Scientific Research Publishing

Journal of Biosciences and Medicines, 2026, 14(5), 517-526
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

MRCK and Myocardial Infarction: A Prospective Perspective on Cytoskeletal Kinases in Post-Infarction Repair and Ventricular Remodeling

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How to cite this paper: Ai, Y.N. and Gao, W.Q. (2026) MRCK and Myocardial Infarction: A Prospective Perspective on Cytoskeletal Kinases in Post-Infarction Repair and Ventricular Remodeling. *Journal of Biosciences and Medicines*, **14**, 517-526.
https://doi.org/10.4236/jbm.2026.145034

Received: May 10, 2026
Accepted: May 26, 2026
Published: May 29, 2026

Abstract

This article is a Perspective and prospective hypothesis-generating review, rather than a systematic evidence-based review. Direct evidence linking myotonic dystrophy kinase-related Cdc42-binding kinase (MRCK) to myocardial infarction (MI) remains limited. Therefore, the purpose of this article is not to conclude that MRCK is an established therapeutic target in MI, but to propose that MRCK is a biologically plausible and underexplored regulator of post-infarction repair. MI remains a major cause of heart failure and cardiovascular death despite advances in reperfusion therapy and guideline-directed medical treatment [1] [2]. Post-infarction repair involves ischemia-reperfusion injury, microvascular dysfunction, endothelial barrier disruption, inflammatory cell recruitment, fibroblast activation, scar formation, and ventricular remodeling [3]. These processes are not only governed by inflammatory, metabolic, and neurohormonal pathways, but also by cytoskeletal remodeling and cellular mechanical forces. MRCK, a Cdc42-associated serine/threonine kinase family, regulates myosin light-chain phosphorylation, actomyosin contraction, cell polarity, migration, and junctional stability. These functions overlap with several key cellular events after MI. This Perspective discusses why MRCK has been neglected in MI research, how it differs from ROCK, and which testable hypotheses may guide future studies. We propose that MRCK may represent a mechanobiological node linking local cellular contractility to endothelial

integrity, inflammatory trafficking, fibroblast-mediated scar mechanics, and ventricular remodeling.

Keywords

MRCK, Myocardial Infarction, Perspective, Cytoskeleton, Actomyosin, Endothelial Barrier, Fibroblast, Ventricular Remodeling

1. Introduction: A Perspective Rather than a Conventional Review

Myocardial infarction is most commonly caused by rupture or erosion of a coronary atherosclerotic plaque, followed by platelet activation, thrombus formation, and acute coronary occlusion. Because cardiomyocytes rely heavily on continuous oxygen delivery and mitochondrial oxidative phosphorylation, interruption of coronary blood flow rapidly induces ATP depletion, ionic imbalance, calcium overload, mitochondrial injury, and cell death. Early reperfusion, antiplatelet therapy, lipid-lowering treatment, and modern heart failure therapy have substantially improved survival [1] [2]. Nevertheless, many patients still develop adverse ventricular remodeling.

Reperfusion is essential for salvaging ischemic myocardium, but it may also trigger oxidative stress, mitochondrial permeability transition, endothelial injury, inflammatory activation, and microvascular dysfunction, collectively contributing to ischemia-reperfusion injury [3] [4]. Because adult mammalian cardiomyocytes have limited regenerative capacity, necrotic myocardium is largely replaced by fibrotic scar tissue. A stable scar prevents ventricular rupture, whereas excessive or persistent fibrosis increases ventricular stiffness, reduces compliance, and promotes heart failure [5]-[7].

Post-infarction repair is therefore a multicellular process involving endothelial cells, immune cells, fibroblasts, vascular smooth muscle cells, and surviving cardiomyocytes. A shared feature of these cells is reliance on cytoskeletal reorganization and actomyosin-mediated force generation. MRCK is positioned within this biological context. However, direct MI-specific evidence remains scarce. Thus, this article should be read as a prospective conceptual framework: MRCK may be important in MI not because it has already been proven to determine infarct formation, but because its known functions match several underexplored mechanical aspects of post-infarction repair.

2. Molecular Basis of MRCK

MRCK belongs to the myotonic dystrophy kinase-related serine/threonine kinase family. The major mammalian isoforms are MRCKα, MRCKβ, and MRCKγ, encoded by CDC42BPA, CDC42BPB, and CDC42BPG, respectively [8]-[11]. MRCKα and MRCKβ are the best characterized and participate in actin organization, cell

polarity, migration, cell junction regulation, and tissue remodeling.

MRCK proteins contain an N-terminal kinase domain, a central coiled-coil region, and C-terminal regulatory domains involved in membrane localization, small GTPase binding, and autoinhibition [12]. Their best-known upstream regulator is Cdc42, a Rho-family small GTPase that controls cell polarity, protrusion formation, directional migration, and junctional organization [8] [10] [11]. Through this structure, MRCK converts spatial Cdc42-related signals into localized actomyosin contractility.

A major downstream function of MRCK is regulation of myosin light-chain phosphorylation and non-muscle myosin II activity [9] [13]. This enables MRCK to influence cell shape change, leading-edge dynamics, matrix traction, junctional tension, and cell migration. These are precisely the types of cellular behaviors required during tissue repair after MI.

3. Why Has MRCK Not Been Systematically Studied in MI?

The absence of extensive MRCK research in MI does not necessarily mean that MRCK is unimportant. Several reasons may explain this gap.

First, MI research has traditionally emphasized coronary occlusion, cardiomyocyte death, reperfusion injury, inflammation, fibrosis, and neurohormonal activation. Local cytoskeletal mechanics, junctional tension, and cell migration machinery have received comparatively less attention, especially in translational cardiovascular studies.

Second, ROCK has dominated the field of actomyosin-related cardiovascular research. RhoA-ROCK signaling is closely linked to vascular tone, vasospasm, hypertension, smooth muscle contraction, and cardiac hypertrophy [13]-[15]. Because ROCK has available inhibitors and obvious hemodynamic relevance, many questions involving myosin light-chain phosphorylation have been interpreted mainly through the ROCK pathway. MRCK, which overlaps with ROCK at the level of actomyosin regulation, may therefore have been considered redundant.

Third, selective MRCK tools have historically been limited. Early pharmacological inhibitors lacked sufficient selectivity or were developed mainly in cancer and cell migration research. In addition, MRCK isoforms may show functional compensation and cell type-specific behavior, making whole-body inhibition or non-specific knockout models difficult to interpret.

Finally, MRCK may have bidirectional roles after MI. It may stabilize endothelial junctions in one context but promote leakage in another; it may support early scar formation but worsen late fibrosis. Such stage- and cell-dependent effects make MRCK harder to classify as simply protective or harmful. This complexity may have delayed its systematic evaluation in MI.

4. MRCK versus ROCK: A Centralized Comparison

MRCK and ROCK both regulate myosin light-chain phosphorylation and actomyosin contraction, but they are not interchangeable. ROCK is mainly activated

by RhoA and is commonly associated with global cellular tension, central stress fiber formation, vascular smooth muscle contraction, vasospasm, hypertension, and cardiac hypertrophy [13]-[15]. In contrast, MRCK is primarily linked to Cdc42-related signaling and more often regulates local contraction, cortical tension, cell polarity, leading-edge dynamics, and junctional remodeling [8]-[11].

This distinction is particularly relevant to MI. ROCK may better explain changes in vascular tone, coronary spasm, and systemic contractile load. MRCK may be more relevant to local cellular behaviors: endothelial junction repair or disruption, leukocyte migration, fibroblast traction, collagen compaction, and scar architecture. Thus, MRCK should not be viewed merely as a weaker or redundant ROCK-like kinase. It may regulate different subcellular compartments, different cell types, and different stages of post-infarction repair.

From a therapeutic perspective, ROCK inhibition may influence vascular tone and global cytoskeletal tension, whereas MRCK modulation may affect localized cellular mechanics. Whether these pathways compensate, cooperate, or diverge after MI remains unknown and should be tested directly in comparative experimental models.

5. Potential Roles of MRCK in Post-Infarction Repair

5.1. Ischemia-Reperfusion Injury and Microvascular Dysfunction

Ischemia-reperfusion injury involves oxidative stress, calcium overload, mitochondrial injury, inflammation, endothelial dysfunction, and microvascular obstruction [3] [4]. Even after successful reopening of the epicardial coronary artery, no-reflow or microvascular obstruction may occur and is associated with larger infarct size and worse prognosis [16] [17]. Mechanisms include endothelial swelling, capillary plugging, leukocyte accumulation, platelet aggregation, microthrombi, vasospasm, and interstitial edema.

MRCK may participate by regulating endothelial contraction and junctional tension. MRCKβ has been shown to localize at endothelial junctions under Rap1 signaling and to spatially regulate myosin II activity and actin organization, thereby strengthening cell-cell contacts [18]. This suggests that endothelial integrity depends not simply on reduced contractility, but on correctly localized contractile force. In MI, junctional MRCK activity may preserve barrier function, whereas excessive or mislocalized MRCK activation may promote endothelial retraction, vascular leakage, edema, and microvascular compression.

5.2. Endothelial Barrier Function

The endothelial barrier controls permeability, inflammatory cell entry, and tissue edema after MI. VE-cadherin-mediated adherens junctions, cortical actin, and matrix adhesion maintain vascular integrity under physiological conditions [19] [20]. During ischemia and reperfusion, reactive oxygen species, cytokines, and altered shear stress can disrupt this balance.

MRCK may be important because it regulates spatial actomyosin organization.

At endothelial junctions, MRCK may reinforce barrier stability; away from junctions, it may increase contractile stress and open intercellular gaps [18]-[20]. Therefore, future studies should not measure only total MRCK expression, but should analyze isoform-specific activation and subcellular localization.

5.3. Inflammatory Cell Recruitment

Inflammation is essential for repair after MI. Neutrophils and monocytes enter the infarcted myocardium to clear dead cells and matrix debris, while macrophages later contribute to inflammation resolution, angiogenesis, and scar maturation [5] [7] [21]-[23]. Excessive or persistent inflammation, however, enlarges injury and promotes adverse remodeling. Clinical evidence also supports the importance of inflammatory pathways in ischemic cardiovascular disease [24].

Leukocyte recruitment requires polarization, adhesion, crawling, transendothelial migration, and tissue movement. These steps depend on actin remodeling and myosin-mediated contraction. Because Cdc42 regulates leukocyte polarity and MRCK is a Cdc42 effector, MRCK may influence inflammatory cell trafficking [8] [10] [11]. However, this role may be double-edged: MRCK inhibition could reduce excessive infiltration, but it might also delay debris clearance and impair reparative inflammation.

5.4. Fibroblast Activation and Scar Mechanics

Cardiac fibroblasts are central to scar formation after MI. Under stimulation by TGF-β, inflammatory mediators, mechanical stretch, and matrix stiffening, fibroblasts proliferate, migrate, and differentiate into myofibroblasts. These cells express α-smooth muscle actin, form stress fibers, generate traction, and deposit collagen-rich extracellular matrix [5] [6] [25]-[28].

Fibroblast activation is strongly mechanosensitive. Fibroblasts sense matrix stiffness through integrins and generate actomyosin-dependent traction. This compacts collagen, reorganizes matrix architecture, and further increases tissue stiffness, sustaining myofibroblast activation [25] [27]. Since MRCK promotes myosin light-chain phosphorylation and contraction [9] [13], it may regulate fibroblast migration, matrix traction, and scar contraction.

The timing of MRCK activity may be crucial. Early after MI, MRCK-mediated fibroblast contraction may help stabilize the infarct and prevent rupture. Later, persistent MRCK activation may contribute to excessive scar stiffening, reduced compliance, and diastolic dysfunction. Therefore, MRCK should be studied as a regulator of scar mechanics rather than simply as a pro-fibrotic molecule.

5.5. Cardiomyocyte and Vascular Cell Adaptation

Although MRCK is not a classical regulator of sarcomeric contraction, it may influence non-sarcomeric cytoskeletal organization, cortical tension, cell shape, and mechanotransduction. Surviving cardiomyocytes in the infarct border zone experience increased wall stress and undergo hypertrophy, cytoskeletal remodeling,

microtubule changes, and altered mechanical signaling [29] [30]. Whether MRCK participates in these adaptations remains unknown.

MRCK may also affect vascular smooth muscle cell migration and phenotypic switching. Compared with ROCK, which is strongly linked to vascular tone, MRCK may be more relevant to polarity, leading-edge dynamics, and adhesion remodeling [8]-[15]. This could be relevant to vascular remodeling after MI or percutaneous coronary intervention, but direct evidence is still lacking.

6. Testable Hypotheses and Suggested Experimental Approaches

As a Perspective, this article should generate experimentally testable hypotheses rather than provide definitive conclusions.

Hypothesis 1: Endothelial MRCKβ regulates microvascular barrier integrity during early reperfusion.

Junction-localized MRCKβ may protect endothelial integrity, whereas mislocalized or excessive activation may promote leakage and no-reflow. This can be tested using endothelial-specific MRCKβ knockout mice, ischemia-reperfusion models, Evans blue or fluorescent albumin leakage assays, coronary perfusion imaging, VE-cadherin staining, and spatial analysis of phosphorylated myosin light chain [18]-[20] [31].

Hypothesis 2: Fibroblast MRCKα/β has stage-dependent effects on scar formation.

Early MRCK activation may promote scar stabilization, whereas late persistent activation may increase collagen compaction and ventricular stiffness. This can be examined using fibroblast-specific, time-inducible MRCKα/β knockout models, collagen gel contraction assays, traction force microscopy, Picrosirius red staining, cardiac MRI, pressure-volume loop analysis, and rupture-risk assessment [25]-[27] [31].

Hypothesis 3: Myeloid MRCK regulates inflammatory cell trafficking after MI.

MRCK may influence neutrophil and monocyte infiltration, macrophage positioning, and inflammation resolution. Myeloid-specific MRCK knockout, bone marrow chimera experiments, flow cytometry, single-cell RNA sequencing, and intravital imaging could clarify these effects [21]-[23] [31].

Hypothesis 4: MRCK and ROCK have nonredundant functions after MI.

MRCK may regulate localized cell migration and junctional mechanics, whereas ROCK may regulate global contractility and vascular tone. Comparative studies using MRCK inhibitors, ROCK inhibitors, dual inhibition, and genetic models should assess vascular leakage, inflammatory infiltration, fibroblast traction, scar architecture, ventricular stiffness, and ejection function [9] [13]-[15] [31].

Hypothesis 5: Cardiomyocyte MRCK contributes to border-zone mechanoadaptation.

Cardiomyocyte-specific MRCK deletion, cyclic stretch models, phosphoproteomics, super-resolution cytoskeletal imaging, and strain analysis may determine

whether MRCK affects non-sarcomeric cytoskeletal remodeling after MI [29]-[31].

These studies should follow a standardized experimental MI model design and should avoid relying solely on systemic pharmacological inhibition, because MRCK function is likely isoform-specific, cell-specific, stage-specific, and spatially localized [31].

7. Translational Considerations

Adverse ventricular remodeling after MI remains a major determinant of long-term heart failure, characterized by ventricular dilation, wall thinning, extracellular matrix remodeling, reduced compliance, and progressive contractile dysfunction [32] [33]. Therefore, any translational strategy targeting MRCK should be evaluated not only by acute infarct size or short-term ejection fraction, but also by scar architecture, ventricular stiffness, microvascular integrity, inflammatory resolution, and long-term remodeling outcomes.

Several MRCK inhibitors, including BDP5290, BDP9066, BDP8900, and DJ4, have been developed mainly as research tools in cancer migration and cytoskeletal studies [34] [35]. They may help interrogate MRCK function in cardiovascular models, but they are not established MI therapies.

Potential applications could include limiting excessive fibroblast contraction, reducing chronic scar stiffening, modulating endothelial leakage, controlling inflammatory cell migration, or affecting vascular remodeling. However, these possibilities remain speculative. MRCK inhibition could also impair endothelial junction stabilization, delay inflammatory clearance, weaken early scar formation, or disturb normal wound healing [27]. Therefore, the translational question is not simply whether MRCK should be inhibited, but when, where, in which cell type, and for how long. Local delivery, short-course treatment, infarct-border-zone targeting, nanoparticles, hydrogels, or device-based delivery may be more realistic than chronic systemic inhibition.

8. Conclusions

This article is a perspective and a hypothesis-generating review. Current evidence is insufficient to define MRCK as an established therapeutic target in MI. Nevertheless, MRCK regulates actomyosin contraction, cell polarity, migration, and junctional remodeling—processes that are central to post-infarction repair. MRCK may influence endothelial barrier integrity, inflammatory cell recruitment, fibroblast-mediated scar mechanics, vascular remodeling, cardiomyocyte mechanoadaptation, and ultimately ventricular remodeling.

The main message is not that MRCK has already been proven to drive MI pathology, but that it represents an underexplored mechanobiological pathway that deserves systematic investigation. Future studies should define their isoform-specific, cell-specific, stage-specific, and spatially localized functions. If these mechanisms are clarified, MRCK may open a new direction for modulating post-infarction repair through control of cellular mechanics.

Funding

This work was sponsored by Tianjin Health Research Project (TJWJ2022XK026), National Natural Science Foundation of China (82370420), and Tianjin Key Medical Discipline Construction Project (TJYXZDXK-3-010B).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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