代谢重编程调控巨噬细胞极化及其在类风湿关节炎中的作用

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摘要: 类风湿关节炎 (rheumatoid arthritis, RA) 是一类以滑膜炎症和软骨破坏为特征的自身免疫性疾病。巨噬细胞极化失衡与RA的发生和发展密切相关, 其中M1型巨噬细胞在RA细胞因子网络环境中发挥了促进炎症和骨破坏的中心作用。RA患者异常的免疫微环境促进巨噬细胞发生代谢重编程, 进而影响巨噬细胞极化状态, 破坏M1/M2动态平衡, 导致组织炎症迁延不愈。采用药物干预M1型巨噬细胞极化或诱导M2型巨噬细胞极化治疗RA, 有望成为药物研发的理想策略。基于此, 本文对RA微环境下巨噬细胞的代谢重编程对其极化类型的影响以及相关信号通路进行综述, 为研发以巨噬细胞代谢为靶点的RA治疗药物提供参考。

关键词: 类风湿关节炎; 巨噬细胞极化; 代谢重编程; 信号通路

中图分类号: R967 **文献标识码**: A **文章编号**: 0513-4870(2020)09-2027-08

Metabolic reprogramming regulates macrophage polarization and its role in rheumatoid arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and cartilage destruction. An imbalance in macrophage polarization is closely related to the occurrence and development of RA, including a central role for M1 macrophages in promoting inflammation and bone destruction in the cytokine network environment of RA. It is a remarkable fact that the abnormal immune-microenvironment in RA patients promotes the metabolic reprogramming of macrophages, which disrupts the dynamic balance of M1/M2 by regulating the polarization of macrophages, leading to a persistent tissue inflammation. Using drugs to inhibit M1 macrophage polarization or induce M2 macrophage polarization is expected to be an ideal strategy for drug development for RA treatment. This review summarizes the effects of metabolic reprogramming of macrophages on polarization phenotype and the metabolism-related signaling pathways in the RA microenvironment, and provides references for the development of RA drugs that can target macrophage metabolism.

Key words: rheumatoid arthritis; macrophage polarization; metabolic reprogramming; signaling pathway

类风湿关节炎 (rheumatoid arthritis, RA) 是一类常见的慢性自身免疫性疾病, 临床表现为多发性小关节炎, 早期呈现手、腕、足等关节红、肿、热、痛和功能障碍, 晚期可出现关节软骨和软骨下骨破坏、关节畸形和失去功能[1,2]。近些年, 免疫细胞代谢紊乱和微环境稳态失衡, 成为RA病理机制的研究热点[3]。研究表明[4,5], 巨噬细胞代谢重编程是影响其表型极化, 导致功能异常和促进RA病程进展的重要因素。M1型巨噬细胞不但可以通过产生大量肿瘤坏死因子α (tumor neurosis factor α, TNF-α)、白介素1β (interleukin-1β,

收稿日期: 2020-03-23; 修回日期: 2020-04-24.

基金项目: 国家自然科学基金资助项目 (81703529); 安徽省博士后科研活动资助项目 (2018B251); 国家大学生创新创业训练计划项目 (201910367036); 蚌埠医学院研究生科研创新计划项目 (Byycx1949, Byycx1812); 蚌埠医学院创新药物创新团队 (BYKC201904).

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DOI: 10.16438/j.0513-4870.2020-0386

IL-1β) 和 IL-6 等促炎症细胞因子参与炎症免疫反应[6,7], 还可通过促进 T、B 细胞、成纤维样滑膜细胞 (fibroblast-like synoviocytes, FLS) 和破骨细胞活化, 在 RA 细胞因子网络环境中发挥了促进炎症和骨质破坏的中心作用[8]。因此, 探讨微环境中巨噬细胞代谢重编程与其表型极化的关系, 将有助于阐明 RA 的免疫病理机制, 为发现新的药物治疗靶点, 提供有价值的参考。

1 巨噬细胞的极化

巨噬细胞是一类具有高度可塑性的固有免疫细胞, 根据其表面分子及所分泌的细胞因子等特点可分为 M1 型 (经典活化巨噬细胞) 和 M2 型 (选择性活化巨噬细胞)[9]。M1 型巨噬细胞主要由脂多糖 (lipopolysaccharide, LPS)、γ-干扰素以及粒细胞−巨噬细胞集落刺激因子等刺激分化, 分泌多种促炎症细胞因子, 如 IL-1β、IL-6、IL-23 和 TNF-α, 并上调 CD86 和 CD80、诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS)、CXC 趋化因子配体 (CXC chemokine ligand, CXCL) 9、CXCL10 和单核细胞趋化蛋白 1 的表达, 促进炎症的发生发展。此外, M1 型巨噬细胞能够诱导初始 T 细胞分化为辅助性 T 细胞 (helper T cells, Th) 1 和 Th17, 进一步加剧炎症反应[10]。而 M2 型巨噬细胞主要由 IL-4、IL-10 和巨噬细胞−集落刺激因子诱导分化, 分泌 IL-10、转化生长因子 β (transforming growth factor-β, TGF-β) 等抗炎细胞因子, 同时上调精氨酸酶 1 (arginase 1, Arg1)、CD206 和 CD163 的表达, 调节并促进 Th2 细胞和调节性 T 细胞的活化, 从而发挥抗炎和免疫调节作用[11]。正常生理状态下, M1/M2 巨噬细胞保持动态平衡, 炎症反应前期, 巨噬细胞被经典激活形成 M1 表型, 引起组织损伤; 炎症反应后期, 巨噬细胞向 M2 型极化减轻局部炎症反应, 促进组织愈合和修复。

2 RA 中巨噬细胞的极化

滑膜组织中大量巨噬细胞浸润被认为是活动性 RA 的早期标志[12]。多项临床试验显示[6], RA 患者体内 M1/M2 巨噬细胞比例失衡。Zhu 等[13]发现, RA 患者滑液巨噬细胞低表达 M2 表型标志物 CD163, 且 M1/M2 比例高达 32.76 ± 11.02; 从转录水平分析显示, RA 患者滑液巨噬细胞中促炎症基因 CXCL17、内皮细胞特异性趋化调节因子和趋化因子受体 2 高表达, 抗炎症基因胰岛素样生长因子 1 和 IL-10 低表达。Yoon 等[14,15]分析 RA 患者外周血单核巨噬细胞表型特征发现, M1 表型标志分子 CD80 和 CD86 表达增加, 而 M2 表型标志分子 CD163 表达降低。在胶原诱导性关节炎 (collagen-induced arthritis, CIA) 小鼠模型上也有相同发现[16], CIA 小鼠腹腔巨噬细胞中 M1 表型标志物 CD86 表达水平升高, M2 表型标志物 CD206 表达减少。本课题组的前期研究[17]结果也表明, 佐剂型关节炎 (adjuvant arthritis, AA) 大鼠腹腔巨噬细胞中 M1 型标志物 iNOS 和多种促炎症细胞因子表达水平升高, M2 型标志物 Arg1 以及多种抗炎细胞因子表达水平降低, 而纠正 M1/M2 巨噬细胞比例后明显缓解 AA 大鼠关节炎症状。

随着对 RA 巨噬细胞极化认识的不断加深, 调控其极化的机制研究也逐渐深入。早期有研究发现[18], RA 滑膜组织中高水平的活化素 A 能介导 M1 型巨噬细胞极化。活化素 A 通过上调脯氨酸羟化酶 3 (HIF-prolyl hydroxylase 3, PHD3) 表达, 激活核转录因子-κB (nuclear transcription factor-κB, NF-κB) 信号通路, 促进 M1 型标志分子表达和炎性介质释放[19,20]。Zhu 等[13]发现, 抗瓜氨酸化蛋白抗体 (anti-citrullinated protein antibody, ACPA) 作为 RA 特异性自身抗体, 可通过激活干扰素调节因子 (interferon regulatory factor, IRF) 信号通路, 促使 RA 患者血清中 M1/M2 巨噬细胞比例升高 (161.01 ± 15.35); 而阻断 IRF 通路则会降低 M1/M2 巨噬细胞比例 (54.97 ± 7.80)。随后的研究发现[21], ACPA 还可通过 NF-κB 通路激活核苷酸结合寡聚化结构域样受体 3 (nucleotide binding oligomerization domain-like receptors 3, NLRP3) 炎症小体, 促进 RA 患者外周血单核巨噬细胞极化为 M1 型。此外, 由 c-Fos 和 c-Jun 组成的转录因子激活蛋白-1 (activated protein-1, AP-1) 在 RA 滑膜组织中高表达, 参与巨噬细胞极化[22,23]。一方面, c-Fos 直接抑制巨噬细胞中 Arg1 的表达, 降低抗炎作用; 另一方面, c-Jun 上调巨噬细胞中环氧化酶-2 表达, 抑制 Arg1 表达, 调控巨噬细胞向 M1 型极化。最近的研究发现[16], G 蛋白偶联受体激酶 2 (G protein-coupled receptor kinase 2, GRK2) 在 RA 巨噬细胞极化中起到关键性的调节作用。高水平的 GRK2 通过诱导前列腺素 E2 受体 4 过度脱敏, 减少细胞内环磷酸腺苷 (cyclic adenosine monophosphate, cAMP) 水平, 引起 cAMP-cAMP 反应元件结合蛋白信号异常, 导致巨噬细胞向 M1 型极化, 加重 CIA 小鼠关节损伤。

综上所述, RA 微环境中多种因素促使巨噬细胞倾向 M1 型极化 (图 1)。活化的巨噬细胞通过分泌大量促炎症细胞因子和趋化因子激活各种免疫细胞, 引发炎症级联反应, 最终导致软骨破坏和骨质侵蚀。调控 M1/M2 巨噬细胞动态平衡有利于促进 RA 炎症消退和组织修复。

3 巨噬细胞代谢

ATP 是维持细胞生命活动的直接能源物质, 但免疫细胞活化不仅需要 ATP 的供给, 还需要代谢中间物来满足生物合成的需求, 从而完成其增殖、分化以及效

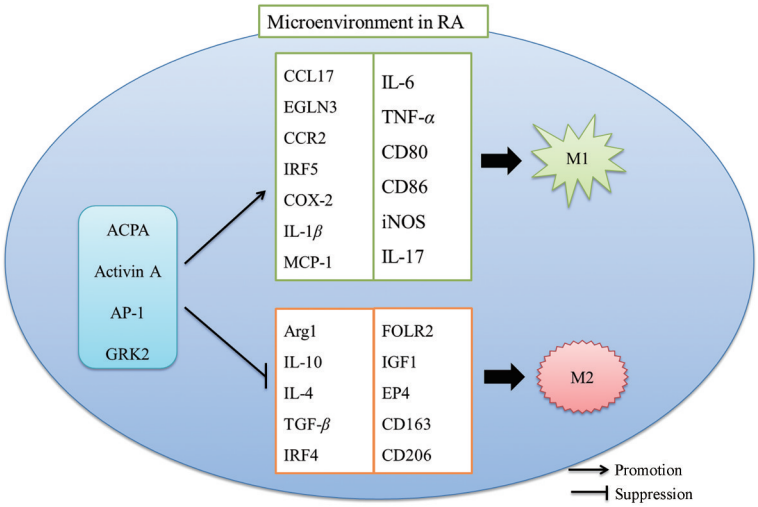

Figure 1　The polarization of macrophages in rheumatoid arthritis (RA). M1 macrophages dominated in RA microenvironment. ACPA: Anti-citrullinated protein antibody; AP-1: Activated protein-1; GRK2: G protein-coupled receptor kinase 2; EGLN3: Egl-9 family hypoxia inducible factor 3; CCR2: Chemokine C-C-motif receptor 2; IRF: Interferon regulatory factor; MCP-1: Monocyte chemotactic protein 1; IL-1β: Interleukin-1β; iNOS: Inducible nitric oxide synthase; TNF-α: Tumor neurosis factor α; COX-2: Cyclooxygenase 2; Arg1: Arginase 1; TGF-β: Transforming growth factor-β; FOLR2: Folate receptor 2; IGF1: Insulin-like growth factor-1; EP4: Prostaglandin E2 receptor

应功能的执行。因此, 免疫细胞由静息状态转变为活化状态时, 其代谢方式也随之发生改变[24], 这种类似于肿瘤细胞快速增殖时所伴随的代谢途径变化称为“代谢重编程”, 包含葡萄糖摄取增加、有氧糖酵解速率(Warburg 效应) 和磷酸戊糖途径 (pentose phosphate pathway, PPP) 上调, 三羧酸 (tricarboxylic acid, TCA) 循环或氧化磷酸化 (oxidative phosphorylation, OXPHOS) 水平降低, 以及蛋白质、脂类和核苷酸合成累积。研究证实[25], M1 型和 M2 型巨噬细胞在代谢方式上具有明显差异, 目前比较一致的观点认为, M1 型巨噬细胞有赖于有氧糖酵解途径和 PPP 提供能量, 而 M2 巨噬细胞主要通过脂肪酸氧化 (fatty acid oxidation, FAO) 和 OXPHOS 获取能量。

3.1　M1 型巨噬细胞代谢特点　相较于 OXPHOS, 糖酵解产生 ATP 的效率较低, 但其产生 ATP 的速度更快, 且为生物合成途径提供代谢中间体以支持核糖、氨基酸和脂肪酸的合成。研究证实[26], 即使在氧气充足的情况下, 活化的巨噬细胞在很大程度上仍然通过糖酵解快速产生 ATP。研究表明[27], LPS 可诱导巨噬细胞代谢途径从 OXPHOS 转变为有氧糖酵解, 促进 M1 型极化。进一步分析发现[28], LPS 通过上调巨噬细胞葡萄糖转运体 1 (glucose transporter-1, Glut1) 表达, 增加葡萄糖摄取, 在糖酵解相关酶的作用下激活糖酵解途径, 最终促进乳酸合成和炎性介质分泌。丙酮酸激酶 M2 (pyruvate kinase M2, PKM2) 是调控巨噬细胞糖酵解重编程的关键酶, 可通过激活巨噬细胞炎症小体和信号传导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 通路促进促炎症细胞因子分泌[29,30]。此外, M1 型巨噬细胞内 TCA 循环被阻断, 导致琥珀酸蓄积, 进而抑制 PHD 的活性, 维持缺氧诱导因子 (hypoxia inducible factor, HIF)-1α 稳定性, 促进炎性介质的产生[31]。利用 2-脱氧-*D*-葡萄糖 (2-deoxy-*D*-glucose, 2-DG) 抑制己糖激酶 2 (hexokinase 2, HK2) 阻断糖酵解途径, 不仅抑制 M1 型巨噬细胞分泌促炎症细胞因子[32], 并且抑制其迁移能力[33]。此外, LPS 能抑制碳水化合物激酶样蛋白 (carbohydrate kinase-like protein, CARKL) 的表达, 上调 PPP, 促进 M1 型巨噬细胞极化; 而过表达 CARKL 则会抑制巨噬细胞内 PPP 和 M1 型极化[34]。PPP 产生的 NADPH 一方面上调 NADPH 氧化酶 (NADPH oxidase, NOX) 活性和 ROS 释放, 同时诱导一氧化氮 (nitric oxide, NO) 产生, 抑制线粒体呼吸作用; 另一方面为脂肪酸生物合成提供基础物质, 调控 M1 型巨噬细胞极化。研究表明[25], 脂质的生物合成是 M1 型巨噬细胞膜重构和炎症介质合成的关键。脂肪酸合成酶 (fatty acid synthase, FAS) 是调节脂肪酸合成的关键酶, FAS 的缺失能够引起巨噬细胞质膜成分发生改变, 抑制巨噬细胞 M1 型极化和炎性介质产生[35]。早期有研究证实[36], FAS 介导的脂肪酸合成参与巨噬细胞 NLRP3 炎性小体激活和炎性介质释放。新近的研究发现[37], 巨噬细胞内 NOX4 能够上调 FAO 水平, 参与 NLRP3 炎症小体的激活, 促进 IL-1β 和 IL-18 分泌, 敲除巨噬细胞中 NOX4 可抑制

FAO反应和NLRP3炎症小体活化, 而这一过程的发生可能需要PPP生成的NADPH上调NOX4活性作为前提。简而言之, 有氧糖酵解和PPP提供能量和代谢中间体, 调控脂质代谢, 为M1型巨噬细胞炎性分子的合成提供前体物质。

3.2 M2型巨噬细胞代谢特点 在IL-4诱导的M2型巨噬细胞中, TCA循环和OXPHOS水平升高, 胞内线粒体耗氧量 (oxygen consumption rate, OCR) 和备用呼吸能力增强[34,38]; 利用寡霉素或线粒体解偶联剂阻断胞内OXPHOS反应则会抑制IL-4诱导的M2型极化[38,39]。此外, IL-4能诱导巨噬细胞表面分子CD36高表达, 增加脂肪酸摄取, 并通过STAT6信号通路上调过氧化物酶体增殖物激活受体-γ共激活因子-1β (peroxisome proliferator-activated receptor γ coactivator-1β, PGC-1β) 和肉碱棕榈酰基转移酶 (carnitine palmitoyltransferase, CPT) 1表达, 促进FAO反应, 为OXPHOS提供所需原料[40]。然而, 有趣的是, 使用CPT1抑制剂阻断FAO反应对IL-4诱导M2型巨噬细胞的激活并没有明显抑制作用[40,41]。Nomura等[42]直接敲除巨噬细胞中CPT2阻断FAO反应后, 同样发现IL-4可以诱导CPT2缺失的巨噬细胞向M2型分化, 提示M2型巨噬细胞的产能途径可能并不限于FAO途径的OXPHOS。Huang等[43]发现, 在IL-4诱导的M2型巨噬细胞中, 雷帕霉素靶蛋白复合体2 (mammalian target of rapamycin complex 2, mTORC2) 和IRF4协同促进胞内糖酵解反应, 而敲除巨噬细胞中mTORC2阻断胞内糖酵解途径的同时, 也抑制M2型极化, 提示糖酵解可能参与M2型巨噬细胞极化。研究者将这一现象归因于糖酵解生成的丙酮酸进入TCA循环[44], 促进OXPHOS水平, 为M2型巨噬细胞提供能源物质。然而, 随后的研究发现[45], M2型巨噬细胞并不依赖糖酵解产生的丙酮酸促进TCA循环, 在阻断糖酵解途径的情况下, 巨噬细胞可通过谷氨酰胺代谢维持TCA循环的完整性, 降低对丙酮酸的需求。有趣的是, 谷氨酰胺代谢产生的α-酮戊二酸可浓度依赖性地上调FAO反应, 促进M2型巨噬细胞极化[46]。因此, 基于目前的研究而言, M2型巨噬细胞代谢网络复杂而紧密联系, FAO和OXPHOS是为其功能活动提供能量基础的主要代谢方式。

3.3 RA中巨噬细胞代谢特点 滑膜巨噬细胞的活化和增殖是RA关节慢性炎症的重要驱动因素[47]。RA关节腔是一个低氧微环境, 且缺氧水平与滑膜炎症加剧呈负相关[48]。研究表明[49], RA滑膜液中存在大量的乳酸和TCA循环中间代谢物, 表明OXPHOS水平降低, 糖酵解代谢活跃。进一步分析发现[50-52], RA患者滑膜巨噬细胞和外周血单核巨噬细胞中关键糖酵解酶α-烯醇化酶、6-磷酸果糖-2-激酶3、PKM2和HK2表达异常增高, 进而促进糖酵解反应, 并抑制FAO反应。这些研究结果提示, 糖酵解是RA巨噬细胞的主要代谢方式。

Littlewood-Evans等[53]发现, RA滑液中存在的琥珀酸能够与巨噬细胞表面的G蛋白偶联受体91 (G protein-coupled receptor 91, GPR91) 结合, 上调巨噬细胞糖酵解水平, 促进M1型极化, 引起关节炎症反应。此外, 琥珀酸的蓄积能诱导巨噬细胞中HIF-1α表达, 增加的HIF-1α又进一步上调Glut1、HK2和乳酸脱氢酶等一系列糖酵解相关基因的转录水平, 促进IL-1β表达以及巨噬细胞迁移和吞噬能力[33,54]。因此, 琥珀酸可能是RA巨噬细胞代谢重编程中的重要信号分子。随后的研究表明[55], RA患者外周血单核巨噬细胞中糖原合成酶激酶3β (glycogen synthase kinase-3β, GSK-3β) 处于失活状态, 失活的GSK-3β通过上调糖酵解通量, 调控巨噬细胞促炎症功能, 提示GSK-3β的失活是影响RA巨噬细胞代谢重编程的关键因素。

总之, 巨噬细胞代谢重编程是一个复杂的过程 (图2), 阐明炎症环境下巨噬细胞的代谢重编程, 有助于明确调控炎症免疫疾病巨噬细胞极化的作用靶点。

4 巨噬细胞代谢相关的信号通路

巨噬细胞能量代谢的转变将直接导致其功能的变化, 进而引起机体免疫稳态失衡, 诱发炎症反应。在机制上, 多条信号通路参与调节巨噬细胞代谢重编程和极化[56], 包括AMP活化蛋白激酶 (AMP-activated protein kinase, AMPK)、NF-κB和磷脂酰肌醇3/蛋白激酶B (phosphatidyl-inositol 3-kinase/protein kinase B, PI3K/AKT) 传导通路 (图3)。

4.1 AMPK信号通路 AMPK是一种能感知能量分子变化的激酶, 被认为是调控细胞能量代谢的开关。当胞内AMP/ATP比值升高或者钙离子通量增加时AMPK被激活, 促进ATP产生的同时抑制消耗ATP的生物合成途径[57]。AMPK不仅上调线粒体相关酶活性促进OHPXOS[58], 而且上调CPT1α和PGC1β的表达, 促进脂肪酸摄取和FAO反应, 减轻巨噬细胞介导的炎症反应[59]。而AMPK失活将会阻断这些代谢通路, 有利于M1巨噬细胞促进其生物合成途径从而产生炎症介质[60,61]。课题组前期研究发现[17], 巨噬细胞向M1极化与胞内AMPK活性降低有关, 上调AMPK活性可促进巨噬细胞向M2极化, 抑制促炎症因子的分泌。此外, AMPK可通过抑制mTORC1活性阻断蛋白质合成, 调控巨噬细胞糖代谢和增殖[61,62]。近些年, HIF-1α的激活被认为是调控巨噬细胞有氧糖酵解和M1型极化的关键信号[63]。干扰巨噬细胞中HIF-1α表达, 不仅抑制糖酵解水平和M1型极化, 并且减弱细胞迁移和杀菌功能[33,64]。

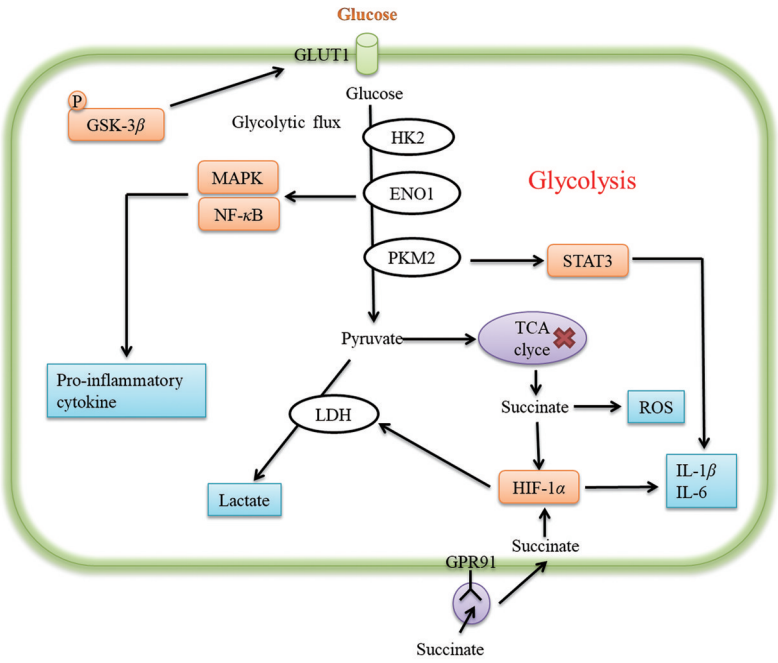

Figure 2　Glycolysis is the main metabolic pathway of macrophages in RA. GLUT1: Glucose transporter 1; HK: Hexokinase; ENO1: *α*-Enolase; PKM2: Pyruvate kinase M2; TCA: Tricarboxylic acid cycle; HIF-1*α*: Hypoxia inducible factor 1*α*; STAT3: Signal transduction and transcriptional activators 3; LDH: Lactic dehydrogenase; GSK-3*β*: Glycogen synthase kinase-3*β*; ROS: Reactive oxygen species; MAPK: Mitogen-activated protein kinases; NF-*κ*B: Nuclear transcription factor-*κ*B; PHD: HIF-prolyl hydroxylase

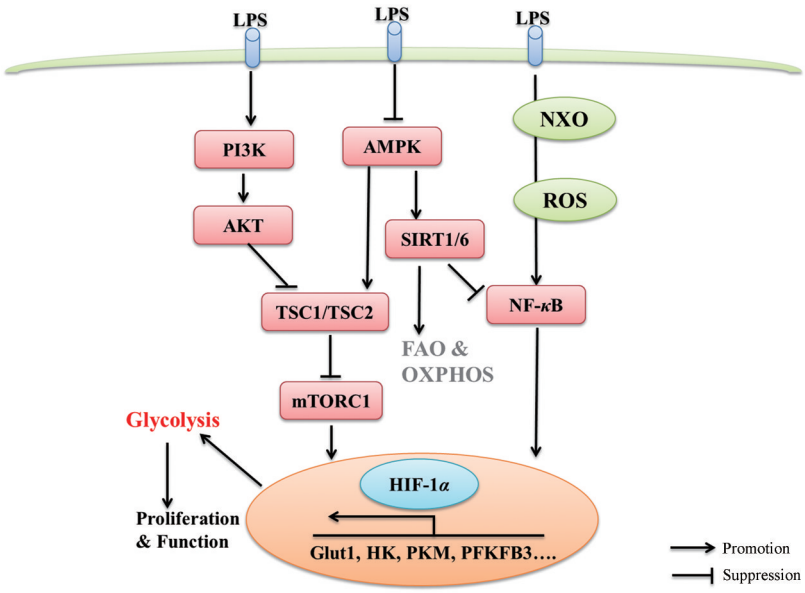

Figure 3　Signaling pathways related with macrophage metabolism. AMPK: AMP-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTORC1: Mammalian target of rapamycin complex 1; NOX: NADPH oxidase; SIRT1/6: Sirtuin-1/6

4.2　NF-*κ*B信号通路　NF-*κ*B是参与调控M1型巨噬细胞代谢和极化的重要分子。研究表明[65], LPS通过激活NF-*κ*B信号通路上调Glut6的表达, 促进M1型巨噬细胞糖酵解反应和炎性介质的分泌。进一步研究发现[66,67], 激活的NF-*κ*B能上调HIF-1*α*转录水平, 进而促进巨噬细胞糖酵解和M1型极化, 增强其杀菌功能。早期的研究表明[68-70], 沉默信息调节因子2相关酶1 (sirtuin-1, SIRT1) 可上调巨噬细胞内CPT1依赖的FAO水平, 促进M2型极化, 且SIRT1能与AMPK相互作用进而抑制NF-*κ*B信号通路, 减弱M1型巨噬细胞迁移和侵袭能力[71]。SIRT6也被发现能够抑制巨噬细胞内NF-*κ*B和HIF-1*α*活化, 下调糖酵解相关基因的表达,

促进M2型极化, 分泌大量抗炎细胞因子[68]。本课题组的研究也表明[17], 活化的AMPK可通过抑制NF-κB信号通路, 调控M1/M2巨噬细胞平衡, 减轻AA大鼠炎症反应和骨质破坏。

4.3 PI3K/AKT信号通路 PI3K/AKT通路是调节细胞周期的重要胞内信号通路。有文献报道[72], LPS通过激活PI3K/AKT信号通路上调Glut1以及糖酵解关键酶HK2和磷酸果糖激酶2 (phosphofructokinase 2, PFK2)的表达, 实现葡萄糖的快速摄取和糖酵解反应, 促进M1型巨噬细胞极化。干扰巨噬细胞内PI3K/AKT信号通路可抑制M1型极化和促炎症细胞因子分泌, 减轻关节炎小鼠的炎症反应[73]。相反, 活化AKT可诱导GSK-3β失活并上调mTORC1活性, 促进巨噬细胞糖酵解反应和M1型极化, 增加NO和炎性介质释放, 引起炎症反应[74,75]。

5 总结与思考

虽然, 近年来对炎症微环境下巨噬细胞代谢重编程已进行较为广泛的研究, 但能量代谢重编程背后的驱动机制及其灵活的调节方式仍然不完全清楚。可以确定的是, 巨噬细胞代谢重编程是组织微环境中多种信号分子相互作用共同调控的结果。认识和阐明巨噬细胞代谢重编程的驱动和调节机制, 将对治疗包括RA在内的巨噬细胞相关疾病, 具有十分重要的意义。

代谢组学和蛋白组学的快速发展为临床认识和治疗RA提供了新的角度和途径。虽然抗代谢药物已在临床上用于治疗RA, 并取得一定的疗效, 但其容易引起多种不良反应, 并非目前治疗RA的理想药物。因此, 针对过度活化免疫细胞 (巨噬细胞、T细胞、B细胞)内的代谢反应, 探寻代谢通路以及代谢相关酶作为药物靶标, 进行特异性调节, 以达到适度调控机体免疫应答的目的, 将是未来治疗RA的理想策略。但是, 一方面RA涉及多种免疫细胞和滑膜组织中FLS的能量代谢改变和异常活化, 分子机制十分复杂; 另一方面, RA免疫代谢相关研究尚处于起步阶段。因此, 关于免疫代谢的临床资料、临床前研究数据有待于进一步挖掘和总结, 同时, 对进入临床试验的相关药物, 其治疗效果也需要更多研究证实。

作者贡献: 余芸和魏芳负责文章的选题、思路和框架的提出以及文章撰写和修改; 蔡伟伟和周静负责制图和资料收集。

利益冲突: 全体作者无利益冲突。

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