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炎症反应在心肌缺血再灌注损伤中的研究进展

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摘　要

随着医疗技术的不断进步，溶栓和经皮冠状动脉介入等治疗手段显著降低了急性心肌梗死的死亡率。然而，当缺血心肌细胞的血流恢复之后，随之而来的心肌再灌注损伤却可能进一步加重心肌损伤。心肌再灌注损伤的机制复杂多样，主要包括钙超载、炎症反应、氧化应激、内皮功能障碍、免疫反应、线粒体功能障碍、心肌细胞凋亡、自噬和细胞焦亡等。其中，炎症反应在心肌再灌注损伤中扮演着关键角色，抑制炎症反应可以有效减轻心肌再灌注损伤。文章重点介绍炎症在心肌再灌注损伤中的作用机制，为提升心肌再灌注损伤的临床治疗效果和改善患者预后提供新的策略。

关键词

缺血再灌注损伤，炎症，细胞焦亡，通路

Research Progress on Inflammatory Response in Myocardial Ischemia-Reperfusion Injury

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Abstract

With the continuous advancement of medical technology, treatment methods such as thrombolysis and percutaneous coronary intervention have significantly reduced the mortality rate of acute myocardial infarction. However, after the blood flow to ischemic myocardial cells is restored, the subsequent myocardial reperfusion injury may further exacerbate myocardial damage. The mechanisms of

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myocardial reperfusion injury are complex and diverse, mainly including calcium overload, inflammatory response, oxidative stress, endothelial dysfunction, immune response, mitochondrial dysfunction, myocardial cell apoptosis, autophagy, and pyroptosis. Among them, the inflammatory response plays a crucial role in myocardial reperfusion injury, and inhibiting the inflammatory response can effectively alleviate myocardial reperfusion injury. This article focuses on introducing the mechanism of action of inflammation in myocardial reperfusion injury, aiming to provide new strategies for improving the clinical treatment effect of myocardial reperfusion injury and the prognosis of patients.

Keywords

Ischemia-Reperfusion Injury, Inflammation, Pyroptosis, Pathway

1. 引言

心血管疾病(Cardiovascular Diseases, CVD)是一种死亡率很高的心脏疾病，与冠状动脉急性、持续的缺血和缺氧引起的心肌细胞凋亡和坏死有关。迅速恢复血流是治疗心肌梗死(Myocardial Infarction, MI)的有效策略。然而，矛盾的是，缺血心肌血流的恢复会加重血管损伤和炎症的爆发，进一步增加心肌梗死面积，这种现象被称为心肌缺血再灌注损伤(Myocardial Ischemia Reperfusion Injury, MIRI) [1] [2]。MIRI涉及多种病理生理过程，包括钙超负荷、炎症、氧化应激、内皮功能障碍、免疫反应、线粒体功能障碍、心肌细胞凋亡、自噬、细胞焦亡、血小板聚集等[3]-[7]。炎症是一种防御反应，但当这种反应被各种因素过度激活时，它会加剧组织损伤。宿主免疫防御机制可分为先天免疫和适应性免疫反应。炎症反应和先天免疫系统的激活是 MIRI 的重要特征[8]。当冠状动脉血流中断时，会导致细胞死亡和强烈的无菌性炎症，通过及时再灌注治疗也会导致心肌细胞进一步死亡并释放炎性细胞因子加剧炎症反应，从而导致心肌梗死面积扩大和随后的心脏重塑和伤口愈合。因此，有效清除受损细胞和抑制炎症反应被认为对于最大化再灌注治疗的益处至关重要[9]-[12]。现将炎症在 MIRI 中的研究进展综述如下。

2. 中性粒细胞与炎症

MIRI 后最先募集到心脏的髓系细胞是中性粒细胞，在稳态条件下，中性粒细胞处于静止状态，面对缺血再灌注，中性粒细胞会在数分钟到数小时内，沿着细胞因子和细胞碎片的趋化梯度，迁移至受损的心脏。这种对环境信号的快速状态转变，称为“就绪”状态，也就是所谓的“预激活”，且已被证实能增强中性粒细胞合成炎症介质的效应功能。中性粒细胞的预激活由缺血再灌注诱导产生的损伤相关分子模式(Damage-Associated Molecular Pattern, DAMPs)，如肿瘤坏死因子-α (Tumor Necrosis Factor-α, TNF-α)、粒细胞－巨噬细胞集落刺激因子(Granulocyte-Macrophage Colony-Stimulating Factor, GMCSF)引发。预激活的中性粒细胞会增加包括白细胞介素-1α (Interleukin-1α, IL-1α)、白细胞介素-1β (Interleukin-1β, IL-1β)、白细胞介素-6 (Interleukin-6, IL-6)、TNF-α 等在内的炎症介质合成与后续释放。中性粒细胞分泌的炎性细胞因子/趋化因子会刺激单核细胞和巨噬细胞的募集以及促炎分化，从而加剧损伤[11]。

3. 巨噬细胞与炎症

巨噬细胞在心肌缺血再灌注损伤中起着不可替代的作用。具体表现为单核细胞/巨噬细胞介导的心肌

炎症促进细胞死亡[13]。GMCSF 是一种主要来源于内皮细胞、成纤维细胞和造血细胞的单体糖蛋白。GMCSF 主要在炎症刺激过程中释放，能有效促进骨髓来源的细胞，如单核细胞、巨噬细胞和树突状细胞的成熟和活化[14]。在急性 MIRI 过程中，GMCSF 的释放会募集大量免疫细胞浸润损伤部位，促进炎症反应。在 MIRI 的早期阶段表现为，血液单核细胞浸润受损的心脏组织并转化为促炎的 M1 型巨噬细胞[15] [16]。然后释放各种炎症介质，如 TNF-α、IL-1β、IL-6 和白细胞介素-8 (Interleukin-8, IL-8)以促进炎症反应，加重 MIRI [17]-[20]。

随着急性损伤期炎症反应的消退，巨噬细胞主要转化为修复性 M2 表型，可通过分泌抗炎细胞因子白细胞介素-10 (Interleukin-10, IL-10)和促进调节性 T 细胞(Regulatory T cell, Treg)的分化来消退炎症，从而帮助抑制 MIRI 早期的 M1 巨噬细胞介导的炎症反应。M2 型巨噬细胞还能通过释放转化生长因子-β (Transforming Growth Factor-β, Tgf-β)以促进成纤维细胞转化为肌成纤维细胞[20]-[23]。进而产生胶原蛋白和纤连蛋白，有利于梗死心脏组织的修复和重塑，同时也促进瘢痕形成和心肌纤维化进展[24]-[26]。

4. 损伤相关分子模式与炎症

缺血造成的初始损伤以及再灌注带来的继发性损伤，都会导致心脏内大量心肌细胞死亡，进而使梗死心肌释放出 DAMPs。这些物质包括心肌的细胞核成分，如高迁移率族蛋白 B1 (High Mobility Group Box 1, HMGB1)；胞质成分，如 RNA；细胞外基质成分，如纤连蛋白；线粒体成分，如线粒体 DNA，以及收缩蛋白成分，如心肌肌球蛋白。这些 DAMPs 中的许多成分可作为模式识别受体(Pattern Recognition Receptors, PRRs)的配体，其中包括 Toll 样受体(Toll-Like Receptors, TLR)、NOD 样受体(NOD-Like Receptors, NLR)、晚期糖基化终末产物受体(Receptors for Advanced Glycation End Product, RAGE)以及补体受体。这些受体在心脏中广泛表达，可通过在多种细胞类型中的信号传导，促使缺血再灌注损伤的发生[11]。Toll 样受体 2 (TLR2)和 4 (TLR4)以及 RAGE 的结合，会促进核因子 κB (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells, NF-κB)的激活，从而上调促炎基因的表达并启动 NOD 样受体蛋白 3 (NOD-Like Receptor Protein-3, NLRP-3)炎症小体并释放炎症介质，如 IL-1β、IL-6 和 TNF-α [11] [27]。除此之外，心脏的固有细胞在缺血再灌注诱导的炎症中发挥着独特作用。损伤发生后，心肌细胞、心脏成纤维细胞和固有巨噬细胞会释放炎症分子和趋化分子，如 IL-1β、TNFα、IL-6 和趋化因子(C-C 基序)配体 2 (C-C Motif Chemokine Ligand 2, CCL2)，以形成趋化梯度，将炎症髓系细胞募集到梗死区域[11] [28]。

5. 铁死亡与炎症

铁死亡(Ferroptosis)在 MIRI 引发的炎症过程中起着关键作用：MIRI 后，细胞通过包括铁死亡在内的调节性细胞死亡(Regulated Cell Death, RCD)组合方式死亡；这会导致 DAMPs 的释放，一旦从细胞中释放出来，DAMPs 就会通过与 PRRs 结合来促进非感染性炎症反应。例如，HMGB1 是铁死亡细胞死亡过程中释放的 DAMPs，它与 PRRs 结合并通过激活巨噬细胞产生促炎细胞因子来驱动炎症[29] [30]。在炎症过程中，DAMPs 的产生伴随着磷脂酶 A2 (Phospholipase A2, PLA2)促使花生四烯酸(Arachidonic Acid, AA)生成增加。当 AA 被 PLA2 和磷脂酶 C (Phospholipase C, PLC)从磷脂中释放出来时，它会作为生物活性促炎介质的前体，这些促炎介质包括前列腺素、IL-1、IL-6 以及 TNF，它们会推动炎症级联反应。其中的 AA 在环氧化酶-2 (Cyclooxygenase-2, COX2)的作用下代谢为具有生物活性的前列腺素，这些前列腺素会进一步激活巨噬细胞以及其他炎症细胞，包括中性粒细胞、T 淋巴细胞和 B 淋巴细胞。这些促炎介质连同干扰素-γ (Interferon-γ, IFN-γ)，参与组织铁储存和铁蛋白合成的调节。异常的炎症反应可能导致铁代谢紊乱，并影响氧化还原系统的平衡。例如，核受体辅激活因子 4 (Nuclear Receptor Coactivator 4, NCOA4)调节铁蛋白自噬，使得铁蛋白被自噬溶酶体降解。这一过程会导致细胞内铁过载，引发氧化应激并加剧

炎症[29]。此外，心肌细胞铁死亡通过移植物内皮细胞中 TLR4/Trif 依赖性信号通路，促进中性粒细胞与冠状血管内皮细胞的黏附，从而启动炎症反应[30]。反过来，炎症的激活又会导致铁死亡更广泛地被激活[31]。

6. 细胞焦亡与炎症

细胞焦亡(Pyroptosis)是一种细胞死亡，其特征是 NLRP3 炎性小体激活和炎症反应[32]。在 MIRI 中，NLRP3 炎性小体激活引发炎症反应，导致细胞信号通路的级联反应和炎症介质的释放，这对免疫调节和炎症至关重要[33]。NLRP3 炎性小体是一组由 NLRP3、半胱天冬酶原-1 (pro-caspase-1)和含半胱天冬酶募集结构域(Caspase Recruitment Domain, CARD)的凋亡相关斑点样蛋白(Apoptosis-Associated Speck-Like Protein, ASC)组成的多聚体蛋白复合物[34]-[37]。在 MIRI 期间，NLRP3 炎性小体的富含亮氨酸重复序列(Leucine-Rich Repeat, LRR)结构域可识别内源性信号，如钾离子外流、溶酶体不稳定和线粒体活性氧生成。当 NLRP3 的 LRR 结构域在识别上述内源性信号并被激活后，NLRP3 的 Pyrin 结构域(Pyrin Domain, PYD)会与凋亡相关斑点样蛋白(Apoptosis-Associated Speck-Like Protein, ASC)的 PYD 发生同源相互作用，诱导 ASC 寡聚化。然后，ASC 的 card 招募 pro-caspase-1，形成激活半胱天冬酶-1 (caspase-1)的复合物。而激活的 caspase-1 会将 IL-1β 前体和 IL-18 前体加工成具有生物活性的成熟形式，并释放到细胞外，促进对组织细胞的炎症反应。此外，caspase-1 的激活会触发 Gasdermin-D (GSDMD)的裂解，导致其 N 端结构域释放。随后，该结构域与质膜结合并形成孔道，促进成熟的 IL-1β 和 IL-18 向细胞外释放。通过这种方式，该过程会通过促进炎症级联反应和细胞焦亡而加剧 MIRI [2] [3] [38]-[40]。

7. 线粒体与炎症

线粒体与各种细胞过程密切相关，并参与调节细胞氧化还原状态、钙水平、炎性小体活化和细胞死亡。当线粒体受损后，线粒体活性氧(mtROS)和线粒体 DNA (mtDNA)可导致 NLRP3 炎性小体的激活。此外，线粒体脱氧核糖核酸以及其他与线粒体相关的蛋白质和脂质在引发 NLRP3 炎症小体激活过程中也起着关键作用。例如，在 MIRI 期间，基质金属蛋白酶(Matrix Metalloproteinase 2, MMP-2)会因氧化应激而迅速激活。线粒体功能的调节蛋白，包括线粒体融合蛋白-2 (Mitofusin-2, Mfn-2)，在 MIRI 中会缺失，进而触发 NLRP3 炎症小体和先天免疫反应[3] [41] [42]。

线粒体自噬(Mitophagy)在控制 NLRP3 炎症小体激活方面至关重要，主要通过线粒体自噬-NLRP3 通路实现。线粒体自噬对 NLRP3 炎性小体激活起负调节作用，这对免疫平衡至关重要。当线粒体自噬功能出现障碍会导致活性氧(Reactive Oxygen Species, ROS)积累，从而触发 NLRP3 炎性小体的激活[2]。

研究表明，自噬有助于清除细胞内 NLRP3 激活的触发因素，并降解炎症小体成分以及如 NLRP3、ASC 和 IL-1β 等细胞因子[43]。但与上述研究相反，有研究发现自噬也能正向调节 NLRP3 炎症小体的激活。在他们的研究中，饥饿条件下发生的自噬可增强半胱氨酸蛋白酶抑制剂 1 的激活，促进炎症小体的激活，增加 IL-1β 和 IL-18 等促炎细胞因子的合成。同时，由于一些细胞质蛋白缺乏信号肽，IL-1β 和 IL-18 等促炎因子无法通过内质网进入自噬的经典途径进行降解，反而在细胞质中促进其外流，这进一步加剧了组织中的炎症损伤[3]。半胱天冬酶(Caspases)是一类半胱氨酸蛋白酶，包含炎性 caspase-1 [44]。在细胞焦亡中激活的 caspase-1 可将 IL-1β 前体和 IL-18 前体加工成具有生物活性的成熟形式，促进炎症反应。自噬通过增强半胱氨酸蛋白酶抑制剂 1 的激活进而抑制半胱氨酸蛋白酶活性，即 caspase-1 的活性被抑制后，NLRP3 炎性小体仍可激活。这与先前的研究结论相反，其原因需要进一步研究。

8. PI3K/AKT 通路与炎症

PI3K/Akt 是一种广泛存在于细胞中的信号转导通路，参与炎症和细胞激活、存活和细胞凋亡。通常

认为 PI3K/Akt 信号转导通路的激活可以保护心肌免受致命的 MIRI。PI3K/AKT 信号通路的抑制伴随着 TNF-α、IL-6 和 IL-1β 水平的降低，导致炎症细胞浸润减少[45]。内皮型一氧化氮合酶(Endothelial Nitric Oxide Synthase, eNOS)在哺乳动物心肌细胞中连续表达，是 Akt 的下游效应子，受 PI3K/Akt 信号通路调节[46]。现有证据表明，PI3K/Akt/eNOS 信号转导通路通过各种干预措施(如延迟预处理、右美托咪定和黄芩苷)在心脏保护机制中发挥重要作用。研究显示，高胆固醇血症可通过增强炎症反应和抑制 PI3K/Akt/eNOS 信号通路的激活，显著加重 MIRI [47]。还有研究表明小檗碱除了通过抑制 PI3K/AKT 信号传导以及随后的炎症反应来预防 MIRI 外，还通过核因子 NF-κB 信号通路减少炎症反应[45]。

9. NF-κB 与炎症

研究表明，在 MIRI 过程中，TLR4/NF-κB 信号通路被激活，进而诱导 TNF-α 的产生，并触发炎症级联反应。当 TLR4 被激活时，TLR 会募集含有 Toll/白细胞介素-1 受体(Toll/Interleukin-1 Receptor, TIR)结构域的衔接蛋白，如髓样分化因子 88 (Myeloid Differentiation Primary Response 88, MyD88)，刺激肿瘤坏死因子受体相关因子 6 (Tumor Necrosis Factor Receptor-Associated Factor 6, TRAF6)的磷酸化，并通过信号级联反应使 NF-κB 抑制蛋白(Inhibitor of Nuclear Factor Kappa B, IκB)降解，从而促使 NF-κB 转移至细胞核内，进而促进下游 NF-κB 的激活。其激活会启动与心脏不可逆损伤相关蛋白质的转录，尤其是炎症蛋白和凋亡蛋白。因此，抑制 NF-κB 以及炎症信号通路，对 MIRI 的防治具有积极意义[48]。

10. 钙/钙调蛋白依赖性激酶 II 与炎症

钙/钙调蛋白依赖性蛋白激酶 II (Calcium/Calmodulin-Dependent Protein Kinase II, CaMKII)是一个多功能丝氨酸/苏氨酸蛋白激酶家族，在多种心脏疾病的发病机制中起着核心作用，这些疾病包括急性缺血再灌注损伤、慢性心脏重构以及心力衰竭。CaMKII 有 4 个基因编码，即 CaMKII-α、β、γ 和 δ，其中 CaMKII-δ 是心脏中的主要异构体。CaMKII-δ 会发生可变剪接，产生 11 种不同的变体。先前的研究表明，不同的 CaMKII-δ 剪接变体对心肌细胞活力具有截然不同甚至相反的作用。从功能上看，位于细胞质中的 CaMKII-δ2 会加重 MIRI，而位于细胞核中的 CaMKII-δ3 则对心肌有保护作用，其差异作用可通过其对 NF-κB 或 TNF-α 的作用来实现[49] [50]。CaMKII-δ9 是心脏中最丰富的 CaMKII-δ 剪接变体。研究表明，CaMKII-δ9 抑制可以改善心脏炎症并抑制 MIRI 诱导的 NF-κB 活化。CaMKII-δ9-IKK/IkB-NF-κB 信号通路可调节心肌细胞炎症，从而改善心室重塑和心力衰竭[49]。

11. 间充质干细胞来源的外泌体与炎症

近年来，间充质干细胞衍生的外泌体(Mesenchymal Stem Cell-Derived Exosomes, MSC-EXOs)在治疗疾病方面显示出巨大的潜力。尤其是 MSC 来源的外泌体非编码 RNA (Noncoding RNAs, ncRNA)在 MIRI 中显示出治疗潜力[51]。人类基因组的转录除了产生核糖体 RNA 和转运 RNA 外，还会生成大量的非编码 RNA，包括微小 RNA (miRNA)、长链非编码 RNA (lncRNA)和环状 RNA (circRNA) [52] [53]。过表达 miR-181a 的骨髓间充质干细胞外泌体(Bone Marrow MSC-EXOs, BMSC-EXOs)不仅在 MIRI 模型中下调 TNF-α 和 IL-6，而且在单核细胞中上调抗炎细胞因子 IL-10 [54]。负载 miR-182 的骨髓间充质干细胞外泌体(BMSC-EXOs)可以促进 M1 巨噬细胞向 M2 表型的极化，不仅可以减轻 MIRI 诱导的炎症反应，还可以促进病变组织的修复。动物实验证实，其机制可能涉及 TLR4/NF-κB 通路抑制和 PI3K/Akt 通路激活[55]。有可能是 MyD88 从 TIR 结构域分离后与 PI3K 的 p85 调节亚基结合，促使从 TLR4/NF-κB 激活转变为 TLR4/PI3K/AKT 通路激活，从而减轻 MIRI [56] [57]。人脐带 MSC-EXO 递送 miR-182 可以抑制炎症反应，从而缓解 MIRI [58]。然而外泌体对心肌保护或损伤的分子机制并未完全阐明，需要更深入的探讨与研究。

12. 右美托咪定与炎症

有研究显示右美托咪定(Dexmedetomidine, DEX)降低了 TNF-α 和 IL-1β 等炎症因子的表达，并在体内抑制了炎症反应。TLR4/MyD88/NF-κB 信号通路在炎症调节中起着关键作用。DEX 预处理可下调 HMGB1 介导的 TLR4/MyD88/NF-κB 信号通路，减轻 MIRI。人们认为，抑制 HMGB1 介导的 TLR4/MyD88/NF-κB 信号通路可能是 DEX 诱导心肌保护的抗炎机制之一。有趣的是，在糖尿病患者下肢手术中，DEX 还可通过 TLR4/MyD88/NF-κB 通路减轻全身炎症反应。然而，DEX 是否能通过抑制 HMGB1 介导的炎症来减轻糖尿病患者的 MIRI 仍不清楚[59]。

13. 小结与展望

MIRI 是一个复杂且机制尚未完全明晰的过程。在已认知的机制里，炎症反应作为关键因素之一，近年来备受关注。当下，大多数治疗方案通过单一机制来抑制炎症反应，而同时作用于多个机制的治疗方式能否更有效地改善 MIRI，仍有待进一步探索。本综述所提及的炎症反应涵盖多种机制，这些机制彼此既相互独立，又存在关联，如中性粒细胞、巨噬细胞、线粒体、铁死亡、细胞焦亡和信号通路等均与 DAMPs 和 PRRs 相关。它们或许能为改善 MIRI 的预后、降低心血管疾病相关死亡率提供全新的治疗靶点。

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