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TRPV2在心肌缺血再灌注损伤中的作用及干预进展

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摘　要

心肌缺血再灌注损伤(myocardial ischemia/reperfusion injury, MI/RI)是制约急性心肌梗死再灌注获益的核心瓶颈，钙超载为其关键枢纽。瞬时受体电位香草酸亚型2 (TRPV2)是心脏主要的机械敏感钙通道，兼具动态膜转位与钙通透特，在稳态与病理损伤中作用迥异。本文系统梳理TRPV2的分子特征与“拷贝数－门控”双层调控模式，阐述其在心肌、成纤维细胞及巨噬细胞中响应牵张、生长因子与氧化应激的时空激活规律；重点解析TRPV2介导的病理钙内流如何经calcineurin/NFAT轴、线粒体损伤及炎症－吞噬耦联驱动心肌死亡与不良重构，并归纳粉防己碱、曲尼司特及miR-202-5p等靶向策略的干预效应。在此基础上，围绕靶点选择性、再灌注时间窗与细胞偏向性三大转化难点，提出以“降低质膜TRPV2密度”为核心的精准调控方向，为MI/RI的靶向防治提供新思路。

关键词

TRPV2，心肌缺血再灌注损伤，钙超载，巨噬细胞，靶向干预

TRPV2 in Myocardial Ischemia-Reperfusion Injury: Roles and Advances in Intervention

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Abstract

Myocardial ischemia/reperfusion injury (MI/RI) remains the principal constraint on reperfusion

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therapy in acute myocardial infarction, with calcium overload acting as a central pathogenic hub. Transient receptor potential vanilloid 2 (TRPV2) is a major mechanosensitive cation channel in the heart, characterized by Ca^{2+} permeability and activity-dependent plasma membrane translocation—properties that confer its dual, context-dependent roles in homeostasis and disease. This review synthesizes current understanding of TRPV2's structural architecture, regulatory landscape, and "copy number-gating" dual-layer logic. We delineate its spatiotemporal activation across cardiomyocytes, fibroblasts, and infiltrating macrophages under superimposed mechanical strain, IGF-1 signaling, and ROS-mediated Met oxidation. Central to this narrative is how TRPV2-evoked pathological Ca^{2+} entry drives damage through three convergent pathways: (i) calcineurin/NFAT-dependent transcriptional reprogramming, (ii) mPTP opening and mitochondrial collapse, and (iii) inflammation-phagocytosis coupling that sustains sterile inflammation. We then appraise emerging interventions—tetrandrine, tranilast, and miR-202-5p-mediated silencing—with emphasis on mechanistic insight, efficacy, and translational limitations. Finally, we outline a precision framework that addresses three persistent bottlenecks—TRP-selective targeting, early reperfusion time window, and cell-type bias—by prioritizing selective reduction of pathological membrane-resident TRPV2 over global ablation, thereby uncoupling maladaptive Ca^{2+} amplification from physiological mechanosensing.

Keywords

TRPV2, Myocardial Ischemia-Reperfusion Injury, Calcium Overload, Cardiac Macrophage, Targeted Therapy

1. 引言

急性心肌梗死(acute myocardial infarction, AMI)及其继发的心力衰竭仍是全球致死率和致残率最高的心血管疾病之一。尽管经皮冠状动脉介入治疗与溶栓等再灌注策略已显著降低急性期死亡率，但血运重建本身诱发的心肌缺血再灌注损伤(myocardial ischemia/reperfusion injury, MI/RI)依然是制约患者预后的核心瓶颈[1]。MI/RI 的本质是能量代谢崩溃、活性氧(reactive oxygen species, ROS)爆发性生成与钙稳态失衡形成的正反馈环路；该环路驱动从钙超载、线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)开放、炎症激活到细胞死亡的损伤级联，而钙超载因串联并放大各节点损伤，被广泛认为是 MI/RI 的核心枢纽，也由此成为近年研究的主要聚焦点[2] [3]。

瞬时受体电位香草酸亚型 2 (TRPV2)是心脏主要的机械敏感性非选择性阳离子通道，对 Ca^{2+}具有明确通透性，生理状态下仅维持低水平质膜定位，参与心肌力学信号转导与钙稳态维持[4]-[6]。心肌梗死及再灌注应激下，TRPV2 经胞内储存池向质膜异常富集并活性上调，介导病理性持续钙内流，最终诱发钙超载[7] [8]。靶向抑制 TRPV2 可显著减轻该病理进程并改善心功能[9]-[11]，但 TRPV2 全身缺失即导致闰盘紊乱与心功能衰退[6]，提示其具有“生理必需、病理致伤”的双向特征——理想策略为选择性解除再灌注期的病理性过度激活。需特别说明的是，当前以曲尼司特为代表的部分 TRPV2 干预分子，其靶点特异性与作用直接性仍存在较大学术争议，不同研究团队在机制层面得出了不一致结论。本文在梳理干预策略时将客观呈现正反两方证据，明确现有研究的局限性，以保证综述的中立性与严谨性。

基于上述背景，本文围绕 TRPV2 的细胞分布与“拷贝数–门控”双层调控，阐述其在牵张、生长因

子及氧化应激共同作用下的激活特点及心肌–巨噬细胞协同效应，并追踪从钙紊乱到细胞损伤的演进路径；在此基础上，针对靶点选择性、干预时机与细胞特异性等现实难题，提出以“减少质膜 TRPV2 定位”为重点的精准干预方向，为再灌注损伤防治提供参考。

2. 多细胞分布与双层门控：TRPV2 在心肌 MI/RI 中的协同放大

2.1. 心脏中 TRPV2 的细胞类型特异性分布与功能架构

在成年心脏中，TRPV2 呈细胞类型特异的分布与功能分化：

- **心肌细胞**：TRPV2 主要锚定于闰盘，并富集于胞内池，质膜功能性密度较低[6] [12]；机械牵张与 IGF-1 为并存生理输入，协同调控通道：牵张激活 TRPV2 并促进其由胞内池向质膜转位[6] [12]；IGF-1 主要经 IGF-1R/PI3K 明确驱动质膜转位并敏化通道反应性[6]；二者时空耦合，共同限定生理 Ca^{2+}信号的量、时程与亚细胞分布。
- **心脏巨噬细胞**：组成型表达，静息时滞留于内体/肌浆网，炎症刺激下经 PI3K 依赖转位至质膜，以亚膜 Ca^{2+}微域驱动趋化与清创[13] [14]。
- **心脏成纤维细**：转录组学证据表明 TRPV2 稳定表达，提示其可能参与基础力学感知，但 MI/RI 中功能尚待阐明[15]。

MI 后，梗死周边心肌细胞 TRPV2 呈转录–蛋白–质膜转位三级上调[7] [10]；同期浸润巨噬细胞亦同步上调 TRPV2，增强向损伤区迁移与促炎输出，参与梗死周边急性炎症放大[7] [8]。上述多细胞、多层级的“储备池扩容 + 膜投递”格局，为 MI/RI 中跨细胞协同损伤提供了结构基础。

2.2. 分子架构与双层级调控

TRPV2 由 TRPV2 基因编码，经可变剪接产生包括 f-TRPV2 全长亚型(约 760 aa)和 s-TRPV2 截短剪接体在内的多种异构体，为六次跨膜同源四聚体通道[16]，二者结构与功能存在显著差异：

- f-TRPV2 保留完整 N 端锚蛋白重复区与跨膜孔道区，是质膜功能性通道的主要形式，响应机械牵张、生长因子信号，介导钙离子内流；
- s-TRPV2 缺失 N 端部分锚蛋白序列，跨膜区完整但门控特性改变，主要滞留于内质网/内体储备池，钙通透活性显著低于全长型，部分研究提示其可通过竞争结合转运蛋白，负向调控质膜通道密度。

MI/RI 病理状态下，不仅 TRPV2 总表达上调，还伴随 f/s 亚型比例向全长型偏移，这一亚型转换是质膜钙通道功能异常增强的重要分子基础，也增加了干预的复杂性。单亚基呈“N 端胞内长臂–跨膜核心–C 端胞内长尾”构型：N 端锚蛋白重复区(ARD)作为蛋白相互作用平台，介导与调节因子及转运系统的结合[17] [18]；S1-S6 跨膜区中，S5-孔螺旋-S6 围成中央离子孔道，通透 Na^+、K^+及 Ca^{2+} ($P_{Ca}/P_{Na} \approx 2.94$) [16] [19]；C 端 TRP 盒下游富集 PIP_2 及 PKA 等磷酸化调控位点，是 PI3K 依赖转位与门控调节的核心平台[20]。2016 年兔源与大鼠源全长冷冻电镜结构从三维层面确认了该模型，也为理解其在心肌再灌注损伤中的异常激活奠定了分子基础[21] [22]。

功能上，TRPV2 的活性受“质膜功能性拷贝数”与“单通道开放概率”双重维度调控[23] [24]：静息时主要滞留于早期/循环内体及内质网，仅少量定位于质膜[16] [23]；机械牵张、IGF-1 或激动剂可经 PI3K 动员其向质膜转位，决定上层“拷贝数层”，并构成病理条件下信号放大的结构基础[24]-[26]。

2.3. 生理状态下的门控整合

定位于质膜的 TRPV2 通过多层级门控实现精细调节，其开放概率与开放时程由多维生理信号整合决定：

- 生理范围机械牵张：作为核心力学输入，经机械感受结构域响应力信号介导 Ca^{2+}内流，是心脏力学信号转导的关键分子界面[27] [28]；
- 化学配体与生长因子：2-APB、工具性激动剂 probenecid、大麻二酚(CBD)可激活通道；IGF-1/PI3K 通路驱动通道向质膜转位并维持高敏态，钌红、Tranilast 可阻断其活性[6] [29]-[31]；
- 理化刺激：>52℃高温与弱酸(pH 6.5~6.8)降低激活阈值，使孔区维持预开放柔性[32] [33]；

上述输入并非独立开关，而是依据强度与组合实时加权，使 TRPV2 表现为非二元“开/关”、而是动态响应的分子传感器。

2.4. MI/R 中 TRPV2 的多模态激活与心肌－巨噬协同放大

在 MI/RI 中，TRPV2 的激活是力学、生长与氧化三类输入在心肌与浸润巨噬细胞中时空叠加的结果。MI 后，梗死周边区因存活心肌与丧失收缩性的坏死心肌之间的力学失匹配形成局部牵张应力[34] [35]，该应力通过 TRPV2 的机械敏感性激活闰盘驻留的 TRPV2，并驱动其由内体/肌浆网储备池向质膜转位，为病理性钙内流提供结构基础[6] [12]。牵张-TRPV2-Ca^{2+}轴还可诱导存活心肌细胞上调 IGF-1，形成以自分泌为主的生长因子微环境[6] [36]-[38]；IGF-1 经 IGF-1R/PI3K/Akt 信号巩固心肌 TRPV2 的质膜定位，将力学启动的瞬时激活转化为心肌侧持续性钙信号增强[6]。该微环境下，浸润的巨噬细胞上调 TRPV2 表达并转位至质膜，增强向梗死坏死区的定向迁移，并促进炎症因子释放，从而将心肌源性钙异常初步转化为局部炎症损伤[8] [13]。再灌注期爆发性 ROS 作为第三重输入，直接氧化 TRPV2 胞内区保守甲硫氨酸残基(Met^{528}/Met^{607})敏化已就位的质膜通道[32]，这一机制可能将受控的生理性钙瞬变转化为病理性持续内流，构成再灌注期钙超载的重要上游事件之一。

3. TRPV2 介导 MI/RI 的分子机制：从钙信号到细胞命运

3.1. 钙超载与线粒体功能障碍

再灌注期胞质钙超载由质膜钙内流与肌浆网钙释放协同驱动，进而触发 mPTP 开放及线粒体功能障碍，构成 MI/RI 的核心病理环[39]。近年研究证实，TRPV2 在再灌注应激下发生病理性质膜转位，加剧钙超载；抑制 TRPV2 (基因或药理水平)可改善钙处理稳态与线粒体功能[9] [40] [41]。miR-202-5p 与粉防己碱均通过下调 TRPV2 减轻钙超载与心肌细胞凋亡、改善心功能[40] [41]：TRPV2 介导的胞质钙升高，可通过线粒体钙单向转运体(MCU)加速线粒体基质钙摄取，当基质钙超过阈值后触发 mPTP 开放，进而导致线粒体膜电位崩溃、呼吸链解偶联与细胞色素 c 释放，完善从质膜钙内流到线粒体损伤的完整分子逻辑链。综上，TRPV2 既是 MI/RI 钙超载的关键效应节点，也是具转化潜力的干预支点[9] [40] [41]。

3.2. Calcineurin/NFAT 信号通路

钙调磷酸酶(calcineurin)/活化 T 细胞核因子(NFAT)通路是 TRPV2 介导 MI/RI 及远期病理性重塑的核心下游效应轴[10] [42]。TRPV2 激活所致持续 Ca^{2+}内流可特异性活化 calcineurin，诱导 NFAT 去磷酸化并核转位，驱动促肥大、促纤维化及促凋亡等病理基因转录程序[10] [42]。该轴虽不直接决定再灌注早期坏死，但持续放大线粒体损伤、推动晚期心肌丢失与心室重构。粉防己碱通过下调 TRPV2 阻断该通路，减轻梗死面积、改善心肌细胞凋亡并抑制 ROS 与 Ca^{2+}超载[10]。值得注意的是，TRPV4 与 TRPC6 等其他 TRP 通道亦经 calcineurin/NFAT 轴介导心肌损伤[43] [44]，表明该通路是 TRP 家族致心脏病变的保守下游汇聚点；而 TRPV2 凭借其在 MI/RI 中的显著上调及对 Ca^{2+}稳态的核心调控作用，构成该病理进程中的关键上游启动者[10] [42]。

3.3. 心肌细胞程序性死亡的多模式调控

MI/RI 中，心肌细胞死亡呈现多种程序性死亡形式共存的特征。TRPV2 通过介导病理性钙超载，触发线粒体膜电位崩溃与 mPTP 开放，显著促进心肌细胞凋亡[40] [41]。粉防己碱通过靶向下调 TRPV2 表达，可有效抑制 cleaved caspase-3 表达、上调抗凋亡蛋白 Bcl-2 表达、下调促凋亡蛋白 Bax 表达，从而提高 Bcl-2/Bax 比值，显著缩小心肌梗死面积[11] [41]。此外，TRPV2 在浸润性巨噬细胞中高表达，其活性与吞噬功能正向耦联；TRPV2 缺失可减弱巨噬吞噬活性，过度激活通过增强 peri-infarct 巨噬细胞活性加剧炎症性心肌损伤[9] [45]。

3.4. 炎症反应与巨噬细胞功能调控

MI 后单核/巨噬细胞迅速浸润梗死周边并启动清创与修复。TRPV2 在 peri-infarct 区聚集的巨噬细胞中高表达，并可增强其向损伤心肌的迁移能力[8]。TRPV2 在巨噬细胞吞噬早期(颗粒识别与膜包裹)即参与调控，其缺失可减弱吞噬活性[45]；Entin-Meer 等证实，TRPV2 KO 小鼠 MI 后心功能改善，归因于 peri-infarct 巨噬细胞活性衰减(含促炎输出降低)，提示 TRPV2 介导的巨噬过度活跃可放大炎症性心肌损伤[9]。药理学抑制 TRPV2 亦减弱巨噬吞噬及 LPS 诱导迁移[46]。

炎症具双刃性：适度激活支持修复，持续过度则加重微血管障碍与纤维化。TRPV2 作为调控巨噬吞噬、迁移及促炎输出的阈值节点，其时空动态(表达、膜定位、阶段特异性功能)及“促修复/促损伤”的临界转换，仍是待阐明的关键问题。

4. 靶向 TRPV2 的干预策略

4.1. 药理学抑制剂：曲尼司特(Tranilast)

曲尼司特最初作为抗过敏药物获批临床，早期研究提示曲尼司特可能具有 TRPV2 抑制活性，并由此被长期用作 TRPV2 抑制剂候选分子。Iwata 等首先报道曲尼司特在肌营养不良相关扩张型心肌病小鼠中改善终末期心衰，早期被认为归因于抑制 TRPV2 介导的钙内流[25]；后续研究在肺高压相关右室重构与房颤模型中得出类似结论[31] [47]。肌营养不良相关晚期心衰患者的单臂开放多中心研究进一步显示，曲尼司特可长周期抑制外周血单核细胞 TRPV2 表达，并使 BNP、ANP、左室短轴缩短率等心脏指标保持稳定，提高患者生存率[48] [49]。但曲尼司特靶向 TRPV2 的直接性始终存疑：2018 年已证实其抗肥厚效应独立于心肌细胞 TRPV2，近期更明确其不直接阻断 TRPV2 通道，心脏保护主要经 TGF-β 等旁路介导[50] [51]。这既限定了曲尼司特作为 TRPV2 探针的适用性，也凸显直接靶向 TRPV2 的高选择性抑制剂开发迫切性。综上，曲尼司特并非 TRPV2 的直接高选择性抑制剂，其心脏保护作用是多靶点协同的结果，将其作为 TRPV2 特异性研究探针需十分谨慎。

4.2. 中药活性成分：粉防己碱(Tetrandrine, TET)

粉防己碱是从粉防己(Stephania tetrandra)中提取的双苄基异喹啉类生物碱，以抗炎、抗氧化作用著称，并具有钙通道阻滞活性，对心肌缺血及再灌注损伤具有明确的保护效应[52]-[54]。近年证据提示，该心肌保护部分由 TRPV2 介导：粉防己碱上调 miR-202-5p 进而抑制 TRPV2 表达，减轻 I/R 中的病理性 Ca^{2+}内流、线粒体损伤及心肌细胞凋亡[11] [41]；同时阻断 TRPV2-Ca^{2+}/calcineurin/NFAT 轴，抑制心肌细胞凋亡与肥大相关转录程序[10]。

4.3. miR-202-5p 与 TRPV2 调控轴

miRNA 通过与靶基因 3′-UTR 碱基配对，募集 miRISC 复合物，介导翻译抑制和/或 mRNA 降解等转

录后调控，在心肌 I/R 损伤中发挥关键作用[55]-[57]。miR-202-5p 为 TRPV2 的直接负调控因子：缺血再灌注时其表达下调致 TRPV2 升高、钙超载与凋亡；过表达 miR-202-5p 可下调 Trpv2 表达，减轻钙超载并抑制心肌细胞凋亡[11] [40]。该轴与粉防己碱上调 miR-202-5p 的效应形成功能耦合，为“中药成分-miRNA-离子通道”协同干预提供了概念支持[11] [41]。

4.4. 基因干预、靶向抗体与药理学工具：从全身敲除到选择性膜转运调控

全身性 TRPV2 敲除可减轻心肌梗死后损伤并改善心功能[9]，但致闰盘超微结构紊乱及基础收缩下降[6]，提示长期完全阻断存在潜在风险。相比之下，抗 TRPV2 单抗 mAb88-2 在扩张型心肌病与心衰模型中改善功能，为“降膜表达而非全局缺失”的靶向干预提供了新方向[58]。SKF-96365、钌红等传统 TRPV2 工具药选择性有限，其中 SKF-96365 仅能部分抑制 TRPV2，钌红虽抑制效力较强但是非特异性孔阻断剂；2-APB 可激活啮齿类 TRPV2 但对人 TRPV2 无效且种属差异显著——这些工具目前限于机制研究[59]。鉴于 TRPV2 功能高度依赖向质膜的动态转位，靶向膜定位(促内化或阻转位)较单纯门控抑制更具特异性与病理选择性，该策略已在扩张型心肌病模型中获初步验证[25]。

5. 临床转化瓶颈与未来展望

尽管 TRPV2 在 MI/RI 中的致病作用及干预潜力已获初步验证，其临床转化仍面临多重瓶颈。

5.1. 靶点选择性不足

曲尼司特、粉防己碱等代表性分子对 TRPV2 选择性有限。最新电生理证据表明，曲尼司特直至 1 mM 均不直接抑制 TRPV2 介导的电流，其作用是间接降低 ROS 而非直接阻断通道，且同时影响 TRPA1 和电压门控钠通道[50]；在压力超负荷模型中，曲尼司特的短期抗肥厚/抗纤维化获益不通过心肌细胞 TRPV2 实现[51]。粉防己碱虽可下调 TRPV2 表达改善 MI/RI，但其心脏保护主要经 MAPK/NF-κB 通路介导，同样难以确立“TRPV2 抑制↔心肌保护”的严格因果[60]。近期 IV2-1 (选择性阻断剂，IC_{50} = 6.3 μM，对 TRPV1/3/4 无作用)、AV2-1(正变构激活剂，通过 Cys157/His165 稳定激活构象)、plumbagin(负变构调节剂，IC_{50} = 0.85 μM，选择性 > 14 倍)等 TRPV2 选择性探针的发现，为开发高亲和力、高亚型选择性的构象型调节剂奠定了基础[46] [61] [62]。未来需进一步构建细胞偏向性递送体系(如巨噬靶向 AAV-shTRPV2、心肌归巢肽偶联抑制剂)——该方向目前仍处于探索阶段，旨在确证靶点价值并降低脱靶风险。

5.2. “保护－损伤”平衡难控

全身性 TRPV2 缺失损害闰盘结构与基础收缩，提示完全阻断不可取[6]；而通道在再灌注期过度激活驱动损伤，又是生理力学感知与巨噬清创所必需[7] [8]。理想策略应抑制病理性质膜转位、保留低水平生理门控，实现“增池不减感、敏化不失控”的动态平衡。

5.3. 巨噬细胞 TRPV2 的时间异质性与干预窗口

髓系 TRPV2 在 MI 后呈功能分期：早期主导趋化与炎症释放，修复期通过炎症微环境间接参与基质重塑与瘢痕成熟[8] [63]。干预时机偏移可致“过早抑炎削弱清创、晚期持续激活加重纤维化”[9]。因此，建立基于时序生物标志物的再灌注干预窗，并开发单核/巨噬亚群特异性递送，是精准化的关键[7]。

5.4. 未来研究方向与转化路径

未来研究应聚焦三大关键路径：转化推进需聚焦三点：① 结构驱动药物设计：依托 TRPV2 高分辨结构(apo、激动剂态及潜在调控界面)开展变构抑制剂与抗转位抗体筛选；② 人心脏 TRPV2 图谱：整合 scRNA-seq、空间转录组与多重成像，解析梗死周边 TRPV2 的细胞梯度与微环境依赖定位；③ 临床概念

验证：在急性 STEMI 直接 PCI 人群中开展I/II期研究，以 CMR (T2/T1 mapping、微血管梗阻)为替代终点，验证安全性与心肌保护效应。

上述路径协同推进，有望推动 TRPV2 从机制认知迈向 MI/RI 的精准防治实践。

6. 结语

TRPV2 是心肌中高表达的机械敏感钙通透性阳离子通道，在 MI/RI 中呈“心肌局部上调、外周血下调”的时空与细胞类型依赖性表达特征。其致病机制涵盖病理性钙内流与线粒体损伤、calcineurin/NFAT 信号异常激活、心肌细胞程序性死亡及炎症–吞噬耦联等多个层面。以曲尼司特、粉防己碱及 miR-202-5p 为代表的多层次干预策略已初步显示出靶向 TRPV2 的防治潜力，但靶点选择性不足、“保护–损伤”平衡难控、炎症调控时间窗不清等瓶颈仍待突破。深入解析 TRPV2 的精细调控网络并开发高选择性干预工具，可为 MI/RI 的精准防治提供新的转化思路。

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