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炎症性肠病中的巨噬细胞糖代谢重编程

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摘 要

炎症性肠病(IBD)是肠道免疫系统过度激活所致的一种慢性炎症性疾病。巨噬细胞在肠道免疫中发挥重要作用，其极化表型及功能受细胞代谢的调控。在炎症性肠病的发生发展中，巨噬细胞表现出明显的糖代谢重编程，即出现从氧化磷酸化向糖酵解转变，并且出现磷酸戊糖途径的上调、三羧酸循环受损，促进M1型巨噬细胞的极化及炎症因子的表达，进而加重炎症性肠病。这一代谢重编程受多种信号分子的调节，肠道菌群及代谢物，包括短链脂肪酸、色氨酸、胆汁酸等也在这一代谢过程中发挥不可替代的作用。因此，对炎症性肠病中的巨噬细胞糖代谢重编程进行阐述，不仅深化了炎症性肠病免疫代谢理论的理解，也为开发干预代谢通路缓解炎症性肠病的新治疗策略提供重要科学依据。

关键词

炎症性肠病，巨噬细胞，糖代谢重编程

Macrophage Glucose Metabolism Reprogramming in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory disease caused by abnormal activation

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of the intestinal immune system. Macrophages play an important role in intestinal immunity, and their polarized phenotype and function are regulated by cellular metabolism. In the development and progression of inflammatory bowel disease, macrophages exhibit a significant reprogramming of glucose metabolism, shifting from oxidative phosphorylation to glycolysis, with upregulation of the pentose phosphate pathway and impaired tricarboxylic acid cycle. This further promotes M1 macrophage polarization and the expression of inflammatory cytokines, exacerbating inflammatory bowel disease. This metabolic reprogramming is regulated by multiple signaling molecules, and gut microbiota and metabolites such as short-chain fatty acids, tryptophan, and bile acids also play irreplaceable roles in this metabolic process. Therefore, elucidating the reprogramming of macrophage glucose metabolism in inflammatory bowel disease not only deepens our understanding of the immuno-metabolic theory underlying inflammatory bowel disease but also provides crucial scientific evidence for developing novel therapeutic strategies that target metabolic pathways to alleviate inflammatory bowel disease.

Keywords

Inflammatory Bowel Disease, Macrophage, Glucose Metabolism Reprogramming

1. 引言

炎症性肠病分为克罗恩病和溃疡性结肠炎，是一种由免疫介导的慢性、难治性胃肠道疾病[1] [2]。炎症性肠病的发病率在全球范围内不断上升，目前已经成为一种全球性疾病[3] [4]。有相关研究预测未来十年炎症性肠病的患病率仍不断升高，这给全球卫生医疗系统带来了巨大的负担[5]-[7]。炎症性肠病的发病机制尚未研究清楚，目前认为可能是遗传易感、环境因素、肠道微生物群紊乱及屏障功能受损之间相互作用引发免疫失调所致的一种非特异性肠道炎症[8]。巨噬细胞是肠道固有免疫系统的重要成分，在肠道稳态及肠道炎症调节上发挥关键作用[9]。它不仅参与了肠道基本生理过程，还在炎症性肠病患者的肠外稳态方面发挥作用[10]。巨噬细胞具有高度表型可塑性，一般可分为 M1 型巨噬细胞(经典活化/促炎)和 M2 型巨噬细胞(替代激活/抗炎) [11]。在炎症性肠病中巨噬细胞能促进炎症消退及组织修复，是炎症性肠病的理想治疗靶点之一[12]。临床上通过抗肿瘤坏死因子药物实现的病情缓解与 M1 型巨噬细胞活性降低息息相关[13]。之前大多数研究侧重于细胞因子及信号通路，随着代谢免疫领域的不断发展，研究人员发现代谢重编程在巨噬细胞的功能及活化上发挥着关键作用[14]。相关研究指出巨噬细胞代谢紊乱与肿瘤、动脉粥样硬化、类风湿性关节炎等多种疾病的发生发展密切相关[15]-[17]，但以炎症性肠病为背景的相关研究较为有限。糖酵解、磷酸戊糖途径、三羧酸循环、氨基酸代谢、脂肪酸的氧化及合成是巨噬细胞内主要涉及的代谢途径[14] [18]。但不同表型巨噬细胞的能量需求及代谢途径具有差异性，例如 M1 型巨噬细胞的激活表现出和肿瘤细胞类似的 Warburg 效应，即能量获取方式会从高效的氧化磷酸化向低效快速的糖酵解转变，同时还可以观察到三羧酸循环受损和磷酸戊糖途径通量的增加[18] [19]。巨噬细胞代谢重编程在炎症性肠病的发生发展中发挥关键作用，深入理解巨噬细胞代谢重编程调控的分子机制，为开发靶向代谢通路的新型炎症性肠病治疗策略提供坚实的理论基础。本文主要以巨噬细胞糖代谢重编程为主要切入点，系统探讨其在炎症性肠病发生发展中的核心调控作用，并进一步探讨靶向巨噬细胞糖代谢通路作为炎症性肠病治疗新策略的潜力和挑战，为开发新型炎症性肠病治疗干预手段提供理论框架。

2. 炎症性肠病中的巨噬细胞

巨噬细胞广泛存在于肠道的各层组织中，其功能与位置相关。例如固有层中巨噬细胞在维持 T 细胞及肠道干细胞功能上发挥重要作用，肌层外巨噬细胞能与神经元细胞进行相互作用[20]。巨噬细胞具有高度可塑性，在包括转录因子、非编码 RNA、细胞外囊泡等在内的多种信号分子及通路的调节下可分化成不同表型的巨噬细胞，M1 型、M2 型巨噬细胞在炎症性肠病的发生发展中发挥重要作用[21]。在炎症性肠病中往往可以观察到 M1 型巨噬细胞的增多及 M2 型巨噬细胞的减少。然而，改善炎症性肠病并不能靠单纯增加 M2 型巨噬细胞，有关研究表明，保持 M1、M2 型巨噬细胞之间的平衡更重要[22]。靶向巨噬细胞调节其表型变化是改善炎症性肠病的有效治疗策略。

3. 糖酵解途径的重编程

糖酵解是细胞将葡萄糖分解生成丙酮酸及其他产物的代谢过程。虽然这一过程产能效率低，一分子葡萄糖仅能生成 2 分子 ATP，但能产生还原型辅酶 I (NADH)维持细胞的氧化还原平衡以及满足快速增殖细胞自身对能量和生物合成原料的需求[19]。糖酵解在巨噬细胞极化过程中发挥重要作用。炎症性肠病中的炎性病灶处于缺氧环境中，为了满足缺氧及炎性环境的能量需求，巨噬细胞进行了代谢重编程，其中比较典型的是 M1 型巨噬细胞从氧化磷酸化转向糖酵解[22]。在这一过程中起主要调控作用的是缺氧诱导因子 1α (HIF-1α)。有研究表明，在 HIF-1α 过表达的小鼠模型中发现促炎型巨噬细胞的表达升高[23]。在炎症性肠病患者的血液中也可以检测到 HIF-1α 水平的升高[24]。很多研究指出在脂多糖诱导的巨噬细胞中可以观察到 HIF-1α 能够诱导磷酸果糖激酶 1 (PFK-1)、葡萄糖转运蛋白 1 (GLUT1)、丙酮酸脱氢酶(PDH)、己糖激酶 2 (HK2)、乳酸脱氢酶(LDH)等多基因表达，进一步推动糖酵解的发生[25] [26]。氧浓度并不是 HIF-1α 的唯一调节因子，代谢物也能够影响 HIF-1α 的活性，例如琥珀酸通过抑制脯氨酰羟化酶来稳定 HIF-1α，进一步强化糖酵解[27]。

丙酮酸激酶 M2 (PKM2)作为糖酵解的关键酶之一，在 M1 型巨噬细胞的糖酵解重编程中发挥独特且重要的作用。有研究观察到炎症性肠病患者的血清样本中 PKM2 的浓度远高于健康人群[28]。然而 PKM2 在炎症性肠病中的作用并不是单一的，PKM2 在高活性的四聚体与低活性的二聚体之间相互转换。在脂多糖诱导的 M1 型巨噬细胞中的 PKM2 主要以低活性的二聚体形式存在，其可以进入细胞核与 HIF-1α 形成复合物，结合在白细胞介素-1β (IL-1β)及 HIF-1α 依赖基因的启动子区域，进一步发挥促炎作用，并且能够形成糖酵解中间产物的堆积(如琥珀酸)，稳定 HIF-1α 的活性；使用 PKM2 激活剂可将其转化为高活性的四聚体，高活性的四聚体不能进入细胞核与 HIF-1α 结合，减少了糖酵解中间产物的堆积，进一步抑制了 M1 型巨噬细胞的极化，促进了 M2 型巨噬细胞的极化，减少促炎因子的产生[29] [30]。有研究表明哺乳动物雷帕霉素靶蛋白(mTOR)是细胞代谢的调控因子，在炎症反应和糖酵解中也发挥重要作用[31]。在炎症性肠病患者的肠道粘膜中可以观察到 mTORC1 的高度活化，同时在结肠炎小鼠模型抑制 mTORC1 信号能够改善结肠炎，临床上常见的改善结肠炎的药物美沙拉嗪就是通过这一机制发挥作用[32]。mTORb 不仅能够通过增加 HIF-1α 的表达进而影响糖酵解相关酶，同时它还在脂质的合成中起调控作用[33]。抑制 mTOR 的活性可影响糖酵解及巨噬细胞功能，改善结肠炎[34]。糖酵解的代谢物乳酸也对糖酵解有一定的调控作用，乳酸在不依赖缺氧的情况下仍能调控 HIF-1α 的活性[35]。相关研究表明，在肿瘤巨噬细胞中乳酸产量的不断增加能够激活 HIF-1α 和 mTOR 信号通路，促进糖酵解[36]。在由 2,4,6-三硝基苯磺酸(TNBS)诱导的结肠炎模型中，也能够观察到乳酸介导的抗炎反应[37]。

4. 三羧酸循环的异常重塑

三羧酸循环是包括葡萄糖、脂肪酸及氨基酸等在内的有机物彻底氧化的共同途径，能高效生成 ATP，

同时其中间产物也可用于支持其他代谢途径。三羧酸循环是细胞的核心代谢枢纽及真核生物生命中的核心生化过程，其代谢物琥珀酸、α-酮戊二酸、柠檬酸及三羧酸循环的衍生代谢物衣康酸，都在炎症基因的表达上起调控作用，同时也在巨噬细胞的活化过程中发挥重要作用，不同于 M2 型巨噬细胞具有完整的三羧酸循环，M1 型巨噬细胞中通常可以观察到三羧酸循环的受损重构[18]。在炎症性肠病的微环境中，巨噬细胞中的三羧酸循环进行了代谢重塑，这个过程涉及了功能性的断裂及代谢重构。在维持巨噬细胞炎性表型及疾病的发生发展中发挥重要作用。目前普遍认为在 M1 型巨噬细胞中三羧酸循环发生两个代谢断点[38]。第一个断点发生在异柠檬酸脱氢酶(IDH)处，受阻的异柠檬酸脱氢酶导致柠檬酸在细胞内大量蓄积[39]。累积的柠檬酸通过线粒体柠檬酸载体(CIC)从线粒体转运至细胞质并裂解为乙酰辅酶 A，参与脂质及炎症介质的合成[40] [41]。在柠檬酸代谢重编程这一过程中往往伴随着一氧化氮合酶(iNOS)的激活及高浓度一氧化氮(NO)的产生，虽然 NO 能够参与组织修复与免疫调节，但在高浓度下会导致肠道粘膜的损伤加重[42]。第二个断点位于琥珀酸脱氢酶(SDH)处，导致琥珀酸大量积累。在这一过程中可以观察到琥珀酸脱羧酶 1 (ACOD1/IRG1)表达水平的上调，其通过催化顺式柠檬酸酐脱羧生成反式柠檬酸酐，抑制琥珀酸脱氢酶活性，使琥珀酸不能生成为富马酸，进而干扰三羧酸循环[43] [44]。琥珀酸作为 α-酮戊二酸(α-KG)的竞争性抑制剂能够抑制脯氨酰羟化酶(PHD)，稳定 HIF-1α，进一步促进糖酵解和 IL-1β 等炎症因子的表达[26] [45]。有研究表明，这一过程的驱动依赖于丙酮酸脱氢酶复合体(PDHC)和 α-酮戊二酸脱氢酶(OGDC)的抑制[46]。有研究表明表观遗传调控也在这一过程中发挥不可替代的作用[47]。α-酮戊二酸和衣康酸是三羧酸循环的代谢物，在细胞代谢中发挥重要作用。α-酮戊二酸是 DNA 和组蛋白去甲基酶的辅因子，在表观遗传调控上发挥重要作用[48]。衣康酸是在乌头酸脱羧酶 1 的催化下生成的，有研究表明，衣康酸在结肠炎模型中发挥抗炎作用[49]。

5. 磷酸戊糖途径

磷酸戊糖途径是细胞代谢中能量生成的途径。在糖代谢重编程中，除通过糖酵解供能外，还有一部分葡萄糖分流进入磷酸戊糖途径。磷酸戊糖途径发生在葡萄糖代谢的第一步关键反应，糖酵解的代谢物 6-磷酸葡萄糖酸内酯(G6P)脱氢后生成 6-磷酸葡萄糖酸(6PG)，在 6-磷酸葡萄糖酸脱氢酶(6PGD)的作用下生成核苷酸-5-磷酸(Ru5P)，同时这一过程是产生还原型辅酶 II (NADPH)的主要途径[50]。M1 型巨噬细胞中的磷酸戊糖途径表达趋势与糖酵解一致，在脂多糖诱导的 M1 型巨噬细胞中可以观察到磷酸戊糖途径的通量增加[18]。该代谢途径的代谢物 NADPH 在细胞代谢中发挥重要作用。NADPH 作为 NADPH 氧化酶(NOX)复合物的必需底物，在呼吸爆发期间能够产生高水平的活性氧(ROS)以杀灭病原体并参与炎症信号转导，同时它还是谷胱甘肽还原酶的辅因子，能够将氧化型谷胱甘肽(GSSG)还原为还原型谷胱甘肽(GSH)，进而维持细胞内的氧化还原平衡，防止过度的氧化应激对宿主组织造成损伤[19] [51]。碳水化合物激酶样蛋白(CARKL)能够调控磷酸戊糖途径的代谢重编程，有关研究表明抑制碳水化合物激酶样蛋白可以促使巨噬细胞向 M1 型极化，反之上调其表达可以维持 M2 型巨噬细胞表型[52]。但这些研究基于脂多糖诱导的体外巨噬细胞模型，在炎症性肠病患者中的证据仍需进一步探索。有研究指出，在肿瘤细胞中 P53 也与该代谢重编程相关，P53 通过促进磷酸戊糖途径进一步促进 M1 型巨噬细胞的极化[53]。但目前没有证据表明，P53 能通过上述途径影响炎症性肠病的发生发展。

6. 肠道微生物与巨噬细胞糖代谢重编程

肠道菌群在维持肠道稳态中发挥重要作用，肠道菌群与宿主代谢之间的相互作用是炎症性肠病病理过程中的关键组成部分。进一步了解肠道菌群对炎症性肠病中巨噬细胞糖代谢的影响对未来成功塑造炎症性肠病新的治疗靶点非常重要。短链脂肪酸(SCFAs)包括丁酸、丙酸和乙酸，是肠道微生物群发酵膳食

纤维的产物[54]。糖酵解的中间产物丙酮酸也可通过代谢生成短链脂肪酸[55]。有研究表明短链脂肪酸可以抑制组蛋白去乙酰化酶(HDAC)的活性，进而抑制巨噬细胞中促炎因子的表达，促进抗炎成分的表达[56]。有研究指出丁酸可以抑制糖酵解，从而增强巨噬细胞中的抗炎能力，这一过程是通过抑制组蛋白去乙酰化酶 3 (HDAC3)、mTOR 的激活所介导的[57]。此外，肠道菌群可通过琥珀酸途径生成短链脂肪酸，在三羧酸循环中以琥珀酸为底物，经过中间体的转化最后生成丙酸，短链脂肪酸和琥珀酸相互作用，在维持肠道稳态及控制肠道炎症中发挥重要作用[58]。有研究表明丙酸可以通过激活游离脂肪酸受体和抑制组蛋白脱乙酰化酶，发挥免疫代谢调节及抑制炎症的作用[59]。色氨酸是来自膳食蛋白的必需芳香氨基酸。在肠道菌群的作用下，分解产生吲哚，例如吲哚丙酸(IPA)、吲哚乳酸(ILA)、吲哚乙酸(IAA)等[60]。一项研究表明吲哚丙酸能通过靶向已糖激酶 2 (HK2)抑制糖酵解，进而抑制炎症，这一途径是通过 JNK/MAPK 途径所介导的[61]。胆汁酸是由肝脏合成，能被肠道菌群改造的一种代谢物质。有研究表明胆汁酸具有双重作用，高浓度下能够激活 NLRP3 炎症小体和细胞焦亡；而处于生理相关的低浓度下，能够通过促进线粒体融合进一步加强氧化磷酸化水平，促进巨噬细胞介导的细菌吞噬作用[62]。

7. 靶向糖代谢重编程的治疗策略

巨噬细胞的糖代谢重编程在炎症性肠病的发生发展中发挥重要作用，开发靶向巨噬细胞糖代谢重编程的疗法具有巨大的潜力。目前一些关于调节糖代谢重编程的临床前研究已经得到了一定成效。如一项关于钠－葡萄糖协同转运蛋白 2 (SGLT2)抑制剂的研究结果提示，SGLT2 能够下调糖酵解水平减弱结肠炎小鼠模型中的炎症[63]。硫胺素的缺乏通过削弱丙酮酸脱氢酶的活性重编程糖代谢，上调 M1 型巨噬细胞中的糖酵解水平，进而加重小鼠溃疡性结肠炎[64]。吲哚-3-丙酸通过抑制糖酵解及 M1 型巨噬细胞的极化，发挥抗炎作用[61]。CaGA 纳米酶通过影响三羧酸循环和尿素循环，调节溃疡性结肠炎中的肠道功能[65]。然而这些研究基本在动物模型及体外细胞模型中开展，缺乏临床验证。尽管炎症性肠病的治疗已经引入了一些新的治疗药物，如肿瘤坏死因子(TNF-α)抑制剂、白细胞介素(IL)拮抗剂等[66] [67]，但这些药物仍存在反应率有限、副作用大等问题，如接受英夫利昔单抗的治疗的一些患者表现无效应答，一些出现包括急性炎症、癌症等并发症[68]。为了改善这些问题，很多研究人员开始探索炎症性肠病的给药技术，如一项研究表明纳米配方药物能够更好地改善炎症性肠病[69]。糖代谢作为人体的基本代谢方式，全身抑制可能会带来副作用，并且炎症性肠病不同分型及不同患者之间的微生物群和代谢谱上存在差异[70]。因此，对炎症性肠病患者进行精准靶向代谢给药的可能成为未来的新治疗方向，并且随着对巨噬细胞糖代谢网络理解的深入、药物设计及递送技术的不断发展，安全有效的代谢调节药物有希望投入临床使用，为炎症性肠病患者提供从对症治疗到代谢重塑的精准治疗，进一步实现长期缓解。

8. 结论

巨噬细胞的糖代谢重编程在炎症性肠病的发生发展中发挥核心作用。处于肠道炎症微环境中的巨噬细胞发生了显著的代谢重编程，主要表现为糖酵解、磷酸戊糖途径的上调，三羧酸循环的重构。这些代谢的重编程不仅受细胞信号通路的调控，肠道菌群及代谢物也在调控过程中发挥重要作用。随着免疫代谢领域的不断发展，针对巨噬细胞代谢重编程的治疗策略具有广阔的临床前景。根据炎症性肠病中巨噬细胞代谢的特点，开发新药物、发展新给药技术，将为提升炎症性肠病治疗的有效性及安全性打下坚实的基础。总之，深刻理解巨噬细胞糖代谢与免疫功能之间的内在联系，将为炎症性肠病的精准治疗及长期缓解提供新的理论基础及干预方式。

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