

糖酵解调控巨噬细胞极化及其在动脉粥样硬化病理过程中的作用

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【摘要】 动脉粥样硬化(AS)是动脉粥样硬化性心血管疾病的主要诱发因素,巨噬细胞极化在 AS 炎症发生发展过程中扮演着重要角色。近年来研究发现,代谢途径的改变是诱发巨噬细胞极化的关键环节,其中糖酵解是与 AS 关系最密切的免疫代谢途径。基于此,现从巨噬细胞免疫代谢途径的可塑性入手,对糖酵解调控巨噬细胞极化在 AS 病理进程中扮演的角色,以及调控上述途径的缺氧诱导因子-1 α /磷酸果糖激酶-2/果糖-2,6-二磷酸酶 3 信号通路进行综述,以期对未来 AS 防治研究提供新方向。

【关键词】 动脉粥样硬化;巨噬细胞极化;糖酵解;免疫代谢

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Glycolytic Modulation of Macrophage Polarization and Its Role in Pathological Process of Atherosclerosis

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【Abstract】 Atherosclerosis(AS) is the main inducing factor of atherosclerotic cardiovascular disease. Macrophage polarization plays an important role in the occurrence and development of AS inflammation. Recently, it has been found that the change of metabolic pathway is the key link to induce macrophage polarization, and glycolysis is the immune metabolic pathway most closely related to AS. Therefore, starting with the plasticity of macrophage immune metabolic pathway, this paper discusses the role of glycolysis in regulating macrophage polarization in the pathological process of AS and HIF-1 α /PFKFB3 signaling pathway. This is reviewed to provide a new direction for the prevention and treatment of AS in the future.

【Key words】 Atherosclerosis; Macrophage polarization; Glycolysis; Immune metabolism

心血管疾病给居民和社会带来的经济负担日渐加重。据《全球心血管疾病和危险因素负担 1990—2019》统计,以缺血性心脏病和卒中为主的动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD),是全球致死和致残的主要原因,占全球总死亡人数的 1/3,其中心血管死亡发生率最高的国家是中国^[1]。《中国心血管健康与疾病报告 2019》显示,ASCVD 是中国城乡居民总死亡原因的首位^[2],其中农村为 45.91%,城市为 43.56%。因此,ASCVD 是严重危害人类健康的首要公共卫生问题。

动脉粥样硬化(atherosclerosis, AS)是 ASCVD 的主要诱发因素^[3]。既往认为,脂质沉积及炎症反应是

参与 AS 形成的关键病理环节^[4]。CANTOS 研究^[5]首次证实抗炎药物在 ASCVD 治疗领域具有巨大应用价值。然而,新近发表于 *N Engl J Med* 杂志的 CIRT 研究^[6]结果表明,广谱抗炎药物甲氨蝶呤治疗并未降低 ASCVD 死亡率。因此,寻找阻断与 AS 相关的特定炎症途径药物靶点可作为新的突破口。研究^[7]表明,巨噬细胞极化在 AS 炎症发生发展过程中扮演着重要角色。近年来研究^[8]发现,代谢途径的改变是诱发巨噬细胞极化的关键环节。基于此,现从巨噬细胞免疫代谢途径的可塑性入手,对免疫代谢途径调控巨噬细胞极化在 AS 病理进程中扮演的角色及研究进展进行阐释,引领未来 AS 防治研究的新方向,具有重要的科学

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价值和社会意义。

1 免疫代谢途径在 AS 中的作用

免疫细胞的功能与细胞内能量代谢途径之间的关系,以及二者在疾病中的调控作用被视为“免疫代谢”^[9]。2019 年,欧洲心脏病学会 AS 和血管生物学工作组发布《免疫代谢与 AS: 前景及临床意义》意见书^[10],阐释了免疫细胞代谢途径的改变在 AS 发展过程中的作用,掀起了“免疫代谢”这一新的研究热潮。首先证明免疫代谢途径改变诱导 AS 形成及发展的证据基于¹⁸F-氟代脱氧葡萄糖(¹⁸F-fluorodeoxyglucose, ¹⁸F-FDG)正电子发射断层成像技术。¹⁸F-FDG 是葡萄糖的放射性核苷类似物,通过葡萄糖转运蛋白被细胞吸收,磷酸化为¹⁸F-FDG-6-磷酸盐沉淀在细胞内。研究^[11-12]显示,¹⁸F-FDG 的高表达与血管炎症及 AS 斑块的易损程度正相关。另外一项临床研究^[13]纳入 159 例行动脉内膜剥脱术的患者,对高危和稳定斑块患者的颈动脉斑块进行代谢分析,结果发现,高危易损斑块中代谢途径的改变与糖酵解、氨基酸代谢等途径的改变密切相关。由此可见,糖酵解、氨基酸代谢等免疫代谢途径的改变与 AS 的发生发展密切相关,该学说的兴起开启了 AS 防治的新篇章,前景广阔。

2 糖酵解是与 AS 关系最密切的免疫代谢途径

糖酵解是参与 AS 形成最重要的免疫代谢途径之一^[14]。在低氧条件下,葡萄糖首先通过葡萄糖转运蛋白被转移到细胞中,然后被己糖激酶磷酸化为 6-磷酸葡萄糖,6-磷酸葡萄糖经过一系列酶的作用被转化为丙酮酸,并产生少量的三磷酸腺苷,这个过程被称为糖酵解^[15]。动物实验^[16]结果表明,敲低 AS 小鼠中葡萄糖转运蛋白 1 的表达水平,可降低小鼠骨髓和 AS 斑块中糖酵解通量,从而发挥抗 AS 的作用。另外一项研究^[17]结果表明,通过抑制葡萄糖-6-磷酸脱氢酶的活性减少糖酵解与磷酸戊糖途径的交互作用,可降低血管中超氧化物水平,进一步减轻 AS 的损伤。由此可见,通过降低糖酵解水平,可达到抗 AS 的目的。大量研究^[18]已证实,巨噬细胞中糖酵解水平与 AS 过程中炎症的发生密切相关。因此,研究巨噬细胞糖酵解途径及其调控机制,将其作为干预靶点至关重要。

3 巨噬细胞极化是导致 AS 发展的主要病理生理过程

AS 的发展涉及不同类型免疫细胞的内流、增殖和激活,其中与 AS 发生和发展关系最密切的是巨噬细胞^[19]。动脉壁中的巨噬细胞清除脂蛋白颗粒,转化为泡沫细胞,分泌炎症因子,促进脂蛋白滞留,加剧 AS 病变的进展^[20]。

巨噬细胞具有可塑性和多样性,在 AS 发生发展

的每一个环节均有巨噬细胞亚型的浸润。不同微环境信号刺激会将其诱导分化为经典活化的 M1 型巨噬细胞和选择性活化的 M2 型巨噬细胞,这种巨噬细胞炎症功能变化的过程称为巨噬细胞极化^[21]。其中, M1 型巨噬细胞极化分泌肿瘤坏死因子- α 、白介素-1 和白介素-6 等因子,促进炎症反应加速 AS 进展; M2 型巨噬细胞分泌精氨酸酶 1、几丁质酶 3 样蛋白 3 和白介素-10 等因子,发挥抗炎和促进组织修复的作用^[22]。除此之外,极化过程中, M2 型巨噬细胞可通过吞噬凋亡的 M1 型巨噬细胞调节 M1/M2 稳态,促进炎症消退,防止 AS 易损斑块破裂^[23]。由此可见,巨噬细胞极化过程中 M1 促炎和 M2 抗炎的平衡,在 AS 发展过程中扮演着极其重要的角色^[24]。因此,深入探讨 M1/M2 型巨噬细胞极化平衡的调控机制,已成为 AS 防治研究领域的焦点。

4 糖酵解是调控巨噬细胞极化的重要机制

新近研究^[25]表明,以巨噬细胞免疫代谢为作用靶点进行干预可稳定斑块,改善 AS 的结局。糖酵解是一种已被证实的可调控巨噬细胞极化的免疫代谢途径,与巨噬细胞极化过程密切相关。在巨噬细胞中,缺氧诱导因子-1 α (hypoxia inducible factor-1 α , HIF-1 α) 的激活使细胞由氧化磷酸化向糖酵解转化,进而促进炎症相关基因的转录^[26]。研究^[27]表明,过表达葡萄糖转运蛋白 1 可使巨噬细胞糖酵解水平增强,进而导致促炎表型的 M1 型巨噬细胞高表达;反之,抗炎表型的 M2 型巨噬细胞极化程度增加。同样,敲除丙酮酸脱氢酶 1 使糖酵解水平降低, M2 型巨噬细胞表型增加,进而减缓炎症反应^[28]。在脂多糖和 II 型干扰素诱导的 M1 巨噬细胞中,大部分糖酵解产物丙酮酸被转化为乳酸,打破三羧酸循环,导致柠檬酸的积累,驱动琥珀酸生成,促进炎症因子高表达,诱导糖酵解的始动因子(HIF-1 α)合成增加,再次反向激活糖酵解,致使恶性循环发生;仅少部分丙酮酸在白介素-4 诱导的 M2 型巨噬细胞中,以乙酰辅酶 A 的形式进入完整的三羧酸循环,通过氧化磷酸化产生三磷酸腺苷^[29]。因此,糖酵解在 M1/M2 型巨噬细胞极化平衡中起着关键作用^[30],二者的关联可被视为与 AS 相关的特定炎症途径药物靶点,为 AS 防治研究提供了全新的视角和思路。

5 HIF-1 α /磷酸果糖激酶-2/果糖-2,6-二磷酸酶 3 是介导糖酵解调控巨噬细胞极化的经典通路

在糖酵解通量的调控机制中,磷酸果糖激酶-2/果糖-2,6-二磷酸酶 (phosphofructokinase-2/fructose-2,6-bisphosphatase, PFKFB) 为关键控制因子, PFKFB 通过调节果糖-2,6-二磷酸在细胞内环境中的聚集,进一步

激活磷酸果糖激酶-1 的活性,促使果糖-6-磷酸转化为果糖-1,6 二磷酸,进而介导糖酵解这一生理过程,其中,PFKFB3 在 PFKFB 家族中具有最高的激酶活性,研究证实其可作为驱动糖酵解水平的调节器^[31-32]。新近研究^[33]发现,抑制 PFKFB3 的活性,可降低糖酵解水平,进一步减缓 AS 发展过程中的炎症反应。除此之外,在缺氧条件下,巨噬细胞 PFKFB3 表达上调,糖酵解通量增加^[34]。由此可见,PFKFB3 在巨噬细胞糖酵解过程中发挥重要作用。HIF-1 是碱性螺旋-环-螺旋转录因子家族亚家族的高度保守成员,是由 α 与 β 亚基组成的异源二聚体,HIF-1 α 是 α 亚基的一种类型。既往研究^[35]表明,HIF-1 α 是 PFKFB3 上游调控因子,通过抑制 HIF-1 α /PFKFB3 活性,巨噬细胞的炎症水平以及糖酵解活性均降低,进一步证实巨噬细胞糖酵解与炎症水平之间的紧密联系。综上所述,HIF-1 α /PFKFB3 通路是介导糖酵解发生应用最广泛、研究最深入的信号通路^[36]。因此,抑制 HIF-1 α /PFKFB3 通路活性,可降低糖酵解水平,进一步调控巨噬细胞极化,抑制炎症反应,从而达到抗 AS 的目的。

6 小结及展望

M1/M2 型巨噬细胞极化平衡是当下 AS 防治研究领域的焦点,糖酵解是目前免疫代谢领域的前沿热点,且与 AS 发生发展过程中的巨噬细胞极化密切相关。综上所述,糖酵解是可控调控巨噬细胞极化参与 AS 形成的最重要的免疫代谢途径之一,HIF-1 α /PFKFB3 通路是介导糖酵解发生应用最广泛、研究最深入的信号通路。既往研究^[37]表明,通过降低糖酵解速率,可增加巨噬细胞线粒体氧化代谢,调控巨噬细胞极化,抑制炎症反应,从而减轻 AS,提示调控巨噬细胞糖酵解水平有望成为 AS 的治疗策略。但是,目前仍面临众多挑战,例如在体斑块内巨噬细胞代谢表型鉴定技术仍不完善,斑块内巨噬细胞糖酵解代谢相关分子靶点仍有待探索等。因此,深入开展糖酵解及巨噬细胞极化的机制研究,有望从抑制 AS 中巨噬细胞糖酵解代谢的角度为防治 AS 提供新的科学依据。

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