Review Article

Cardioprotection at the Molecular Interface: Extracellular and Intracellular Targets in MI Management

Hardik Koria[1, 2], Anita Mehta[3*]

[1] *Research Scholar, Gujarat Technological University, Ahmedabad - 382424, Gujarat, India, ORCID: 0000-0001-7950-2975.*

[2] *Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology (CHARUSAT), CHARUSAT campus, Changa - 388421, Gujarat, India.*

[3] *Department of Pharmacology, Anand Pharmacy College, Anand - 388001, Gujarat, India, ORCID: 0000-0001-7036-3833.*

***Corresponding author's E-mail:** dranitalmcp@gmail.com

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ABSTRACT

Myocardial infarction (MI) continues to be a leading cause of death and disability globally. While reperfusion strategies such as percutaneous coronary intervention have significantly improved early survival, long-term outcomes are hindered by secondary injury mechanisms including inflammation, oxidative stress, mitochondrial dysfunction, and maladaptive remodeling. Recent advances in molecular cardiology have highlighted a range of extracellular and intracellular targets that play critical roles in the pathogenesis and repair of infarcted myocardium. Extracellular mediators such as pro-inflammatory cytokines (e.g., IL-1β, TNF-α), matrix metalloproteinases, growth factors, and vascular regulators like VEGF and nitric oxide orchestrate immune responses, fibrosis, and neovascularization. Concurrently, intracellular targets including PI3K/Akt and MAPK pathways, mitochondrial regulators (e.g., mPTP, Drp1), redox modulators, autophagy, calcium-handling proteins, and gene expression regulators are central to cardiomyocyte survival and adaptation. This review synthesizes current knowledge of these targets and their therapeutic relevance, emphasizing integrative strategies that modulate both extracellular and intracellular mechanisms. Leveraging advances in RNA therapeutics, gene editing, nanotechnology, and regenerative medicine may pave the way for precision interventions that enhance myocardial recovery and reduce the burden of post-MI complications.

Keywords: Myocardial infarction; Extracellular targets; Intracellular signaling; Cardioprotection; Inflammation; Oxidative stress; Mitochondrial dysfunction; Fibrosis; Molecular therapeutics; Regenerative cardiology.

INTRODUCTION

Myocardial infarction (MI), commonly referred to as a heart attack, remains one of the leading causes of death and disability worldwide. It is primarily caused by an acute obstruction of coronary blood flow, leading to ischemic injury and irreversible cardiomyocyte death[1]. Despite advances in early reperfusion strategies such as percutaneous coronary intervention (PCI) and pharmacological thrombolysis, the prognosis for many MI patients remains suboptimal due to secondary complications, including reperfusion injury, inflammation, ventricular remodeling, and chronic heart failure [2].

Over the past decade, increasing attention has been directed toward understanding the molecular and cellular mechanisms underlying MI to identify novel therapeutic targets. The myocardial tissue environment undergoes dynamic changes following infarction, involving both extracellular and intracellular alterations. These include inflammatory cascades, oxidative stress, mitochondrial dysfunction, and extracellular matrix remodeling — all of which contribute to cardiac injury and repair [3].

Targeting these mechanisms offers promising avenues for developing therapies that go beyond symptom management or mechanical reperfusion. This review aims to comprehensively explore the extracellular and intracellular therapeutic targets currently under investigation or in clinical use for the treatment and management of MI. By focusing on these molecular-level interventions, we seek to highlight novel strategies that could potentially improve patient outcomes and limit post-infarction complications.

PATHOPHYSIOLOGICAL MECHANISMS OF MYOCARDIAL INFARCTION

Myocardial infarction (MI) initiates a complex cascade of pathophysiological events that span from the initial ischemic insult to long-term cardiac remodelling [4]. These processes involve both extracellular and intracellular responses and are pivotal in determining the extent of myocardial damage and functional recovery [5]. Understanding these mechanisms is essential for identifying therapeutic targets that can attenuate injury and enhance repair.

MI typically begins with the rupture of an atherosclerotic plaque in a coronary artery, leading to thrombus formation and occlusion of blood flow. The resulting ischemia deprives myocardial tissue of oxygen and nutrients, causing a rapid shift from aerobic to anaerobic metabolism. This leads to ATP depletion, lactic acid accumulation, ionic imbalances, and increased intracellular calcium levels — early triggers of cellular injury and death [6].

While restoring blood flow through reperfusion therapies is essential, the sudden return of oxygen can paradoxically exacerbate tissue damage — a phenomenon known as

ischemia-reperfusion injury. IRI is characterized by the overproduction of reactive oxygen species (ROS), activation of the complement system, neutrophil infiltration, mitochondrial dysfunction, and calcium overload. These effects collectively worsen myocardial necrosis, increase infarct size, and contribute to adverse remodelling [7].

Inflammation plays a dual role in MI. In the acute phase, it is essential for clearing necrotic debris and initiating repair. However, excessive or unresolved inflammation can cause additional injury [8]. Following MI, damage-associated molecular patterns (DAMPs) released by dying cells activate innate immune receptors such as toll-like receptors (TLRs) and the NLRP3 inflammasome. This leads to the production of pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6) and recruitment of neutrophils and monocytes to the infarct zone [9]. Monocyte-derived macrophages can polarize into pro-inflammatory (M1) or anti-inflammatory/pro-reparative (M2) phenotypes. An imbalance between these subsets influences the healing outcome. Inappropriate or prolonged M1 dominance is associated with impaired repair and increased fibrosis [10].

Oxidative stress arises from an imbalance between ROS production and antioxidant defenses. Reperfusion triggers a burst of ROS generation, especially from dysfunctional mitochondria and NADPH oxidase enzymes. ROS not only damage proteins, lipids, and DNA but also modulate signaling pathways involved in inflammation and cell death [11].

Multiple cell death mechanisms are activated during and after MI [12]. The predominant form of cell death in the ischemic core is necrosis, resulting from severe energy depletion and ionic imbalance. Necrotic cells lose membrane integrity, leading to the uncontrolled release of intracellular contents, which in turn amplifies the local inflammatory response [13]. Surrounding the necrotic zone, cardiomyocytes undergo apoptosis, a form of programmed cell death characterized by caspase activation, DNA fragmentation, and cell shrinkage without eliciting inflammation [14]. In recent years, necroptosis has emerged as another regulated form of cell death, particularly relevant during ischemia-reperfusion injury. This pathway involves receptor-interacting protein kinases RIPK1 and RIPK3, along with mixed lineage kinase domain-like protein (MLKL), and results in a controlled form of membrane rupture [15]. Autophagy, a process of lysosome-mediated degradation of cellular components, is also activated during myocardial infarction. While moderate autophagy may serve a protective role by removing damaged organelles and proteins, excessive or dysregulated autophagy can contribute to cardiomyocyte loss [16]. The interplay between these cell death pathways determines the extent of myocardial damage and represents a critical area for therapeutic intervention aimed at preserving cardiac function.

Following infarction, the extracellular matrix undergoes dynamic remodeling to replace necrotic tissue with fibrotic scar. Matrix metalloproteinases (MMPs) are upregulated and degrade existing ECM components. This degradation is necessary for immune cell migration but can also destabilize the infarcted wall and promote ventricular dilation [17]. TGF-β is a key mediator of fibrosis, promoting fibroblast-to-myofibroblast transition and collagen deposition. Chronic activation of this pathway contributes to stiffening of the myocardium and impaired contractile function [18].

Long-term consequences of MI include changes in the size, shape, and function of the left ventricle — termed ventricular remodeling. Persistent inflammation, fibrosis, and loss of viable cardiomyocytes lead to reduced systolic function, arrhythmias, and eventual progression to heart failure. These processes are influenced by both systemic neurohormonal activation (e.g., RAAS, sympathetic nervous system) and local molecular events [19].

THERAPEUTIC TARGETS FOR THE MANAGEMENT OF MYOCARDIAL INFARCTION

Extracellular Therapeutic Targets

The extracellular environment of the myocardium plays a pivotal role in orchestrating the body's response to myocardial infarction (MI). It is within this compartment that critical signals are exchanged between dying cardiomyocytes, infiltrating immune cells, fibroblasts, and vascular elements. These signals not only drive the progression of tissue injury but also dictate the quality and efficiency of the reparative process [20]. Therefore, targeting extracellular mediators offers a valuable strategy to modulate pathological responses and promote myocardial healing.

One of the most immediate responses following myocardial infarction is the robust activation of the inflammatory cascade, largely mediated by extracellular pro-inflammatory cytokines and chemokines [21]. Among these, interleukin-1β (IL-1β) plays a central role by initiating and amplifying the inflammatory response through the activation of endothelial cells and the recruitment of leukocytes into the infarcted tissue. Persistently elevated IL-1β levels can extend myocardial damage and impair healing, whereas its inhibition has been associated with reduced infarct size and improved ventricular function [22]. Similarly, interleukin-6 (IL-6), produced by various immune and non-immune cells, drives systemic inflammation, promotes adverse cardiac remodeling, and correlates with worse clinical outcomes in MI patients. Reducing IL-6 activity has the potential to mitigate chronic inflammation and subsequent structural deterioration [23]. Tumor necrosis factor-alpha (TNF-α), another key cytokine, contributes to cardiomyocyte apoptosis, endothelial dysfunction, and contractile impairment. Although complete blockade of TNF-α has produced mixed results in heart failure trials, selective modulation of its signaling axis could attenuate inflammation without interfering with necessary repair mechanisms [24].

As the inflammatory phase progresses, the extracellular matrix (ECM) becomes a dynamic site of both degradation and regeneration. Matrix metalloproteinases (MMPs),

particularly MMP-2 and MMP-9, are secreted by neutrophils, macrophages, and fibroblasts and are responsible for degrading structural ECM proteins such as collagen and elastin. This activity facilitates immune cell infiltration and tissue clearance but, when excessive, contributes to infarct expansion, ventricular wall thinning, and mechanical instability [25]. Controlling MMP activity through upregulation of endogenous tissue inhibitors of metalloproteinases (TIMPs) or by direct inhibition of MMPs could help preserve ECM integrity, limit maladaptive remodeling, and reduce the risk of post-infarction heart failure [26].

Fibrosis, a hallmark of the reparative phase post-MI, is governed by a complex interplay of extracellular signals, among which transforming growth factor-beta (TGF-β) is paramount. TGF-β is released in response to tissue injury and promotes the activation and differentiation of cardiac fibroblasts into myofibroblasts, which are responsible for collagen synthesis and scar formation. While scar tissue is essential for maintaining structural integrity and preventing ventricular rupture, excessive or prolonged TGF-β signaling can result in diffuse interstitial fibrosis, impaired myocardial compliance, and diastolic dysfunction [27]. Targeting TGF-β or its downstream signaling components may reduce pathological fibrosis, preserve myocardial elasticity, and improve cardiac output without compromising necessary healing [28].

Vascular targets also represent an important subset of extracellular mediators in the post-MI setting [29]. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that promotes the proliferation and migration of endothelial cells, facilitating the formation of new capillaries in the infarct border zone. Enhancing VEGF activity could improve tissue perfusion, oxygen delivery, and metabolic support to the regenerating myocardium [30]. Conversely, unregulated angiogenesis may lead to fragile or non-functional vessels, highlighting the need for controlled modulation [31]. Nitric oxide (NO), primarily produced by endothelial nitric oxide synthase (eNOS), serves as a vasodilator and anti-inflammatory molecule. Restoring NO bioavailability in the infarcted heart could protect against endothelial dysfunction, reduce leukocyte adhesion, and enhance coronary blood flow [32]. In contrast, endothelin-1, a potent vasoconstrictor, is upregulated following MI and contributes to ischemia, oxidative stress, and vascular remodeling. Downregulating endothelin-1 or blocking its receptors could help normalize vascular tone and protect against adverse microvascular changes [33].

Emerging attention has also been given to extracellular vesicles (EVs), particularly exosomes, as novel mediators and potential modulators of the cardiac repair process. These vesicles, secreted by a variety of cell types including cardiomyocytes, fibroblasts, immune cells, and stem cells, carry a rich cargo of microRNAs, mRNAs, proteins, and lipids that reflect the physiological state of their parent cells [34]. In the context of MI, exosomes can influence inflammation, angiogenesis, apoptosis, and fibroblast activity. For instance, exosomes derived from mesenchymal stem cells (MSCs) have been shown to contain cardioprotective microRNAs such as miR-21 and miR-146a, which can modulate inflammatory signaling and promote cell survival [35]. Harnessing or engineering exosomes to selectively deliver regulatory molecules to the injured myocardium could serve as a non-cellular, highly targeted therapeutic approach.

Intracellular Therapeutic Targets

Within the injured myocardium, a wide array of intracellular processes is activated in response to ischemic stress, reperfusion injury, inflammation, and biomechanical strain. These processes influence the survival, death, regeneration, and functional adaptation of cardiomyocytes and other cardiac cells [36]. Intracellular targets represent an especially promising avenue for therapeutic intervention, as they allow modulation of fundamental cellular mechanisms involved in myocardial injury and repair. Several major intracellular compartments and signaling cascades have emerged as central to this effort, including pathways regulating cell survival and death, mitochondrial homeostasis, oxidative stress response, autophagy, calcium signaling, and transcriptional regulation [37].

Ischemic and reperfusion injury triggers an imbalance between pro-survival and pro-death signaling in cardiomyocytes [38]. Central to the survival response is the PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) pathway, which promotes cell survival by phosphorylating and inactivating pro-apoptotic factors such as Bad and caspase-9, and by enhancing nitric oxide synthesis via endothelial nitric oxide synthase (eNOS). Activation of PI3K/Akt also promotes glucose uptake, angiogenesis, and mitochondrial function — all of which are protective during and after MI [39].

In contrast, the MAPK (mitogen-activated protein kinase) family, including p38 MAPK and JNK (c-Jun N-terminal kinase), can be activated in response to stress and contribute to apoptosis and inflammation [40]. While ERK1/2 (extracellular signal-regulated kinases) may support cell survival and proliferation, chronic activation of p38 MAPK and JNK is associated with exacerbated myocardial damage [41]. Modulation of MAPK pathways can therefore help tilt the balance toward cardioprotection.

Apoptosis, one of the main contributors to cardiomyocyte loss in the peri-infarct region, is tightly regulated by the Bcl-2 family of proteins [42]. Pro-apoptotic members like Bax and Bak permeabilize the mitochondrial membrane, while anti-apoptotic members like Bcl-2 and Bcl-xL counteract this effect. Downstream, caspases such as caspase-3 execute the death program [43]. Inhibiting apoptotic mediators or boosting anti-apoptotic signals has the potential to preserve viable myocardium.

In addition to apoptosis, necroptosis has emerged as a regulated form of necrosis that contributes significantly to reperfusion injury. It is driven by the receptor-interacting protein kinases RIPK1 and RIPK3, which form a complex

leading to activation of MLKL (mixed lineage kinase domain-like protein) and membrane rupture [44]. Targeting components of the necroptotic machinery could provide a powerful means to reduce regulated necrosis while preserving innate immune signaling.

Mitochondria are central regulators of cardiomyocyte fate following MI, given their roles in energy production, calcium handling, and redox balance [45]. One of the key determinants of mitochondrial injury is the opening of the mitochondrial permeability transition pore (mPTP) — a non-specific pore in the inner mitochondrial membrane that opens under conditions of calcium overload and oxidative stress, leading to mitochondrial swelling, outer membrane rupture, and cell death [46]. Preventing mPTP opening during reperfusion is one of the most effective strategies for reducing infarct size in preclinical models.

Furthermore, the regulation of mitochondrial dynamics — including fission and fusion processes — influences mitochondrial integrity. Proteins such as Drp1 (dynamin-related protein 1) mediate fission, and excessive Drp1 activation has been associated with mitochondrial fragmentation and dysfunction after MI [47]. Conversely, promoting mitochondrial fusion through proteins like Mfn1/2 and OPA1 may help maintain mitochondrial function and prevent cardiomyocyte loss [48].

Ischemia-reperfusion injury leads to a sharp increase in the production of reactive oxygen species (ROS), which damage DNA, proteins, and lipids, and act as second messengers for inflammatory and cell death pathways. While low levels of ROS are essential for signaling, excessive ROS generation overwhelms antioxidant defenses and contributes to myocardial injury [49]. Key intracellular sources of ROS include mitochondrial respiratory complexes, NADPH oxidases (NOX2, NOX4), and xanthine oxidase [50]. Upregulation of antioxidant defense systems, such as those governed by Nrf2 (nuclear factor erythroid 2-related factor 2), is crucial for neutralizing ROS and protecting myocardial tissue. Nrf2 activates the transcription of detoxifying and antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). Enhancing this pathway can improve redox homeostasis and reduce infarct expansion [51].

Autophagy is a lysosome-dependent degradation process that recycles damaged organelles and proteins. In the context of MI, autophagy serves a protective role by removing dysfunctional mitochondria (mitophagy), limiting ROS accumulation, and maintaining energy homeostasis [52]. However, prolonged or excessive autophagy may lead to autophagic cell death and tissue loss. Key regulators of autophagy include Beclin-1, LC3-II, and ATG (autophagy-related) proteins, all of which coordinate autophagosome formation and degradation [53]. The mTOR (mammalian target of rapamycin) pathway is a major inhibitor of autophagy, and its suppression under ischemic stress allows autophagic activation. Fine-tuning autophagy — enhancing it in the acute phase while limiting it chronically — is critical for myocardial recovery [54].

Disruption of calcium homeostasis is a hallmark of ischemic and reperfusion injury. During ischemia, ATP depletion impairs the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) pump, reducing calcium reuptake and contributing to cytosolic calcium overload. This triggers hypercontracture, mitochondrial dysfunction, and activation of calcium-dependent proteases such as calpains [55]. Restoration of proper calcium cycling by enhancing SERCA2a function or stabilizing ryanodine receptors (RyR2) can improve contractility and reduce arrhythmogenic risk. In fact, impaired calcium handling contributes not only to contractile dysfunction but also to delayed afterdepolarizations and post-MI arrhythmias, making this a critical therapeutic target [56].

Beyond immediate signaling events, long-term changes in gene expression after MI are governed by transcription factors and epigenetic modifications [57]. Transcription factors such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) mediate inflammatory gene expression and are activated by DAMPs and cytokines. Persistent NF-κB activation contributes to chronic inflammation and adverse remodelling [58]. Epigenetic modulators — including histone deacetylases (HDACs), DNA methyltransferases (DNMTs), and non-coding RNAs (e.g., microRNAs) — fine-tune gene expression in response to ischemic stress [59]. For example, miR-21 regulates apoptosis and fibrosis, while miR-199a has been shown to enhance cardiomyocyte proliferation [60]. Modulating these intracellular regulators provides a sophisticated level of control over cellular fate and function during MI recovery.

In addition to classical oxidative stress defenses and mitochondrial regulatory pathways, several inducible cytoprotective systems are activated in cardiomyocytes to enhance cellular resilience during and after myocardial infarction. A central component of this response is the heme oxygenase-1 (HO-1) enzyme, which is upregulated in the ischemic myocardium and catalyzes the degradation of free heme into biliverdin, carbon monoxide (CO), and ferrous iron [61]. These byproducts have potent protective effects—biliverdin and bilirubin scavenge reactive oxygen species (ROS), CO acts as an anti-inflammatory and vasodilatory signaling molecule, and iron is neutralized by ferritin to prevent Fenton-mediated oxidative damage [62]. HO-1 expression is primarily regulated by the transcription factor Nrf2, which also induces other antioxidant genes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, forming a coordinated defense against oxidative injury [63]. Complementing this system, sirtuins (particularly SIRT1 and SIRT3) act as NAD^+-dependent deacetylases that modulate mitochondrial metabolism, suppress ROS generation, enhance autophagy, and inhibit pro-apoptotic signaling [64]. Another crucial layer of inducible protection is provided by heat shock proteins (e.g., HSP70, HSP27), which are upregulated in response to stress and function as molecular chaperones to stabilize protein conformation, prevent aggregation, and inhibit caspase-mediated apoptosis [65]. Additionally, thiol-based redox regulators such as thioredoxin and peroxiredoxins

play pivotal roles in maintaining cellular redox balance and directly regulating cell survival pathways by suppressing oxidative and inflammatory signals [66]. Together, these inducible cytoprotective networks operate in synergy to limit cardiomyocyte death, mitigate ischemia-reperfusion injury, and support myocardial recovery, making them highly attractive targets for therapeutic intervention.

EMERGING THERAPIES

Conventional therapies for myocardial infarction primarily aim to limit infarct size, prevent adverse remodeling, and manage heart failure symptoms. However, they do not address the irreversible loss of cardiomyocytes and functional myocardium that occurs after infarction. To overcome this limitation, recent advances have explored regenerative and emerging therapeutic strategies that focus on replacing lost cells, reprogramming injured tissue, and delivering targeted molecular therapies [67]. These approaches harness principles from stem cell biology, gene therapy, RNA modulation, tissue engineering, and nanotechnology.

One of the most explored strategies in cardiac regeneration is the use of stem cells to replenish lost cardiomyocytes and support tissue repair. Multiple cell types have been investigated, including bone marrow-derived mononuclear cells, mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), induced pluripotent stem cells (iPSCs), and embryonic stem cell-derived cardiomyocytes [68]. These cells can promote regeneration either by direct differentiation into cardiomyocyte-like cells or through paracrine signaling, whereby secreted factors modulate inflammation, promote angiogenesis, and recruit endogenous repair pathways [69]. Despite promising preclinical findings, clinical trials have shown modest functional improvement, likely due to poor cell retention, low engraftment rates, immune rejection, and risk of arrhythmias. Innovations such as tissue-engineered cardiac patches, cell preconditioning, and biomaterial scaffolds aim to enhance the efficacy and safety of cell-based therapy [70].

Gene therapy offers the possibility to modulate disease at the genetic level, either by replacing dysfunctional genes, enhancing protective genes, or silencing pathological ones [71]. Vectors such as adeno-associated viruses (AAVs) have been used to deliver therapeutic genes to the heart. For instance, SERCA2a gene transfer aimed to restore calcium handling in failing hearts, though clinical results have been mixed [72]. Other strategies focus on reprogramming fibroblasts into cardiomyocyte-like cells by introducing transcription factors such as Gata4, Mef2c, and Tbx5 (GMT) [73]. These approaches could potentially regenerate myocardium in situ, though challenges remain with efficiency, safety, and delivery.

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have emerged as critical regulators of cardiomyocyte survival, inflammation, fibrosis, and angiogenesis. For example, miR-21 is implicated in fibrotic remodeling, while miR-199a has been shown to induce cardiomyocyte proliferation [74]. Modulation of these RNAs through antagomirs (inhibitors) or mimics offers a powerful, sequence-specific therapeutic approach [75]. Moreover, mRNA-based therapies, such as those encoding VEGF or cardioprotective proteins, can be delivered transiently to stimulate reparative pathways without genomic integration. These modalities are rapidly advancing, supported by the success of mRNA platforms in other fields (e.g., vaccines) [76].

As a cell-free alternative to stem cell therapy, extracellular vesicles (EVs) — particularly exosomes — are being explored for their ability to deliver cardioprotective cargo such as miRNAs, mRNAs, and proteins [77]. EVs secreted by MSCs or cardiac progenitor cells can modulate inflammation, enhance angiogenesis, and promote cell survival. Because they are smaller, less immunogenic, and easier to store than cells, exosomes may offer improved safety and logistical advantages. Engineering EVs to carry customized therapeutic molecules or to home to ischemic tissue is a promising and rapidly evolving field [78].

To physically replace or reinforce damaged myocardium, tissue engineering approaches have been developed using biomaterial scaffolds, hydrogels, and cardiac patches embedded with cells or bioactive factors [79]. These constructs can be designed to mimic the extracellular matrix, provide mechanical support, and facilitate integration with host tissue. Injectable biomaterials, such as decellularized matrix gels, can also be delivered minimally invasively to modulate post-MI healing [80].

Nanoparticles offer a platform for precise delivery of drugs, genes, or RNAs to the infarcted myocardium, minimizing systemic side effects and enhancing therapeutic efficiency [81]. These carriers can be engineered for responsiveness to pH, enzymes, or oxidative stress, ensuring cargo release in the infarct zone. Additionally, biomimetic nanoparticles coated with cardiac cell membranes or homing peptides can achieve enhanced targeting [82]. Nanotechnology is particularly well-suited for RNA delivery, enabling effective intracellular uptake and endosomal escape [83].

Though still in early stages, CRISPR/Cas9-based gene editing offers the potential for precise, permanent correction of pathogenic gene mutations associated with myocardial dysfunction or remodelling [84]. Approaches being explored include epigenetic editing, gene silencing, and activation of endogenous regenerative programs. Safety, off-target effects, and delivery remain key challenges before clinical translation [85].

CHALLENGES IN TRANSLATING MOLECULAR TARGETS TO THERAPY

Despite major advancements in identifying molecular targets involved in myocardial infarction, the transition from preclinical success to clinically effective therapies remains fraught with challenges. These barriers span the full translational spectrum — from biological complexity and target specificity, to drug delivery, variability in patient responses, safety concerns, and regulatory hurdles [86].

Understanding and addressing these challenges is crucial for the development of truly effective, personalized treatments.

A major limitation lies in the biological complexity and redundancy of signaling networks within the heart [87]. Many extracellular and intracellular pathways are highly interconnected and context-dependent; for example, cytokines like TNF-α or TGF-β play both damaging and reparative roles depending on the timing, dosage, and cellular context. This dual nature makes selective modulation extremely difficult, as overly aggressive inhibition may impair necessary healing, while insufficient inhibition may allow pathological processes to persist [88]. Moreover, compensatory pathways often become activated in response to single-target interventions, reducing the long-term efficacy of therapy [89].

Another substantial challenge is tissue-specific and temporal delivery of therapeutics. Many molecular targets, particularly intracellular ones, require precise spatial and temporal regulation for optimal effect [90]. Achieving targeted drug delivery to the infarcted myocardium — especially for molecules like miRNAs, siRNAs, or proteins — remains technologically difficult due to rapid clearance, immune recognition, or poor cellular uptake. While nanoparticles and biomaterials offer promising solutions, these technologies still face scalability, safety, and regulatory issues [91].

Heterogeneity among patients is another obstacle. Variations in age, genetics, comorbidities (e.g., diabetes, hypertension), sex, and infarct size can significantly influence molecular signaling and treatment responses [92]. A therapy that is beneficial in one population may be ineffective or even harmful in another. This inter-individual variability complicates the design of universal molecular therapies and emphasizes the need for personalized or stratified approaches, possibly guided by genomic and proteomic profiling [93].

Model limitations also contribute to translational failure. Most molecular targets are identified and validated in small animal models (e.g., rodents) under controlled experimental conditions that do not fully mimic the chronic, multifactorial nature of human MI. Factors such as immune system differences, heart size, coronary anatomy, and disease progression all influence translational accuracy [94]. As a result, therapies that demonstrate efficacy in animals often fail to reproduce those results in large animal models or human clinical trials.

Furthermore, safety and off-target effects are significant concerns for intracellular modulation, especially with interventions involving gene editing, RNA interference, or protein overexpression [95]. Even subtle alterations in gene expression or redox balance can lead to unintended consequences, including arrhythmias, immune activation, or oncogenesis [96]. Long-term follow-up and rigorous safety assessments are essential for such approaches but add to the complexity and cost of clinical development.

From a regulatory and commercial standpoint, developing molecularly targeted therapies also faces stringent approval pathways, intellectual property barriers, and high development costs. Complex biologics, cell-based therapies, or RNA molecules require specialized manufacturing and storage, limiting their accessibility and scalability [97]. Additionally, integration into current clinical practice — which is largely protocol-driven and standardized — poses a practical hurdle for personalized molecular therapies

Finally, there is a pressing need for biomarkers and imaging tools that can dynamically monitor target engagement, therapeutic response, and disease progression. Without reliable indicators of efficacy, clinical trials may struggle to detect true therapeutic benefit or stratify responders [98].

FUTURE DIRECTIONS

The future of myocardial infarction (MI) therapy is moving rapidly toward precision medicine, driven by a deeper understanding of molecular mechanisms and advances in biotechnology. Multi-omics approaches, including genomics, proteomics, and metabolomics, are uncovering patient-specific molecular profiles that could guide stratified and individualized treatment strategies [99]. These data, when combined with single-cell sequencing and spatial transcriptomics, offer unprecedented insights into dynamic cellular processes within the infarcted heart [100].

The integration of artificial intelligence (AI) and machine learning is transforming risk prediction, therapy selection, and treatment monitoring. These tools can process vast clinical and molecular datasets to identify novel targets and predict therapeutic outcomes, enabling computationally guided precision cardiology [101].

Looking ahead, MI treatment will likely adopt phase-specific interventions, tailored to acute, subacute, and chronic stages of the disease. Real-time monitoring tools, including molecular imaging and biosensors, will be essential for dynamically assessing target engagement and therapeutic response [102].

Combinatorial therapies targeting multiple pathways—such as inflammation, fibrosis, and regeneration—are expected to offer superior outcomes over monotherapies [103]. In parallel, innovations in RNA-based therapeutics, CRISPR gene modulation, and epigenetic editing are expanding the therapeutic toolkit, offering precise control of gene expression with reduced long-term risk [104].

Finally, tissue engineering and 3D bioprinting may enable physical restoration of damaged myocardium through bioengineered patches and constructs that mimic native cardiac tissue [105].

CONCLUSION

Myocardial infarction remains a major clinical challenge, with current therapies largely focused on restoring perfusion and mitigating damage rather than promoting true myocardial recovery. This review has highlighted the

vast array of extracellular and intracellular targets that contribute to the complex cascade of events following MI — from inflammation, oxidative stress, and cell death to fibrosis, remodeling, and regeneration. Extracellular targets such as cytokines, matrix metalloproteinases, and growth factors play pivotal roles in shaping the tissue microenvironment, while intracellular mechanisms involving mitochondrial function, redox regulation, autophagy, and gene expression critically determine cell fate and functional recovery.

Although numerous molecular targets have been identified, their successful translation into clinical therapies is often hindered by biological complexity, delivery challenges, and patient variability. However, the emergence of precision medicine, multi-omics-guided stratification, and advanced therapeutic platforms — including RNA-based drugs, gene editing tools, and tissue-engineered constructs — is rapidly transforming the treatment landscape.

Ultimately, an integrative therapeutic approach that combines molecular specificity, stage-adapted timing, and personalized delivery strategies holds the greatest promise for reshaping MI management. Continued interdisciplinary research bridging molecular biology, bioengineering, and clinical cardiology will be essential to move beyond damage control toward true cardiac repair and regeneration.

ABBREVIATIONS

AAVs - adeno-associated viruses, ATG - antithymocyte globulin, CPCs - cardiac progenitor cells, DAMPs - damage-associated molecular patterns, DNMTs - DNA methyltransferases, Drp1 - dynamin-related protein 1, eNOS - endothelial nitric oxide synthase, ERK1/2 - extracellular signal-regulated kinases, EVs - extracellular vesicles, GPx - glutathione peroxidase, HDACs - histone deacetylases, HSP27 - heat shock protein 27, HSP70 - heat shock protein 70, iPSCs - induced pluripotent stem cells, IRI - ischemia-reperfusion injury, LC3 - microtubule-associated protein 1 light chain 3, lncRNAs - long non-coding RNAs MAPK - mitogen-activated protein kinase, Mfn1- mitofusin 1, Mfn2- mitofusin 2, MI - Myocardial infarction, miRNAs – microRNAs, MLKL - mixed lineage kinase domain-like protein, MMPs - matrix metalloproteinases, mPTP - mitochondrial permeability transition pore, mTOR - mammalian target of rapamycin, NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells, NLRP3 - NOD-like receptor protein 3, NO - nitric oxide, Nrf2 - nuclear factor erythroid 2-related factor 2, OPA1 - optic atrophy protein 1, PCI - percutaneous coronary intervention, PI3K/Akt - phosphoinositide 3-kinase/protein kinase B, RIPK1 - receptor-interacting protein kinases 1, RIPK3 - receptor-interacting protein kinase 3, ROS - reactive oxygen species, RyR2 - ryanodine receptor 2, SERCA2a - Sarcoplasmic/Endoplasmic Reticulum Ca2+ ATPase 2a, SIRT1 - sirtuin 1, SIRT3 - sirtuin 3, SOD - superoxide dismutase, TGF-β - transforming growth factor-beta, TLRs - toll-like receptors, TNF-α - tumor necrosis factor-alpha, VEGF - vascular endothelial growth factor.

AUTHOR CONTRIBUTION STATEMENT

HK conceptualized the review, conducted the literature search, organized the content structure, and drafted the manuscript. AM provided critical insights, refined the manuscript content, and approved the final version for submission. All content was critically reviewed and revised by the authors to ensure accuracy and alignment with the study's objectives. Both authors have read and agreed to the published version of the manuscript.

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