巨噬细胞异常代谢在类风湿关节炎病理机制中的作用和研究进展

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摘要: 巨噬细胞在类风湿关节炎 (rheumatoid arthritis, RA) 发病机制中起重要作用。研究表明, RA 巨噬细胞的葡萄糖、胆碱、氨基酸和脂质代谢等发生改变, 导致代谢中间物积累, 代谢中间物又可作为炎症信号分子加重炎症反应, 甚至引起一系列并发症。因此, 充分了解 RA 巨噬细胞的代谢过程可为靶向巨噬细胞治疗 RA 奠定基础。本文综述了巨噬细胞异常代谢在 RA 病理机制中的作用, 以及靶向巨噬细胞的药物在 RA 治疗中的研究进展。

关键词: 巨噬细胞; 类风湿关节炎; 代谢; 药物; 治疗

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Research progress on the abnormal metabolism of macrophages in rheumatoid arthritis pathogenesis

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Abstract: Macrophages play an important role in the pathogenesis of rheumatoid arthritis (RA). Previously, studies have shown that changes in the metabolism of glucose, choline, amino acids and lipids in macrophages of patients with RA can lead to the accumulation of metabolic intermediates which can act as inflammatory signaling molecules to aggravate the inflammation and cause complications. Therefore, a full understanding of the metabolic process of macrophages in RA patients will lay the foundation for macrophage-targeted therapy of RA. In this review, not only the role of macrophage abnormal metabolism in the pathogenesis of RA but also the research progress on macrophage-targeted drugs in RA treatment will be discussed.

Key words: macrophage; rheumatoid arthritis; metabolism; drug; therapy

类风湿关节炎 (rheumatoid arthritis, RA) 是一种以慢性滑膜炎为主要特征的自身免疫病, 最终导致关节进行性损害, 甚至功能丧失[1]。巨噬细胞是 RA 发生发展中非常重要的效应细胞, 与多种细胞相互作用 [如 T、B 细胞和成纤维样滑膜细胞 (fibroblast-like synovial cells, FLS) 等] 产生大量炎性细胞因子, 导致血管翳形成, 骨和软骨破坏[2]。巨噬细胞一直被认为主要有两种不同的表型: 经典活化的 M1 型巨噬细胞 (促炎作用) 和选择性活化的 M2 型巨噬细胞 (抗炎作用), 但近年来学者们通过确切的标记发现了具体的巨噬细胞, 如 $CX3CR1^{+}$滑膜衬里层巨噬细胞[3]。RA 滑膜巨噬细胞 (synovial macrophages, SM) 是关节滑膜中的巨噬细胞, 在炎症反应中起重要作用。最近研究发现, SM 至少有两个起源, 即胚胎来源的滑膜巨噬细胞 (embryonic synovial macrophages, ESM) 和骨髓来源的滑膜巨噬细胞 (bone marrow synovial macrophages, BMSM), ESM 分泌白细胞介素-4 (interleukin-4, IL-4) 和 IL-10 具有抗炎作用, BMSM 分泌 IL-1β 和肿瘤坏死因子-α

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(tumor necrosis factor-α, TNF-α) 具有促炎作用[4]。在RA关节中巨噬细胞增多, 需要更多能量发挥其功能, 导致葡萄糖代谢从氧化磷酸化转变为糖酵解、胆碱摄取增加、氨基酸和脂质代谢异常, 进而引起柠檬酸和琥珀酸等中间代谢物累积, 参与RA病理进程。本文综述了巨噬细胞在RA中的异常代谢以及以调控巨噬细胞的药物在RA治疗中的应用。

1 巨噬细胞异常代谢在RA中的作用

近年来, 细胞代谢在疾病中的重要性逐渐引起人们的重视。代谢产物的复杂性和控制代谢的酶一直是了解代谢途径的主要挑战。研究表明, RA患者关节巨噬细胞增多, 导致细胞需氧量增加, 引起滑膜内供氧不足, 引发氧化应激、生物能量学改变, 进一步导致巨噬细胞代谢功能的异常[5,6] (图1)。

1.1 葡萄糖代谢 糖酵解过程中生成的丙酮酸分子在线粒体中被转化为乙酰辅酶A, 乙酰辅酶A进入三羧酸 (tricarboxylic acid, TCA) 循环, 最终生成36分子ATP。虽然糖酵解产生的ATP没有氧化磷酸化过程产生的多, 但是其速度远远快于氧化磷酸化[7]。RA中M1巨噬细胞的糖代谢主要表现为糖酵解[8], 而M2巨噬细胞主要为氧化磷酸化。Anthony等[9]发现大多数RA患者关节SM大量表达低氧诱导因子-1α (hypoxia inducible factor 1α, HIF-1α), 而健康志愿者关节滑膜中无HIF-1α的表达。HIF-1α是糖酵解的重要调节分子, HIF-1α与RA血管生成、滑膜炎症、软骨降解和骨侵蚀密切相关。RA关节滑膜中的低氧环境会激活磷脂酰肌醇激酶3 (phosphoinositide 3-kinase, PI3K)/AKT/HIF-1α通路, 诱导HIF-1α表达增加, 刺激SM和滑液巨噬细胞分泌血管内皮生长因子 (vascular endothelial growth factor, VEGF), 从而促进血管生成, 加重滑膜增生。同时低氧环境和HIF-1α激活葡萄糖转运体1 (glucose-transporter-1, GULT1), 促进巨噬细胞对葡萄糖摄取和糖酵解通量增加, 导致线粒体应激和活性氧簇 (reactive oxygen species, ROS) 产生, IL-1β和TNF-α增多, 这些炎性因子又可上调HIF-1α的表达, 进一步引起滑膜炎症和软骨、骨损伤[5,10]。PI3K、丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 和钙调素依赖性蛋白激酶II (Ca^{2+}/Calmodulin-dependent kinase II, CaMK II) 通路都可调控HIF-1α活性, PI3K抑制剂LY294002已被证明能显著降低RA患者滑液巨噬细胞和THP-1巨噬细胞株中HIF-1α表达, 降低巨噬细胞分泌VEGF、IL-8和基质金属蛋白酶9[11]。在K/BxN

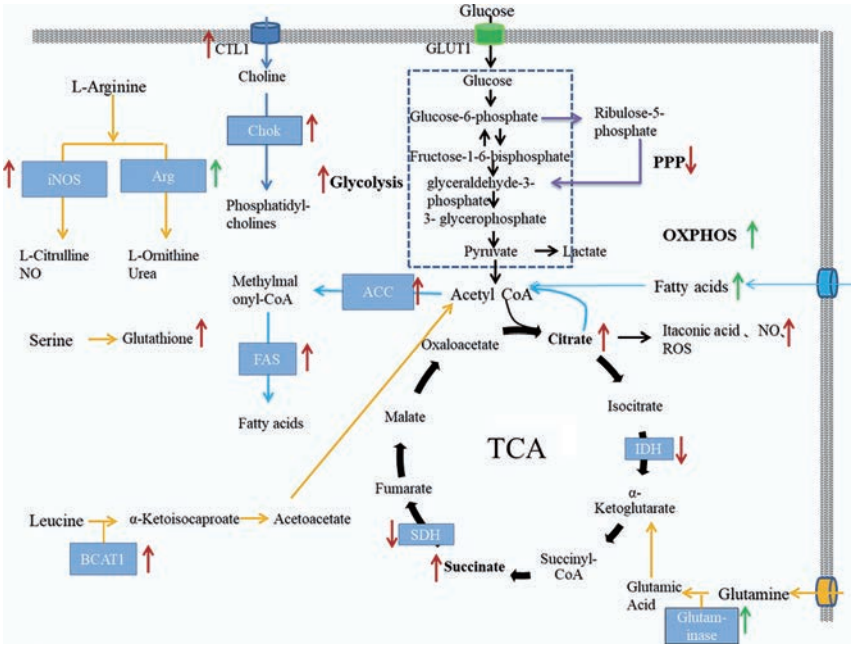

Figure 1 Metabolism of macrophages in rheumatoid arthritis (RA) patients. After glucose is transported into cells through GULT1, most of it is converted to pyruvate by glycolysis, then part of pyruvate is converted to lactate and the other part is converted to acetyl-CoA to participate in blocking TCA. Choline uptake and amino acids metabolism are enhanced. The synthesis and decomposition of fatty acid accelerated, then the generated acetyl-CoA participates in TCA, leading to the accumulation of succinate, citrate, etc., which further aggravates the inflammatory response. The red arrows represent changes in M1 macrophages, and the green represent changes in M2 macrophages. GLUT1: Glucose transporter l; IDH: Isocitrate dehydrogenase; SDH: Succinate dehydrogenase; CTL1: Choline transporter-like 1; Chok: Choline kinase; iNOS: Inducible nitric oxide synthase; Arg: Arginase; BCAT1: Branched-chain aminotransferases 1; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthases; PPP: Pentose phosphate pathway; OXPHOS: Oxidative phosphorylation

血清转移诱导的关节炎模型中, HIF-1α基因敲除的关节炎小鼠关节巨噬细胞浸润和血管翳形成减少, 足爪肿胀程度减轻[12]。RA患者外周血和滑液单核细胞和巨噬细胞中α-烯醇化酶 (α-enolase, ENO1) 表达增加。ENO1是糖酵解途径磷酸甘油转化为烯醇式丙酮酸的催化酶, 可作为抗原与胶原诱导关节炎模型 (collagen induced arthritis, CIA) 小鼠滑液中的巨噬细胞表面的抗ENO1抗体相互结合, 通过p38MAPK和NF-κB通路刺激巨噬细胞产生TNF-α、IL-1α/β, IFN-γ和前列腺素E_2 (prostaglandin E_2, PGE_2)[13]。另有研究发现RA患者滑液巨噬细胞含有大量糖酵解酶丙酮酸激酶M2 (pyruvate kinase M2, PKM2), 随着巨噬细胞对葡萄糖摄取的增加, PKM2二聚化进入细胞核, 磷酸化转录因子STAT3, 诱导巨噬细胞极化为M1巨噬细胞, 分泌IL-6和IL-1β, 参与RA的病理发展[14]。

研究表明, RA患者滑液M1巨噬细胞中TCA循环受阻, 异柠檬酸脱氢酶 (isocitrate dehydrogenase, IDH) 活性降低, 导致柠檬酸盐和衣康酸水平增加。柠檬酸盐积累可用于产生NO、ROS和PG三种重要介质, 促进M1巨噬细胞分泌炎性细胞因子[15]。衣康酸作为抗炎因子, 发挥抑制HIF-1α的作用[16]。研究[8,17]发现RA患者滑液中琥珀酸脱氢酶 (succinate dehydrogenase, SDH) 活性下降导致琥珀酸水平增加。RA患者滑液含有各种内源性Toll样受体配体, 局部激活巨噬细胞, 导致糖酵解增强和巨噬细胞内琥珀酸增加, 促进HIF-1α活化, 诱导巨噬细胞活化产生IL-1β; 同时部分琥珀酸释放到巨噬细胞外, 与琥珀酸受体SUCNR1/GPR91结合, 进一步促进IL-1β产生, 加重炎症反应。CIA小鼠关节滑液中琥珀酸水平与小鼠的足爪肿胀程度有关。在抗原诱导的关节炎 (antigen-induced arthritis, AIA) 小鼠模型中, 基因敲除SUCNR1的小鼠膝关节肿胀程度明显减轻[18]。

1.2 胆碱代谢 胆碱是细胞膜磷脂和乙酰胆碱的前体, 通过特定的转运体吸收并由胆碱激酶 (choline kinase, Chok) 代谢, 转化为磷脂酰胆碱。Beckmann等[19]分析了RA患者有机阳离子转运体 (organic cation transporter, OCT)、胆碱转运体样 (choline transporter-like, CTL) 家族成员和高亲和力胆碱转运体 (high-affinity choline transporter, ChT1) 以及囊泡乙酰胆碱转运体 (vesicular acetylcholine transporter, VACht) 等经典神经元组分在人髋关节和膝关节滑膜和软骨中的表达。研究表明, OCT1、OCT3和CTL1～5蛋白在人关节的滑膜组织和软骨中均有表达, 且RA-SM中高表达CTL1。研究发现, RA患者滑液中总磷脂含量明显增加。RA中活化的巨噬细胞对胆碱有特殊的亲和力, 对胆碱摄取增强, Chok磷酸化胆碱, 产生磷脂, 同时诱导巨噬细胞产生炎性细胞因子[20,21]。Chok对胆碱的摄取、动员、磷酸化至关重要[22-24]。在K/BxN小鼠模型中, Chok抑制剂MN58b降低小鼠关节滑液中磷脂和IL-1β的水平, 减轻关节炎症和软骨破坏[23]。体外用骨髓诱导巨噬细胞 (bone marrow-derived macrophage, BMDM) 研究表明, 当胆碱或Chok受到抑制后, 会导致线粒体损伤, ATP合成酶活性和细胞内ATP降低, 随后激活腺苷酸活化蛋白激酶, 促进巨噬细胞有丝分裂, 抑制巨噬细胞产生IL-1β[20]。

1.3 氨基酸代谢 氨基酸不仅是蛋白质合成的基石, 也是构成关键细胞信号通路的基石。研究发现, RA巨噬细胞需要丝氨酸代谢产生谷胱甘肽来调节IL-1β的转录[25]。高通量代谢谱研究表明谷氨酰胺代谢是M2巨噬细胞的一个特征。TCA循环中几乎三分之一的碳都来自谷氨酰胺[8]。精氨酸是RA巨噬细胞代谢重要氨基酸, 是精氨酸酶 (arginase, Arg) 和一氧化氮合酶 (nitric oxide synthase, NOS) 的底物[26]。RA患者血清中Arg含量和活性升高[27]。M1巨噬细胞优先过表达NOS, 并利用精氨酸产生NO, NO过量反过来增加巨噬细胞的细胞毒性作用。相反, M2巨噬细胞优先大量表达Arg以产生鸟氨酸, 鸟氨酸是多胺的前体, 其有助于巨噬细胞增殖和恢复组织内稳态[26]。RA滑膜富含*L*型氨基酸转运体基因 (*L*-amino acid transporter 1, LAT1), RA患者外周血单核细胞和巨噬细胞中LAT1表达明显升高, 介导支链氨基酸亮氨酸内流, LAT1通过哺乳动物雷帕霉素靶蛋白复合体1诱导的糖酵解重编程促进RA单核细胞和巨噬细胞分泌IL-1β和TNF-α[28]。Papathanassiu等[29]用CIA小鼠模型和BMDM发现, 支链转氨酶1 (branched-chain aminotransferases, BCAT1)是支链氨基酸分解代谢的酶, BCAT1抑制剂ERG 240可降低巨噬细胞耗氧量和糖酵解速率, 抑制炎症巨噬细胞浸润, 减轻CIA关节炎的严重程度。

1.4 脂质代谢 流行病学、临床和实验室研究表明, RA巨噬细胞脂质代谢异常易引起心血管疾病如动脉粥样硬化[30,31]。RA患者动脉粥样硬化的特点是泡沫细胞在动脉内膜层的累积, 而巨噬细胞内胆固醇的累积会形成泡沫细胞。Kiss等[32]发现RA患者血清中IL-34明显升高, 导致巨噬细胞对胆固醇摄取增加, 随后通过p38MAPK信号通路上调CD36表达, 促进泡沫细胞形成。Wen等[33]在CIA模型中检测到腹腔巨噬细胞和外周血巨噬细胞中胆固醇增加, 且细胞内清道夫受体CD36表达增加。使用辛伐他汀治疗后, 小鼠血清中高密度脂蛋白和氧化低密度脂蛋白水平降低, 从而减少了巨噬细胞内脂质累积和CD36表达。脂肪酸代谢是一个动态的合成与分解过程, 维持机体能量平衡。在许多疾病

中, 这种动态平衡被破坏, 导致脂质积累[27]。脂肪酸氧化 (fatty acid oxidation, FAO) 对巨噬细胞在TCA循环中至关重要[34]。RA中M1巨噬细胞脂肪酸 (fatty acid, FA) 合成增加[8]。M2巨噬细胞FA摄取和FAO加强, 但在RA中具体机制有待于进一步研究。研究表明, IL-4和IL-13增加巨噬细胞过氧化物酶体增殖物激活受体γ共激活因子1β的表达, 导致线粒体呼吸链蛋白表达增加, 加快FAO[16,35]。FAO生成的乙酰辅酶A又可导致胆固醇累积, 从而增加动脉粥样硬化的风险。

2 调控巨噬细胞的药物在RA治疗中的作用

目前治疗RA的主要药物有改善病情抗风湿药 (disease-modifying antirheumatic drug, DMARDs)、甾体抗炎药、非甾体抗炎药和天然药物。DMARDs包括传统DMARDs和生物制剂, 靶向JAK/STAT信号通路的多个小分子药物, 近年来也被研发应用于RA的临床治疗[36]。但目前还没有靶向巨噬细胞的药物, 有些药物在发挥作用的同时可以间接地影响巨噬细胞功能。传统DMARDs为一线药物, 最常见的是甲氨蝶呤, 通过抑制NF-κB和NLRP3/Caspase-1通路, 抑制巨噬细胞增多和分泌炎性细胞因子, 干扰巨噬细胞脂质代谢, 减轻关节炎症反应和骨破坏, 是大多数RA患者的首选药物[37]。

研究表明, RA患者滑膜液中性粒细胞−巨噬细胞集落刺激因子 (granulocyte-macrophage colony stimulating factor, GM-CSF) 及其受体表达升高, GM-CSF激活巨噬细胞、中性粒细胞和树突状细胞发挥促炎作用[38]。目前GM-CSF抑制剂 (MOR103[39]、MORAb002、KB003和namilumab[40]) 以及抗GM-CSFRα的抗体 (mavrilimumab)[41]已完成II期临床试验[35], 对传统DMARDs耐受的患者有良好的有效性和安全性。巨噬细胞是TNF-α、IL-1和IL-6等促炎细胞因子的主要来源细胞。靶向TNF-α (etanercept、infliximab、adalimumab、certolizumab和golimumab)[42]、IL-1β (canakinumab和anakinra)[43]和IL-6 (tocilizumab、sarilumab、clazakizumab和ALX-0061)[44]的抑制剂, 通过抑制巨噬细胞极化为M1巨噬细胞, 促进单核细胞和炎性巨噬细胞的凋亡来有效控制RA滑膜炎。酪氨酸激酶抑制剂imatimb[45]和mastinib[46]也可以抑制巨噬细胞产生TNF-α, 缓解全身炎症。早期研究发现, RA组织中巨噬细胞高表达趋化因子受体1 (CC chemokine receptor 1, CCR1), CCR1拮抗剂CCX354-C能调节单核细胞和巨噬细胞向滑膜组织迁移, 减少炎性巨噬细胞浸润, 缓解关节炎症, 目前CCX354-C在临床上具有一定的安全性和有效性[47]。小分子JAK抑制剂的研究可阻止滑膜内STAT转录因子的激活, 如tofacitinib (JAK1/3抑制剂)[48]和baricitinib (JAK1/2抑制剂)[49]抑制巨噬细胞活化和产生IL-6、TNF-α等促炎细胞因子, 有效阻断RA炎症的级联反应。Peficitinib (JAK2抑制剂)[50]、upadacitinib (JAK1抑制剂) 也已用于临床[51]。与tofacitinib具有类似作用机制的filgotinib正在进行III期临床试验, 有良好的有效性[52]。

对于天然药物, 白芍总苷可通过上调Arg-1的产生和活性来抑制M1巨噬细胞的活性, 同时增强M2巨噬细胞的功能, 抑制巨噬细胞分泌IL-1β、IL-6、TNF-α、IL-8、PGE2和环氧合酶-2缓解RA关节炎症和骨破坏[53]。雷公藤中的雷公藤总苷被认为是治疗RA的主要活性成分, 抑制巨噬细胞IL-1α、IL-1β、TNF-α和IL-6基因的表达[54]。青藤根中的青藤碱成分则有效抑制巨噬细胞分泌TNF-α和IL-1β, 目前都用于治疗RA等自身免疫疾病[55]。

3 总结与展望

RA发病机制复杂, 目前还没有较好的治疗药物。传统DMARDs如甲氨蝶呤等起效慢且不良反应大, 生物制剂和小分子抑制剂靶点单一, 具有诱发严重感染和肿瘤的风险, 天然药物成分复杂且易发生过敏反应。

Table 1 Potential therapeutic targets of macrophages metabolic pathway in RA. 2-DG: 2-Deoxyglucose; 3-BP: 3-Bromopyruvate; HIF-1α: Hypoxia-inducible factor-1α; ME-2: Methoxyestradiol-2; CIA: Collagen-induced arthritis; AIA: Antigen-induced arthritis; ENO1: α-Enolase; PKM 2: Pyruvate kinase M2; AA: Adjuvant arthritis; FLS: Fibroblast-like synovial cells; LAT1: *L*-Type amino acid transporter 1

Metabolic pathway	Target	Drug or compound	Disease or animal model
Glucose metabolism	GLUT1[56]	CG-5, WZB-117, STF31, fasentin	RA
	Hexokinase[56]	2-DG, ionidamine, 3-BP	RA
	HIF-1α[11,57]	Genistein, LY294002, KN95, ME-2, Hsp90	RA, CIA, AIA
	ENO1[58]	Anti-ENO1 antibody	Systemic lupus erythematosus
	PKM2[59]	Shikonin	Atherosclerosis
	SUCNR1[60]	BHGZ	AA
Choline metabolism	CTL1[61]	HC3	RA-FLS
	Chok	MN58b	K/BxN
Amino acid metabolism	BCAT1	ERG240	CIA
	LAT1[62]	BCH	RA-FLS
Lipid metabolism	CD36	Simvastatin	CIA

RA关节滑膜中炎性巨噬细胞增多, 在慢性滑膜炎中发挥至关重要的作用。近年来研究发现, 巨噬细胞异常代谢参与了RA的病理机制和发生发展, 尤其是关节处的SM。因此, 通过靶向RA关节滑膜中巨噬细胞的代谢酶或者中间代谢物 (表1[11,56-62]), 纠正活化巨噬细胞的异常代谢, 而通过控制代谢调节巨噬细胞功能用来治疗RA等自身免疫病, 只针对激活的代谢活跃细胞, 不会影响基本免疫功能。这也将最大程度地改善疾病症状, 减轻药物不良反应, 为将来研究炎症免疫反应软调节药物 (选择性调控机体组织或者细胞的药物) 提供新方向[63]。因此, 对巨噬细胞异常代谢的研究有助于全面阐述RA发病机制, 充分了解RA巨噬细胞的代谢途径可为靶向巨噬细胞治疗RA提供新思路。

作者贡献: 王越业是综述的主要撰写人, 完成相关文献资料的查阅以及论文初稿的写作; 常艳教授提供文章的思路和整体的规划, 以及对文章内容和格式的修改等, 是本项目的主要负责人; 魏伟教授给予宏观的指导和思路的设计。全体作者都阅读并同意最终的版本。

利益冲突: 全体作者承诺文章涉及内容无任何利益冲突。

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