

• 综述 •

## PFKM通过经典与非经典途径调控巨噬细胞功能的研究进展

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**[摘要]** 磷酸果糖激酶肌型(phosphofructokinase, muscle type, PFKM)是糖酵解途径关键限速酶,其表达与活性受到缺氧诱导因子-1 $\alpha$ (hypoxia-inducible factor-1 alpha, HIF-1 $\alpha$ )、髓细胞瘤癌基因(myelocytomatosis oncogene, Myc)、磷脂酰肌醇-3-激酶/蛋白激酶B(phosphoinositide 3-kinase/protein kinase B, PI3K/AKT)及腺苷5'-单磷酸活化蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)等信号通路的调控。近年来研究发现,PFKM通过经典糖酵解途径和非经典分子功能影响巨噬细胞功能。微环境中的机械力、葡萄糖、柠檬酸等理化因素可通过调节PFKM四聚体-二聚体的构象平衡,推进PFKM经典与非经典功能之间的转换。目前研究多聚焦于PFKM的经典糖酵解功能,其非经典功能及其中分子机制仍亟待阐明。文章综述了PFKM在巨噬细胞中的经典与非经典功能、上游调控信号及其在感染性疾病与肿瘤中的作用,旨在为靶向PFKM的免疫代谢治疗策略提供新的理论依据与参考。

**[关键词]** 磷酸果糖激酶肌型;糖酵解;巨噬细胞;感染;肿瘤

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### Research progress on the regulation of macrophage function by PFKM through classical and non-classical pathways

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**[Abstract]** Phosphofructokinase, muscle type (PFKM) is a key rate-limiting enzyme in the glycolytic pathway, and its expression and activity are regulated by multiple signaling pathways, including hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), myelocytomatosis oncogene (Myc), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK). Recent studies have demonstrated that PFKM reprograms macrophage functions through both the canonical glycolytic pathway and "non-canonical" functions. Physicochemical factors in the microenvironment, including mechanical forces, glucose, and citrate, can shift the equilibrium between the tetrameric and dimeric conformations of PFKM, thereby facilitating the switch between its classical and non-classical functions. While current research has largely focused on the classical glycolytic role of PFKM, its non-canonical functions and the underlying molecular mechanisms remain to be fully elucidated. This review summarizes the classical and non-canonical roles of PFKM in macrophages, its upstream regulatory signals, and its implications in infectious diseases and cancer, aiming to provide a theoretical foundation and insights for PFKM-targeted immunometabolic therapeutic strategies.

**[Key words]** phosphofructokinase muscle type; glycolysis; macrophages; infection; tumor

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磷酸果糖激酶肌型(phosphofructokinase, muscle

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type, PFKM)是催化糖酵解途径限速步骤的关键酶磷酸果糖激酶-1(phosphofructokinase-1, PFK-1)的一种同工酶,由位于染色体12q13.11的PFKM基因编码,其分子量约为85 kDa<sup>[1]</sup>。已知糖酵解途径中共有3个

关键限速酶,分别为己糖激酶(hexokinases, HK)、丙酮酸激酶(pyruvate kinase, PK)和PFK<sup>[2]</sup>。其中,由于PFK-1的催化效率相对较低,因此PFKM及其同工酶是公认调控糖酵解速率最关键的限速酶<sup>[3-4]</sup>。

传统研究认为,PFKM主要在骨骼肌中高表达,其表达水平与肌肉纤维类型密切相关<sup>[5-7]</sup>。然而,近年来,随着多组学及蛋白质表达谱分析技术的发展,研究发现PFKM蛋白在除了眼球外的组织脏器中均有表达,并且PFKM的表达具备细胞类型特异性:PFKM RNA在单核-巨噬细胞、B细胞、CD4<sup>+</sup>T细胞、嗜酸性粒细胞、外周血单个核细胞(peripheral blood mononuclear cell, PBMC)中丰度较高,而在CD8<sup>+</sup>T细胞、NK细胞、DC细胞、中性粒细胞中丰度较低。最新研究证实,PFKM在单核细胞、巨噬细胞、中性粒细胞等固有免疫细胞中均有表达,且巨噬细胞中PFKM的蛋白表达水平远高于中性粒细胞<sup>[8]</sup>。单细胞转录组学测序发现,糖酵解是驱动巨噬细胞极化及功能改变的重要途径<sup>[9]</sup>,不同来源或同来源但不同亚群的巨噬细胞可呈现出显著的糖酵解代谢差异<sup>[10]</sup>。上述结果共同提示,PFKM可能通过代谢重编程巨噬细胞功能以形成特殊巨噬细胞亚群,参与构建不同的免疫微环境并影响疾病进程。

与肝脏型同工酶及血小板型同工酶类似,PFKM通常以四聚体形式存在并发挥生物学功能,其活性受多种代谢产物的变构调控,包括三磷酸腺苷(adenosine triphosphate, ATP)、二磷酸腺苷(adenosine diphosphate, ADP)、单磷酸腺苷(adenosine monophosphate, AMP)、乳酸及柠檬酸等<sup>[11-12]</sup>。在特定生理条件下,PFKM或其同工酶还可以在Ca<sup>2+</sup>存在时以二聚体形式与钙调蛋白结合,并获得与四聚体相当的催化活性<sup>[13]</sup>。已有研究证实,PFKM的表达水平与巨噬细胞糖酵解水平呈正相关<sup>[14]</sup>。上调PFKM蛋白水平、增强其四聚体稳定性或提高其与底物的亲和力均可有效增强细胞糖酵解通量<sup>[11,14-15]</sup>。值得注意的是,近期研究发现PFKM还具有独立于糖酵解功能之外的“非经典功能”,也称“兼职功能(moonlighting functions)”。例如,PFKM可通过与转录因子结合以增强其对下游靶基因的转录活性,调控细胞骨架重塑<sup>[16]</sup>、抑制巨噬细胞吞噬能力<sup>[8]</sup>;PFKM还可以通过其蛋白激酶活性介导组蛋白H3磷酸化,从而促进细胞增殖<sup>[17]</sup>。上述发现表明,PFKM能够通过经典糖酵解功能和非经典分子功能两种途径共同影响巨噬细胞的命运与功能。

目前,关于PFKM调节细胞糖酵解的研究主要聚焦于肿瘤细胞的Warburg效应,而PFKM在巨噬细胞等免疫细胞功能调控中的作用仍缺乏系统性的认识。因此,文章述旨在解析PFKM在巨噬细胞中的作用及分子机制,总结其上游调控信号通路并探讨PFKM调节巨噬细胞功能及对相关疾病进程的影响,以期为目标免疫代谢的干预策略提供新的视角。

## 1 PFKM在巨噬细胞中的作用

巨噬细胞是固有免疫系统的重要成员之一,高通量单细胞蛋白质组学扩增技术2(single-cell proteomics by multiplexed 2, SCoPE2)分析显示,即使没有外源刺激,相同来源的巨噬细胞表现出显著的蛋白质组异质性<sup>[18]</sup>。巨噬细胞的高度异质性与强大可塑性使其在受到不同刺激时,可极化为经典活化型(M1型)和替代活化型(M2型)<sup>[19]</sup>、氧化磷脂活化型(Mox型)<sup>[20]</sup>、血小板因子活化型(M4)<sup>[21]</sup>等多种亚型。其中,M1型巨噬细胞通常需要在短时间内释放炎症因子与活性氧<sup>[22-23]</sup>,同时消耗大量ATP<sup>[24]</sup>。由于糖酵解的反应速率高于氧化磷酸化,能够在同等时间内输出更多的ATP分子<sup>[25]</sup>,因此,M1型巨噬细胞代谢方式通常以糖酵解为主<sup>[26]</sup>,从而满足所需“局部、短时、大量”的ATP供应。

### 1.1 PFKM通过经典糖酵解途径调节巨噬细胞功能

PFKM四聚体催化果糖-6-磷酸(fructose-6-phosphate, F6P)生成果糖-1,6-二磷酸(fructose-1,6-bisphosphate, F1,6BP),是糖酵解途径中不可逆的关键步骤。PFKM在Cys351位点S-亚硝基化或在K678位点乳酸化修饰能增强其四聚体构象稳定性,提升PFKM对底物的亲和力,导致糖酵解通量升高,即单位时间内转化F6P的流量放大,下游丙酮酸、乳酸及ATP的生成速率随之上升<sup>[11,15]</sup>。

通常认为高糖酵解水平可驱动巨噬细胞极化为M1型<sup>[26-27]</sup>。已有研究证实,上调PFKM蛋白水平或增强PFKM的蛋白稳定性均能够促进巨噬细胞向M1型极化,促进其产生炎症因子如肿瘤坏死因子- $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )<sup>[14,28]</sup>。反之,结核分枝杆菌(*Mycobacterium tuberculosis*)可通过上调miR-21,导致PFKM的mRNA稳定性下降并抑制其翻译,从而降低巨噬细胞的糖酵解通量,抑制巨噬细胞产生白细胞介素(interleukin, IL)-1 $\beta$ 、TNF- $\alpha$ 等促炎因子,降低机体对结核杆菌的清除能力<sup>[29]</sup>。上述研究共同表明,PFKM作为糖酵解的关键限速酶,能够通过经典途径直接调节巨噬细胞糖酵解从而

推动巨噬细胞向 M1 型极化,发挥促炎、杀菌、抗肿瘤等作用,但是 PFKM 调节巨噬细胞极化的具体分子机制仍不清楚。

已知 PFKM 介导的高糖酵解通量可为巨噬细胞合成炎症因子提供大量 ATP 与碳骨架<sup>[30]</sup>,其中间产物琥珀酸能抑制脯氨酰羟化酶,增强缺氧诱导因子-1 $\alpha$  (hypoxia-inducible factor-1 alpha, HIF-1 $\alpha$ ) 蛋白稳定性,直接结合促炎因子 IL-1 $\beta$  的启动子区域并驱动其转录,最终促进巨噬细胞分泌 IL-1 $\beta$ <sup>[31]</sup>。糖酵解下游发酵产物乳酸能够增强 GLI 家族锌指蛋白 3 (GLI family zinc finger protein 3, GLI3) 启动子区域组蛋白 H3 第 18 位赖氨酸的乳酸化,上调 GLI3 的蛋白水平;转录因子 GLI3 能够直接介导 M1 型巨噬细胞表面标志诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS)、CD80、单核细胞趋化蛋白-1 (monocyte chemoattractant protein-1, MCP-1) 等基因的转录<sup>[32]</sup>。然而,需要注意的是,亦有文献报道乳酸能够阻断 Toll 样受体 4 (Toll-like receptor 4, TLR4) -髓样分化因子 88 (myeloid differentiation factor 88, MyD88)-核因子  $\kappa$ B (nuclear factor kappa B, NF- $\kappa$ B) 级联反应,降低 p65 入核<sup>[33]</sup>,同时活化哺乳动物雷帕霉素靶蛋白 (mechanistic target of rapamycin, mTOR) 与细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) 信号通路,导致 M2 型巨噬细胞表面标志精氨酸酶-1 (arginase-1, Arg-1)、CD206 等蛋白上

调<sup>[17,33]</sup>。上述结果提示,PFKM 介导的糖酵解可能在不同微环境中对巨噬细胞功能产生不同的影响 (图1)。

### 1.2 PFKM 通过非经典途径影响细胞功能

最新研究显示,PFKM 还具有不依赖于其酶活性的“非经典”功能。在细菌感染或受到脂多糖 (lipopolysaccharide, LPS) 刺激时,巨噬细胞中的 PFKM 可出现细胞核与细胞质双定位的现象<sup>[8]</sup>。核内 PFKM 并不影响巨噬细胞糖酵解水平,也未影响巨噬细胞极化表型;但是它可通过与转录因子 p53 结合,增强 p53 的转录活性,上调程序性死亡受体-1 (programmed cell death protein 1, PD-1) 的 mRNA 及蛋白水平以抑制巨噬细胞吞噬能力<sup>[8]</sup>。抑制 PFKM 入核或敲除 PFKM 均可增强巨噬细胞吞噬能力,从而加速脓毒症模型小鼠体内细菌的清除<sup>[8]</sup>。

目前尚无研究报道 PFKM 通过非糖酵解途径调节巨噬细胞的其他功能,不过,在模式细胞中的研究显示,PFKM 具备蛋白激酶活性,能够介导组蛋白 H3 上第 10 位丝氨酸 (serine 10 of histone H3, H3S10) 的磷酸化<sup>[17]</sup>。H3S10 磷酸化水平升高或可通过活化信号转导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3)、SMAD 家族成员 3 (SMAD family member 3, SMAD3) 和 NF- $\kappa$ B 等信号通路,上调 IL-1 $\beta$ 、IL-6、TNF- $\alpha$  等炎症因子的表达水平<sup>[34]</sup>。当炎症因子启动子区域的 H3S28 发生磷酸

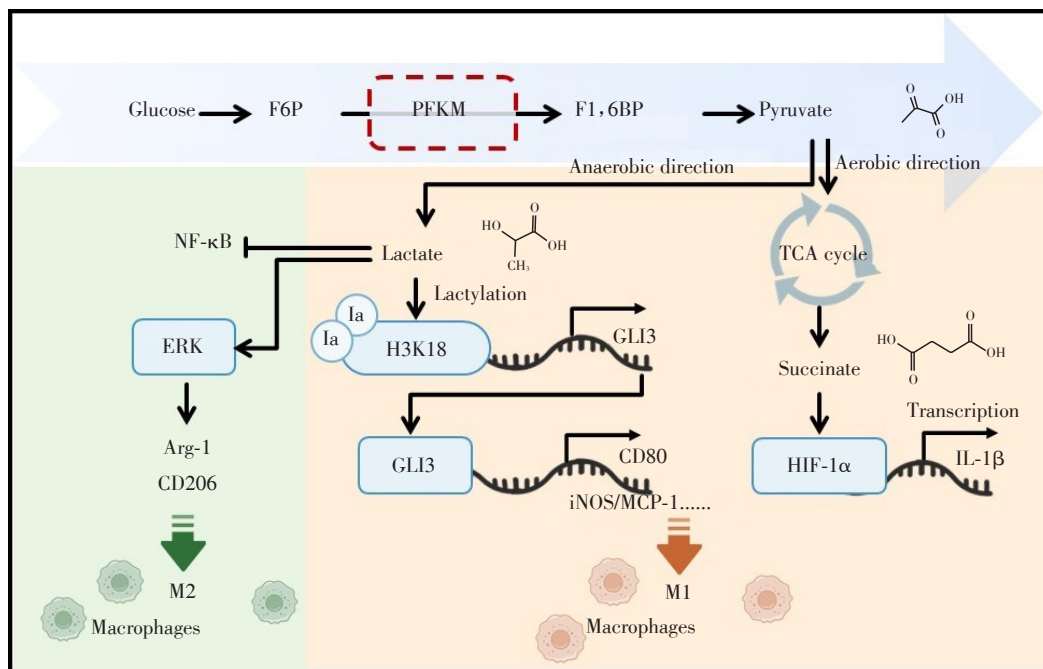


图1 PFKM 通过经典糖酵解途径调节巨噬细胞极化的潜在机制

Figure 1 Potential mechanism of PFKM regulating macrophage polarization *via* the classical glycolysis pathway

化时,可导致染色质松弛,从而推动转录进程,同样能够促进巨噬细胞产生IL-6等炎症因子<sup>[35]</sup>。该过程伴随着较高的糖酵解水平,但PFKM能否参与调节H3S28的磷酸化及其能否通过H3S10或H3S28调节巨噬细胞功能仍有待进一步实验验证。

此外,在胶质母细胞瘤细胞中,PFKM可直接与驱动蛋白家族成员11(kinesin family member 11, KIF11)结合,增强KIF11的蛋白稳定性,从而促进细胞的增殖和侵袭<sup>[16]</sup>。在肿瘤微环境中,KIF11高表达与巨噬细胞浸润呈正相关<sup>[36]</sup>。基于高通量转录组学分析显示,KIF11可能参与调节细菌感染导致的巨噬细胞周期改变<sup>[37]</sup>,提示PFKM或许能够通过非经典途径影响巨噬细胞的细胞周期

及其增殖能力。

## 2 调控PFKM的因素与信号通路

微环境中的物理化学因素主要影响PFKM四聚体的形成与解聚,而PFKM的转录、蛋白稳定性及酶活性受到多种分子和信号通路的调控,例如HIF-1 $\alpha$ <sup>[14]</sup>和髓细胞瘤癌基因(myelocytomatosis oncogene, Myc)<sup>[38]</sup>可分别直接或间接上调PFKM的蛋白表达。磷脂酰肌醇-3-激酶/蛋白激酶B(phosphoinositide 3-kinase/protein kinase B, PI3K/AKT)<sup>[39]</sup>、腺苷5'-单磷酸活化蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)<sup>[40]</sup>通路则主要影响PFKM的酶活性(图2)。

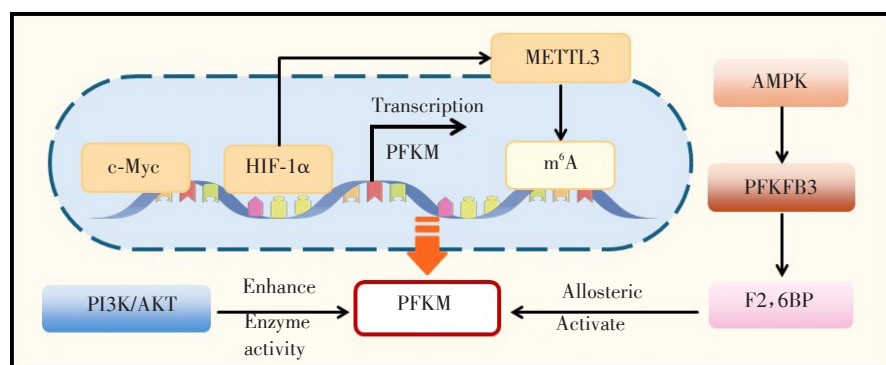


图2 调控PFKM的关键分子及信号通路示意图

Figure 2 Key molecules and signaling pathways regulating PFKM

### 2.1 微环境中的理化因素

PFKM可响应多种物理化学信号,从而调节其表达水平、活性与功能。物理信号如基质硬度可通过机械力促进F-肌动蛋白束的形成,后者与PFKM结合能够稳定PFKM的四聚体构象并提升其糖酵解活性<sup>[41]</sup>。化学信号如高浓度葡萄糖可诱导转录因子ZEB1入核,促进ZEB1结合于PFKM启动子区域,增强PFKM的转录<sup>[42]</sup>;酸中毒伴随的高葡萄糖微环境则通过促进PFKM在Cys351位点的S-亚硝基化,稳定PFKM的四聚体结构<sup>[15]</sup>。近期研究显示,当微环境中葡萄糖充足时,PFKM主要呈现出四聚体构象,执行经典糖酵解功能;当微环境中柠檬酸浓度急剧升高(例如细胞有丝分裂M期,线粒体代谢重组可导致柠檬酸浓度峰值超过1.0 mmol/L),柠檬酸能够结合并破坏维持四聚体构象的关键盐桥,导致PFKM向二聚体构象转变<sup>[17]</sup>。相似的是,低葡萄糖微环境同样能诱导PFKM的同工酶从活性四聚体解聚,暴露新的蛋白互作位点,与脂滴结合从而发挥

脂解等非经典糖酵解功能<sup>[43]</sup>。由此可推测,微环境中的理化信号主要通过影响PFKM的四聚体-二聚体构象平衡以决定其经典功能与非经典功能之间的转换。

### 2.2 HIF-1 $\alpha$

HIF-1 $\alpha$ 作为调控细胞代谢重编程的核心转录因子,可直接调节包括PFK-1、葡萄糖转运蛋白1(glucose transporter type 1, GLUT1)、乳酸脱氢酶A(lactate dehydrogenase A, LDHA)及HK等在内的多种能量代谢相关分子的表达<sup>[44]</sup>,其蛋白水平通常与细胞糖酵解水平呈正相关<sup>[14]</sup>。在肿瘤细胞中,HIF-1 $\alpha$ 能够直接调控PFKM的mRNA水平<sup>[12]</sup>;而在巨噬细胞中,HIF-1 $\alpha$ 并不直接调控其转录,而是通过上调m<sup>6</sup>A甲基转移酶3(methyltransferase-like 3, METTL3)的表达,增强PFKM mRNA的m<sup>6</sup>A修饰水平以提高其mRNA稳定性,从而上调PFKM并提升巨噬细胞糖酵解通量<sup>[14]</sup>。此外,HIF-1 $\alpha$ 还能够通过诱导6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶3(6-phosphofructo-

2-kinase/fructose-2, 6-biphosphatase 3, PFKFB3) 的转录<sup>[45]</sup>, 提高其催化产物果糖-2, 6-二磷酸(fructose-2, 6-biophosphate, F2, 6BP)的水平, 该产物是PFKM的变构激活剂, 能够大大提高PFKM的糖酵解活性<sup>[46]</sup>。

### 2.3 Myc

Myc是介导Warburg效应的核心转录调控因子<sup>[47]</sup>, 其高表达或蛋白稳定性增强均可促进细胞糖酵解<sup>[48-49]</sup>。已有文献证实, Myc可直接结合于PFKM基因的启动子区域<sup>[50]</sup>, 上调其转录水平<sup>[51]</sup>; 相反, 抑制Myc的表达可显著下调PFKM水平<sup>[52]</sup>, 使用c-Myc小分子抑制剂10058-F4抑制其转录活性, 能够有效抑制细胞糖酵解, 并减少乳酸生成<sup>[53]</sup>。

### 2.4 PI3K/AKT信号通路

PI3K/AKT通路是维持细胞代谢稳态的核心信号枢纽, 参与葡萄糖摄取、糖酵解、脂质合成及核苷酸代谢等过程<sup>[54]</sup>。视网膜母细胞瘤结合蛋白7(retinoblastoma-binding protein 7, RBBP7)通过激活PI3K/AKT信号通路, 上调PFKM等关键糖酵解酶的表达, 促进细胞的有氧糖酵解和增殖<sup>[55]</sup>。PI3K/AKT信号通路抑制剂氯喹可通过结合胆碱激酶 $\alpha$ (choline kinase alpha, CHKA)并抑制其活性, 从而降低PFKM的表达及活性, 进而阻断Warburg效应<sup>[39]</sup>。重组蛋氨酸酶通过抑制PI3K/AKT信号通路, 降低葡萄糖转运蛋白1型(glucose transporter type 1, GLUT-1)的表达, 从而下调PFKM等糖酵解酶的表达水平, 抑制有氧糖酵解水平, 进而诱导细胞凋亡并抑制其增殖<sup>[56]</sup>。此外, PI3K抑制剂Idelalisib通过阻断PI3K/AKT/mTOR信号通路, 能够抑制PFKM的转录与活性, 从而降低CD4<sup>+</sup>T细胞的葡萄糖摄取及乳酸生成, 干扰其代谢重编程与活化<sup>[57]</sup>。综上, 激活PI3K/AKT信号通路通常可上调PFKM的蛋白水平, 最终促进细胞糖酵解。

### 2.5 AMPK信号通路

AMPK是监测细胞能量状态和营养供应的关键传感器<sup>[58]</sup>。虽然目前尚无直接证据表明AMPK可调控PFKM的蛋白表达, 但在单核细胞中, AMPK活化可诱导F1, 6BP的积累, 从而变构增强PFKM及其同工酶的催化活性<sup>[40]</sup>。哈巴昔通过促进AMPK磷酸化水平, 能够拮抗TNF- $\alpha$ 对PFKM的抑制作用<sup>[59]</sup>; 反之, 阿霉素通过抑制AMPK信号通路活性, 下调PFKM的表达, 从而抑制心肌细胞糖酵解<sup>[60]</sup>。上述研究提示, AMPK信号通路可通过调节PFKM的表达或活性, 影响细胞糖酵解进程。

## 3 PFKM在疾病发展中的作用

PFKM作为糖酵解过程中的关键限速酶, 参与了多种疾病的发生发展。例如, 在感染进程中, PFKM通过经典与非经典途径调控巨噬细胞极化、吞噬等功能, 从而影响宿主抗感染免疫应答。而在肿瘤进程中, 巨噬细胞中的PFKM可能具备“双重角色”。因此, 深入解析PFKM在疾病中的作用及机制, 将为靶向巨噬细胞的免疫治疗策略提供新的视角。

### 3.1 感染性疾病

#### 3.1.1 细菌、真菌感染

研究发现, 与健康志愿者相比, 脓毒症患者外周血单核细胞中的PFKM蛋白水平显著升高<sup>[14]</sup>。在巨噬细胞中, LPS通过激活HIF-1 $\alpha$ /METTL3信号轴, 上调PFKM的表达, 从而驱动巨噬细胞向促炎表型极化, 加速脓毒症的进展; 反之, 使用重组血栓调节蛋白抑制HIF-1 $\alpha$ /METTL3/PFKM轴则抑制巨噬细胞产生促炎因子, 缓解细菌感染所致脓毒症<sup>[14]</sup>。在结核分枝杆菌感染模型中, 结核分枝杆菌通过上调miR-21抑制巨噬细胞中PFKM的表达, 从而降低其糖酵解水平, 并减少IL-1 $\beta$ 等促炎因子的分泌, 进而削弱巨噬细胞对结核分枝杆菌的杀菌能力<sup>[29]</sup>。值得注意的是, PFK-1蛋白表达于白色念珠菌等真菌中, 并且正向调控真菌的糖酵解水平<sup>[61]</sup>, 促进真菌微菌落的形成<sup>[62]</sup>。因此, 在开发以PFKM为靶点的抗真菌治疗策略时, 需要额外注意药物的靶向性。

#### 3.1.2 病毒感染

柯萨奇病毒B3、寨卡病毒A等病毒入侵可诱导宿主细胞中PFKM蛋白水平上调, 提高细胞糖酵解水平, 从而促进病毒在细胞内的复制<sup>[63-64]</sup>。甲型流感病毒感染后, 葡萄糖代谢关键调节因子4的抑制素结构域被激活, 从而增强PFKM活性, 提升F1, 6BP水平。F1, 6BP抑制热休克蛋白90 $\beta$ (heat shock protein 90 beta, HSP90 $\beta$ )的降解, 稳定HSP90 $\beta$ /I $\kappa$ B激酶 $\beta$ 亚基(I $\kappa$ B kinase beta, IKK $\beta$ )/I $\kappa$ B激酶 $\epsilon$ 亚基(I $\kappa$ B kinase epsilon, IKK $\epsilon$ )复合物, 从而激活NF- $\kappa$ B/干扰素调节因子7(interferon regulatory factor 7, IRF7)信号通路并放大I型干扰素的作用, 进而限制病毒复制<sup>[65]</sup>。1型人类免疫缺陷病毒(human immunodeficiency virus type 1, HIV-1)、丙型肝炎病毒(hepatitis C virus, HCV)、严重急性呼吸综合征冠状病毒2(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)、爱泼斯坦-巴尔病毒(Epstein-Barr virus, EBV)等多种病毒均可感染巨噬细胞<sup>[66]</sup>, M1型巨噬细胞可

限制入侵病毒的复制<sup>[67]</sup>、抑制病毒增殖<sup>[68]</sup>, 巨噬细胞代谢重编程是抗病毒感染的潜在治疗策略<sup>[69]</sup>。

### 3.2 肿瘤

临床研究表明, 靶向肿瘤微环境中的巨噬细胞是肿瘤治疗的潜在有效策略<sup>[70]</sup>。实验动物模型结果也显示, 增强肿瘤相关巨噬细胞中PFKM的蛋白稳定性可促进巨噬细胞向M1型极化, 增强其抗肿瘤活性, 从而抑制结直肠癌的发展<sup>[28]</sup>。然而, 高表达PFKM的巨噬细胞在不同肿瘤微环境中可能发挥完全不同的免疫功能。例如, 在弥漫性大B细胞淋巴瘤患者体内, 单细胞转录组学、空间转录组学和批量转录组学分析发现了一群高糖酵解活性的肿瘤相关巨噬细胞亚群<sup>[71]</sup>。该亚群巨噬细胞高表达的PFKFB3可通过F2,6BP变构激活PFKM<sup>[72]</sup>。然而, 上述高糖酵解巨噬细胞亚群并未发挥抗肿瘤作用, 反而通过产生程序性死亡配体-1 (programmed death-ligand 1, PD-L1)、转化生长因子- $\beta$ 1 (transforming growth factor- $\beta$ 1, TGF- $\beta$ 1)等因子, 抑制CD8<sup>+</sup> T细胞浸润, 参与构建免疫抑制微环境, 最终促进肿瘤进展<sup>[71]</sup>。值得注意的是, 在弥漫性大B细胞淋巴瘤患者肿瘤组织中, PFKM高表达与IFN-TAM细胞浸润水平均可预测患者的不良预后<sup>[71]</sup>。

## 4 总结与展望

作为调控巨噬细胞糖酵解过程的关键限速酶, PFKM通过经典与非经典途径重编程巨噬细胞极化、炎症因子产生、吞噬等多种功能, 参与影响感染性疾病和肿瘤等的发展。靶向PFKM以重塑巨噬细胞的功能是极具潜力的免疫治疗策略。

尽管当前关于巨噬细胞中PFKM的研究取得了初步进展, 但现有研究多聚焦于PFKM通过经典途径驱动巨噬细胞向M1型极化的作用及机制, PFKM在不同巨噬细胞亚群中的表达差异、功能异质性及其动态调控规律尚未见报道。并且, 最新研究揭示PFKM能够通过不依赖于糖酵解的非经典功能调节巨噬细胞吞噬能力, 但PFKM能否通过非经典途径影响巨噬细胞的其他功能尚不清楚, 其中具体分子机制也有待进一步挖掘。

此外, 根据The Human Protein Atlas数据库中的数据, PFKM的RNA仅在骨骼肌和舌组织中丰度较高, 其蛋白则在除了眼球外的绝大多数组织中广泛表达。除了巨噬细胞以外, PFKM还在肾嫌色细胞瘤、星形胶质瘤等肿瘤细胞中高表达且与肿瘤患者不良预后相关; 在成纤维细胞中高表达, 且与肺纤

维化患者不良预后相关<sup>[73]</sup>。由于PFKM的组织特异性与细胞类型特异性, 开发精准靶向PFKM的治疗策略以避免脱靶效应或许是未来临床转化面临的关键挑战。针对此特点开展细胞特异性调控有望为感染性疾病、肿瘤及其他相关疾病的治疗提供新思路与理论依据。

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