以双极化状态存在于 COPD 患者肺组织中，但 M2 的上升速度快于 M1。与体内实验观察到的结果有类似的地方，Smith 等将巨噬细胞同时暴露于 M1 和 M2 激活信号，发现巨噬细胞同时表达 M1 和 M2 标志物，但 M1 标志物的表达水平随时间的推移而逐渐下降，而 M2 标志物表达仍继续升高 [46]。以上结果表明，炎症环境可使巨噬细胞极化状态发生改变。

上述三种观点存在的原因，可能与研究者观察的 COPD 进展阶段不同、取材方式差异和动物种属来源的不同有关，例如 Arg-1、Ym3 和 Ym4 基因在小鼠 M2 中表达，而在人巨噬细胞中则无同源性序列 [39]。

3.2 巨噬细胞极化参与COPD肺部炎症反应

COPD 主要的病理表现为肺部炎症反应。正常情况下，炎症是机体对损伤的适应性反应，在此过程中首先是为了去除有害刺激，然后才是诱导愈合过程。在炎症过程中，M1 和 M2 分工明确。在炎症早期，巨噬细胞受外界刺激后先向 M1 表型极化，导致大量促炎中间介质 (如 IL-1、TNF-α、NO 和 ROS 等) 产生 [47]。M1 分泌的 IL-12 能够刺激 Th1 细胞的扩增，从而促进炎症反应 [21]。最初，这些炎性介质的存在是有益的，有助于消除入侵的病原体，激发适应性免疫；但 NO 和 ROS 本身具有细胞毒性，加之 Th1 促炎细胞的存在，易导致组织损伤 [48]。而在炎症后期，为了中和炎症反应，巨噬细胞可能发生凋亡或向 M2 表型极化，以保护宿主免受炎症性损伤并触发伤口愈合 [49]。COPD 肺部炎症累及气道，造成气流受限，从而造成肺内缺氧。将气道上皮细胞与巨噬细胞共同培养，早期低氧环境刺激气道上皮细胞诱导巨噬细胞向 M1 极化；而长期缺氧后，气道上皮细胞则会刺激巨噬细胞向 M2 极化 [50]。在结核分枝杆菌感染初期，小鼠肺泡灌洗液中 IFN-γ 和 iNOS 含量逐渐增加，表明此时巨噬细胞向 M1 极化。随着炎症反应的推移，这两种 M1 标志物的表达水平降低，而 M2 标志物 IL-4 和 Arg-1 的表达水平逐渐上升，表明巨噬细胞在炎症反应刺激下开始由 M1 向 M2 极化 [51]。因此，为了适应不同的病理发展阶段，COPD 早期可能是以 M1 为主，以激发适应性免疫反应，清除外来入侵的微生物；而在 COPD 中后期，由于炎症反应的持续发展，为了维护机体稳态，M2 将发挥抗炎作用，以抑制过度的炎症反应 [15](图 3)。

3.3 巨噬细胞极化参与COPD肺组织损伤与修复

COPD 反复的炎症刺激，导致肺组织的损伤与修复反复进行，以适应这种病理改变。M2 具有修复受损组织的功能 (图 3)。肺气肿是 COPD 主要的病理表现。COPD 患者肺组织中 M2 可分泌多种炎症介质 (如 MMP-2、MMP-9、MMP-12 和组织蛋白酶 S 等)，造成肺实质的损伤，形成肺气肿，且 M2 数量的增加与肺气肿的严重程度密切相关 [52–54]。嗜碱性粒细胞来源的 IL-4 作用于肺部浸润的单核细胞，使其分化为 M2，后者产生 MMP-12，可导致小鼠肺泡壁破坏而形成肺气肿 [55]。上述结果表明 M2 分泌的 MMP-12 是形成肺气肿的重要原因。Oliveira da Silva 等研究显示，长期的香烟烟雾暴露引起的慢性肺部炎症可导致巨噬细胞高表达 CD206 和生成 TGF-β，从而驱动 M2 表型的适应性免疫应答，完成组织修复的过程 [56]。

3.4 巨噬细胞极化维护COPD肺内微环境

巨噬细胞还具有组织特异性的特点，一旦离开特定的组织微环境，其极化方向也会发生改变。COPD 患者气道和肺泡腔中的巨噬细胞极化存在差异，气道中以促炎性的 M1 为主，而肺泡腔中则以抗炎性的 M2 占主导，且肺泡灌洗液中 M2 数量增加 [57]。COPD 是一种慢性进展性疾病，持续的肺部损伤会引起 COPD 患者肺部微环境发生不断变化，并可能随时间推移影响巨噬细胞的表型。如 Gutierrez 等在 COPD 急性加重期患者痰液中发现 M2 样表型，而在社区获得性肺炎中则发现 M1 样表型 [58]，表明肺内微环境的改变对巨噬细胞的极化方向影响较大。另有研究提示，COPD 加重期炎症反应的程度和持续时间，以及极化分型的相对平衡对疾病的进展又有着较大影响 [59]。临床研究显示，COPD 患者肺组织内抗炎表型 M2a 巨噬细胞比例降低，而治疗 1 年后 M2a 比例恢复至正常水平 [60]。此外，Hiemstra 等研究显示，戒烟可以部分改变肺部巨噬

细胞表型，使之向抗炎的 $CD163^{+}$M2c 表型极化 [52]。上述研究表明，戒烟前后及治疗前后，肺内微环境明显发生改变，从而影响巨噬细胞的极化。

3.5 巨噬细胞极化后其吞噬能力发生改变

吞噬能力是巨噬细胞维护机体免疫安全的重要手段。在生理状态下，巨噬细胞可吞噬凋亡细胞，从而避免因凋亡产生炎症物质的刺激 [61]。研究显示，香烟烟雾会抑制肺泡巨噬细胞的吞噬能力，使其清除凋亡和坏死细胞的能力下降，而死亡细胞的残留物会导致 COPD 患者气道和肺部的细菌定植，进一步加剧肺部炎症 [62]。Berenson 等 [62] 研究显示，COPD 严重程度与巨噬细胞对肺部流感嗜血杆菌和卡他莫拉菌的吞噬能力降低相关。Hodge 等 [63] 研究显示，COPD 患者肺部巨噬细胞吞噬能力的降低与 CD206 及其他几种关键的 M2 标志物 (如清道夫受体 CD163) 的表达减少有关，表明极化后的 M2 可能是 COPD 肺内发挥吞噬和清除能力的主要细胞。M2 具有较高的吞噬凋亡物质活性，在其吞噬凋亡细胞后，从表达促炎细胞因子变为表达抗炎细胞因子 (如 TGF-β)，以抑制炎症反应的增强 [61]。在 COPD 中后期，由于炎症反应的持续存在，M2 的数量会应激性地上升，但其增加的数量不足以吞噬 COPD 早期残留的凋亡物质，所以此时的巨噬细胞表现出吞噬能力相对减弱 (图 3)。

3.6 巨噬细胞极化与COPD靶向治疗

COPD 中存在的巨噬细胞极化可能成为 COPD 治疗的新靶点，研究者们尝试采用药物去干预极化方向，以改善肺巨噬细胞吞噬能力和抑制炎症。Hodge 等 [64] 发现阿奇霉素治疗可以增强 COPD 患者巨噬细胞对凋亡支气管上皮细胞的吞噬作用，并且改善其对细菌的吞噬能力 [65, 66]。最近研究显示，阿奇霉素持续使用 8 周可以明显降低 COPD 患者支气管肺泡灌洗液中 TNF-α、IL-13 和 IL-12 等促炎因子的含量，从而改善肺内微环境 [67]。磷酸二酯酶抑制剂 (如氨茶碱) 可有效地恢复损伤的肺巨噬细胞的吞噬能力；罗氟司特 (磷酸二酯酶抑制剂) 能促进肺巨噬细胞 M2 极化 [68]。有研究显示，胸腺嘧啶醌可通过鞘氨醇 1 磷酸信号转导通路改善 COPD 巨噬细胞的吞噬能力 [69]。他汀类药物 (尤其是洛伐他汀) 可以改善 COPD 患者肺泡巨噬细胞吞噬活性，而且还可以通过下调 MMP-12 的表达抑制肺气肿的形成 [22]。此外，Brown 等 [70] 研究显示，通过口服半胱氨酸或 *N*- 乙酰半胱氨酸可以恢复 COPD 模型大鼠肺泡巨噬细胞对金黄色葡萄球菌的吞噬功能。Barroso 等 [71] 研究显示，蜂胶能通过靶向极化 M2 型巨噬细胞以促进肺气肿小鼠肺损伤的修复，维持肺组织的抗炎环境。

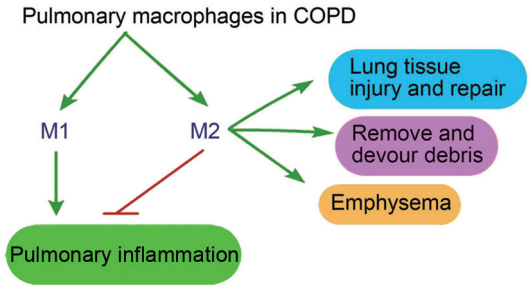

图 3. M1和M2在慢性阻塞性肺疾病(COPD)患者肺组织中的作用

Fig. 3. The role of M1 and M2 in lung tissue of chronic obstructive pulmonary disease (COPD) patients. M1 may play an important role in the early stage of COPD by releasing pro-inflammatory cytokines to expand the inflammatory response in the lungs and eliminate invasive microorganisms. In the middle and late stage of COPD, the lung parenchyma injury (emphysema) was caused by the persistent inflammatory reaction. At this time, M2 plays the role of tissue repair and phagocytosis of the residual apoptotic substance, inhibits the continuous expansion of the inflammatory reaction and delays the development of the course of COPD.

4 小结

肺内巨噬细胞在炎症因子的激活下向 M1/M2 方向极化，分别发挥着促炎 / 抗炎作用，参与 COPD 的炎症全过程、肺实质的损伤 (肺气肿) 和修复 (气道重塑)，吞噬并清除凋亡和坏死组织细胞，共同维护着 COPD 肺内微环境 (图 3)。靶向调控巨噬细胞的极化方向，可为 COPD 的治疗提供新的思路。此外，香烟烟雾 (COPD 的主要诱导因素) 阶段性诱导巨噬细胞极化的动态研究未见报道；在 COPD 肺部的微环境中，启动向 M1 或 M2 极化的关键调控分子间信息对话仍然不清楚；巨噬细胞极化与 T 细胞之间关系不甚明了，这些均有待于深入研究。

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