Review Article

Endothelial-to-Mesenchymal Transition in Post-Myocardial Infarction Fibrosis: A Maladaptive but Targetable Pathway

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Article Info

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Abstract

Myocardial infarction (MI) initiates a healing response in which fibroblasts and other cells deposit extracellular matrix to form a stabilizing scar. This scarring is essential for preventing ventricular rupture, yet when excessive or diffuse, it becomes maladaptive: fibrosis stiffens the ventricle, impairs filling, and drives progression to heart failure. Traditional antifibrotic approaches, such as broad TGF-β blockade or collagen cross-linking inhibition, have largely failed because fibroblast activity is required for early scar integrity, while established fibrosis is difficult to reverse.

This review highlights endothelial-to-mesenchymal transition (EndMT) as a distinct and underappreciated contributor to post-MI fibrosis. Experimental studies indicate that EndMT supplies 10–30% of fibroblast-like cells, and evidence of EndMT is present in human ischemic cardiomyopathy. Unlike fibroblast-driven repair, EndMT is maladaptive in the adult heart: it promotes fibrosis without enhancing scar strength and reduces endothelial cell numbers, leading to microvascular rarefaction and impaired perfusion.

EndMT is regulated by discrete, targetable pathways-including TGF-β/Smad, Notch, Wnt/β-catenin, HIF-1α, and microRNA networks (e.g., miR-21, miR-29)-and exhibits partial reversibility. This opens opportunities for time-limited, pathway-specific interventions during the proliferative phase of healing. Emerging diagnostic tools, such as extracellular volume mapping, fibroblast activation protein PET, collagen peptide assays, and circulating fibrosis-related microRNAs, provide clinical means to detect EndMT activity.

By integrating mechanistic insights with advances in molecular imaging and biomarker profiling, this review proposes EndMT-directed, biomarker-guided therapies as a precision strategy to limit maladaptive fibrosis, preserve vascular networks, and improve outcomes after MI.

Introduction

Myocardial infarction (MI) is among the leading causes of morbidity and mortality worldwide, with millions of patients each year surviving the acute ischemic event but facing long-term complications related to adverse remodeling of the heart. The healing process after MI is marked by a tightly regulated cascade that ultimately replaces necrotic myocardium with a fibrotic scar. This fibrotic tissue is crucial for survival, as it prevents ventricular wall rupture and preserves structural integrity during systole [1,2]. However, fibrosis has both protective and detrimental aspects. When scar formation extends excessively beyond the infarct zone or when interstitial collagen deposition accumulates disproportionately, the result is increased ventricular stiffness, impaired diastolic filling, arrhythmogenic substrate, and progressive heart failure [1,2]. This paradox, fibrosis as both necessary and detrimental, has framed decades of research into myocardial repair.

Much of the literature has focused on the role of cardiac fibroblasts. Fibroblasts are the most abundant non-myocyte cell type in the heart and the principal source of extracellular matrix (ECM) proteins. In response to injury, fibroblasts become activated through signals such as transforming growth factor-β (TGF-β), angiotensin II, and inflammatory cytokines, transitioning into contractile, α-smooth muscle actin (α-SMA)–positive myofibroblasts that deposit collagens I and III [2,7]. These myofibroblasts are necessary for early scar formation; without them, ventricular rupture is inevitable. This central role has naturally led to a fibroblast-centric paradigm in both basic research and therapeutic development. However, this paradigm may be too narrow. The infarcted heart is a highly dynamic microenvironment where multiple cell types contribute to remodeling, and recent advances have revealed that the mechanisms of fibrosis extend beyond resident fibroblasts. Other cellular sources of scar-forming myofibroblasts have been identified, but with variable contributions depending on species, model, and disease stage. These include epithelial-to-mesenchymal transition (EMT) from the epicardium, bone marrow–derived fibrocytes recruited into the injured myocardium, and perivascular cells such as pericytes and vascular smooth muscle cells [2,7]. Historically, these sources were considered minor or secondary, but a growing body of evidence suggests they may influence the quality and persistence of fibrosis in ways not captured by a purely fibroblast-centered view. Among these, EndMT has emerged as particularly significant. EndMT represents a process by which endothelial cells progressively downregulate endothelial markers (e.g., CD^{31}, VE-cadherin) and upregulate mesenchymal markers such as vimentin, fibronectin, and α-SMA, ultimately acquiring a migratory and matrix-secreting phenotype [8–10]. In the context of MI, this transition does more than add scar-forming cells; it simultaneously subtracts from the endothelial cell pool, reducing vascular density and impairing microcirculatory perfusion. This dual maladaptive effect, amplifying collagen deposition while promoting vascular rarefaction, suggests that EndMT may be a crucial but underappreciated driver of adverse remodeling.

Experimental lineage-tracing studies support this view. Zeisberg et al. demonstrated that in murine models, approximately one-quarter to one-third of fibroblast-like cells in the fibrotic myocardium originated from endothelial cells through EndMT [10]. Subsequent work confirmed that TGF-β is sufficient to induce this transition, while bone morphogenetic protein-7 (BMP-7) can oppose it [11]. Evidence of EndMT has since been observed across cardiovascular diseases in both animal models and human tissues [8,9,12], reinforcing its relevance beyond experimental limitations. Yet despite these insights, EndMT remains less visible in mainstream fibrosis research and has not been systematically integrated into post-MI therapeutic frameworks.

The limited progress in translation may be partly explained by the disappointing performance of broad anti-fibrotic therapies. Interventions targeting master regulators such as TGF-β or collagen cross-linking enzymes have failed in clinical trials, largely because they lacked selectivity and were poorly timed [1,7]. Fibroblast activity in the early phase of repair is essential for scar integrity; thus, global suppression during this window risks catastrophic rupture. Conversely, once the scar has matured, fibrosis is largely irreversible, and late interventions provide little functional recovery. These challenges highlight the need for a more careful approach that distinguishes between essential and unnecessary sources of fibrosis. In this regard, EndMT offers a unique therapeutic opportunity. Unlike fibroblasts, EndMT-derived cells are not required for scar stability. Their contribution is maladaptive, adding to fibrotic burden without providing structural benefit and simultaneously compromising vascular supply [8–10]. Moreover, EndMT is regulated by defined and targetable signaling pathways, including TGF-β/Smad, Notch, Wnt/β-catenin, hypoxia-inducible factor-1α, and microRNAs such as miR-21 and miR-29 [8–11]. These nodes provide potential entry points for selective therapies that could modulate EndMT without broadly impairing fibroblast-dependent repair.

Recent advances in imaging and biomarker technologies strengthen the translational potential of such an approach. Cardiac magnetic resonance imaging (MRI) with extracellular volume (ECV) mapping provides quantitative assessment of interstitial expansion and has proven more sensitive than late gadolinium enhancement for diffuse fibrosis [3,6]. Fibroblast activation protein (FAP) positron emission tomography (PET) imaging has emerged as another modality, allowing spatiotemporal visualization of fibroblast activity in vivo and demonstrating dynamic changes in activation after MI [13,14]. At the molecular level, circulating collagen turnover peptides and fibrosis-associated microRNAs, particularly elevated miR-21 and suppressed miR-29, are being developed as non-invasive biomarkers of fibrogenic activity [11]. Together, these tools make it feasible to detect excessive or persistent fibrotic activity and to stratify patients for targeted interventions.

Thus, these developments emphasize an important gap in current knowledge. Contemporary reviews and therapeutic strategies continue to emphasize fibroblast biology and broad anti-fibrotic approaches, which have consistently struggled in the MI setting due to lack of specificity and timing constraints [1,2,7]. By contrast, EndMT represents a non-essential but maladaptive pathway that contributes to fibrosis while simultaneously undermining vascular health. Its regulation by discrete signaling mechanisms, coupled with the availability of emerging imaging and biomarker tools, creates the foundation for a novel therapeutic paradigm. This review therefore seeks to reframe post-MI fibrosis as a process partly driven by endothelial plasticity and to highlight EndMT modulation as a selective, monitoring-guided, and time-limited strategy to reduce pathological fibrosis while preserving the essential role of fibroblasts in scar stability.

Overview of Post-MI Remodeling

Myocardial remodeling after infarction is a dynamic, multi-stage process that determines whether the ventricle recovers or progresses toward dysfunction. Each phase of healing is important for survival but carries risks when unbalanced. Understanding these stages, and the cellular contributors active within them, is critical to identifying therapeutic targets.

The inflammatory phase dominates the first several days following MI (days 0–4). Necrotic cardiomyocytes release danger-associated molecular patterns (DAMPs) such as high-mobility group box 1 and heat shock proteins, which activate complement cascades and Toll-like receptor signaling [15]. This initiates a robust influx of neutrophils, which not only phagocytose cellular debris but also release proteases and reactive oxygen species that can extend tissue injury if unchecked. Monocytes subsequently infiltrate and differentiate into macrophages, with M^1-like pro-inflammatory subtypes promoting clearance and M^2-like reparative subtypes fostering resolution [16]. Failure to transition from inflammation to repair leads to sustained matrix degradation, infarct expansion, and poor outcomes. Thus, while inflammation is necessary to clear necrotic tissue, its resolution is equally important to prevent excessive damage.

The proliferative phase (approximately weeks 1–3) represents the critical window in which infarct stabilization and fibrotic expansion are determined. In this stage, fibroblasts become the dominant effector cells. Activated by TGF-β, angiotensin II, endothelin-1, and inflammatory cytokines, fibroblasts differentiate into myofibroblasts characterized by α-smooth muscle actin (α-SMA) expression, enhanced contractility, and robust production of collagens I and III [17]. These cells form the backbone of the scar, supplying tensile strength that prevents ventricular rupture. However, fibroblast activity alone does not fully account for the heterogeneity of scar composition.

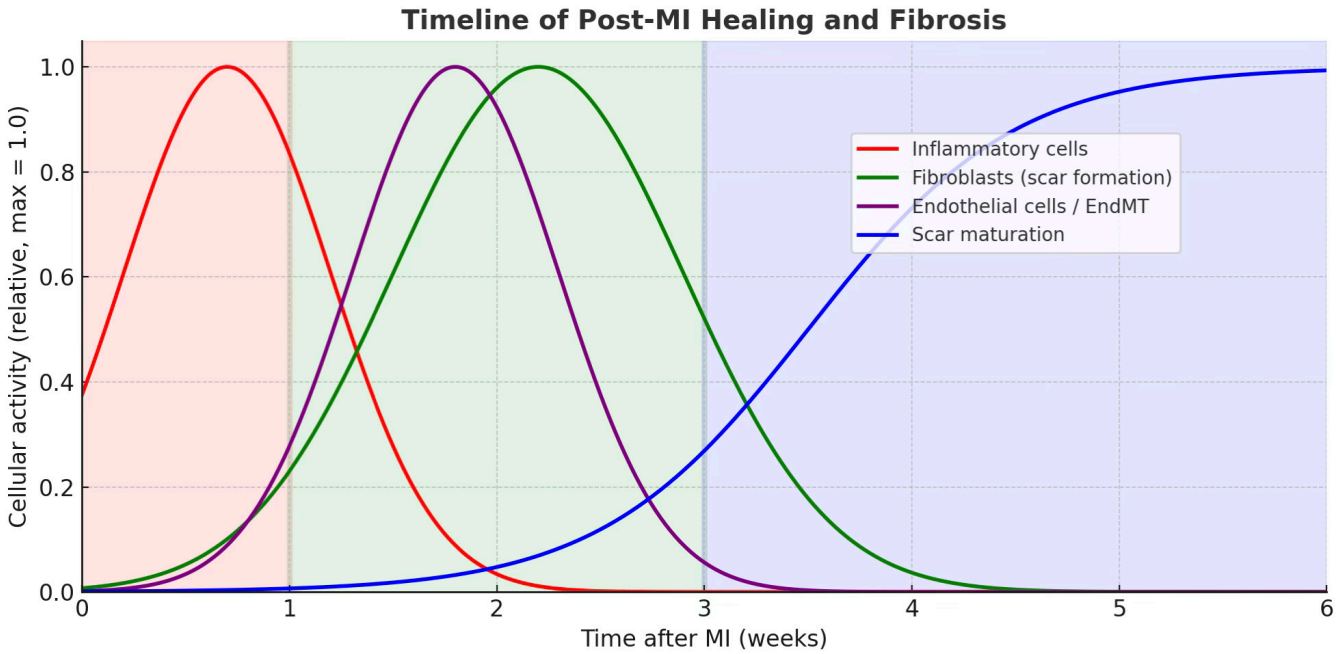
EndMT emerges during this same window, generating fibroblast-like cells of endothelial origin, as confirmed by lineage tracing [18]. EndMT contributes maladaptively by both increasing collagen-producing cells and reducing endothelial populations, impairing neovascularization when oxygen delivery is most needed. Unlike fibroblast-driven repair, which provides structural stability, EndMT-derived cells add fibrosis without proportional benefit-making this pathway an attractive therapeutic target. In parallel, angiogenesis supplies nutrients to the metabolically active scar, guided by VEGF and angiopoietins. Yet when EndMT predominates, endothelial loss restricts vessel growth, promotes hypoxia, and accelerates fibrosis. Thus, the proliferative phase represents a balance between reparative and maladaptive processes.

The maturation phase (from ~4–6 weeks) consolidates earlier changes. Myofibroblasts undergo apoptosis or inactivation, leaving behind an acellular scar. Collagen fibers cross-link and align, increasing tensile strength but reducing compliance [19]. At this point, the scar resists rupture, but stiffness predisposes to diastolic dysfunction. Because structural changes are essentially fixed, therapies after this stage have limited ability to reverse fibrosis.

Underlying all phases is the principle of extracellular matrix (ECM) homeostasis. In healthy myocardium, ECM accounts for ~20–25% of tissue volume, maintained by a balance between matrix metalloproteinases (MMPs), which degrade ECM, and tissue inhibitors (TIMPs), which prevent excessive breakdown [20]. After MI, this balance collapses: early MMP spikes destabilize the infarct wall [21], whereas subsequent TIMP activity and fibroblast-driven deposition overshoot into pathological fibrosis. Excess collagens I and III, fibronectin, and periostin stiffen the ventricle and impair function.

Together, these sequential phases reveal the proliferative stage as the key therapeutic window, where selective modulation of maladaptive processes such as EndMT may improve outcomes without compromising scar stability.

Figure 1: Timeline of Post-MI Healing and Fibrosis.



Schematic of cellular dynamics after myocardial infarction. Inflammation dominates days 0–4, followed by fibroblast activation and peak EndMT during weeks 1–3, driving scar formation and vascular loss. By weeks 4–6, maturation consolidates the scar through myofibroblast inactivation and collagen cross-linking. The overlap of fibroblast and EndMT activity highlights a potential therapeutic window.

Sources of Fibrosis After MI

Fibrosis after MI arises from multiple cellular origins, each contributing to the population of myofibroblasts that deposit extracellular matrix. Although resident cardiac fibroblasts dominate the reparative response, alternative sources, including endothelial-to-mesenchymal transition (EndMT), epicardial epithelial-to-mesenchymal transition (EMT), circulating fibrocytes, and perivascular cells, also participate to varying degrees.

Resident cardiac fibroblasts are the principal and indispensable source of scar-forming cells. In the healthy heart, fibroblasts maintain extracellular matrix turnover and structural integrity. Following MI, they are rapidly activated by TGF-β, angiotensin II, and pro-inflammatory cytokines, differentiating into myofibroblasts characterized by α-smooth muscle actin (α-SMA) expression and high collagen synthetic capacity [22]. These cells accumulate within the infarct, where they produce fibrillar collagens I and III, fibronectin, and periostin, which collectively form the structural scaffold that prevents wall rupture. Without fibroblast activation, repair fails and mortality from rupture is inevitable. Thus, fibroblasts are essential, but if they stay too active, they can cause excessive scarring and ventricular stiffening.

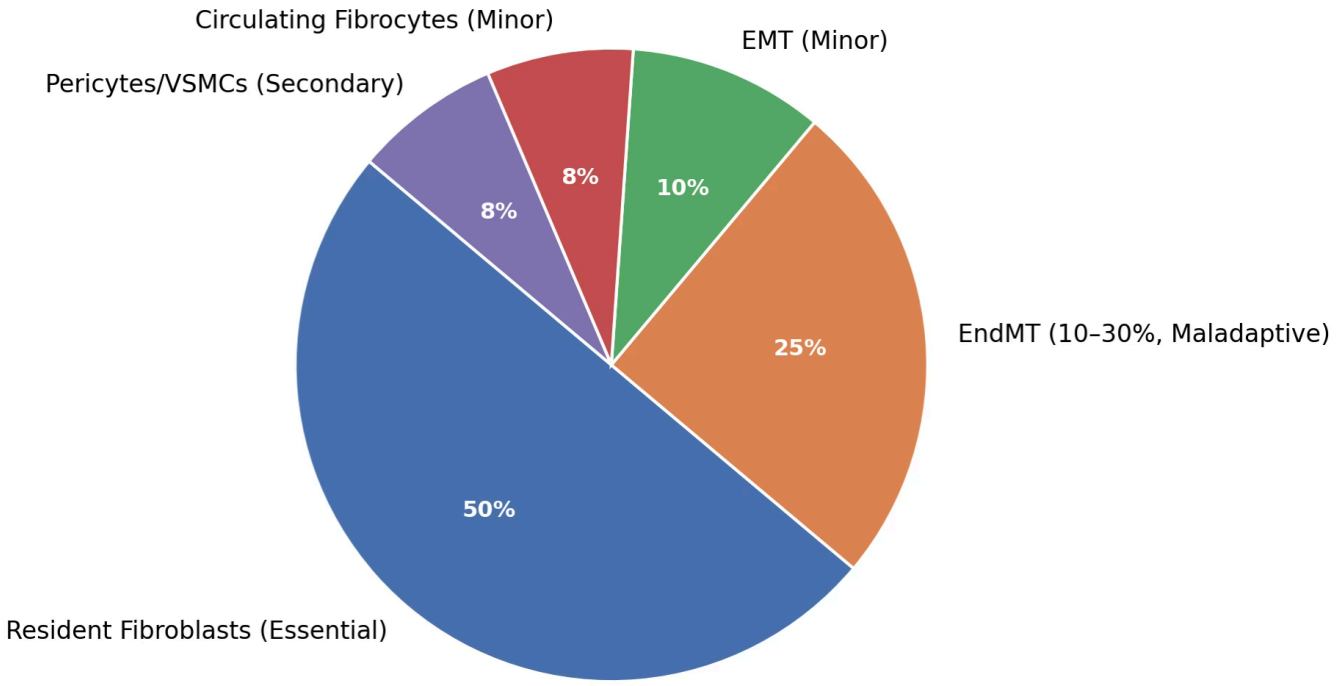
EndMT provides a distinct, maladaptive contribution to the fibrotic response. In EndMT, endothelial cells progressively lose endothelial identity markers such as VE-cadherin and CD^{31} while gaining mesenchymal markers including vimentin, fibronectin, and α-SMA [23]. Lineage-tracing studies in murine models have demonstrated that approximately 10–30% of fibroblast-like cells in the infarcted myocardium arise from EndMT [24]. Unlike fibroblasts, these cells are not required for structural integrity; instead, they amplify scar expansion while simultaneously depleting endothelial cells and impairing neovascularization. Human biopsy studies corroborate the presence of EndMT-derived cells in ischemic heart disease [10,12]. This dual effect, adding scar-forming cells while subtracting endothelial capacity, positions EndMT as a particularly maladaptive and therapeutically attractive target.

EMT represents another source of mesenchymal cells. During embryonic development, EMT is critical for forming the coronary vasculature and interstitial fibroblasts [25,26]. In adult hearts, epicardial cells retain a limited ability to undergo EMT after MI, giving rise to fibroblast-like cells. However, their contribution in adult mammalian models appears minor compared with fibroblasts and EndMT [27]. EMT therefore plays a developmental role but is less significant in the adult fibrotic response.

Circulating fibrocytes are bone marrow–derived cells that enter the circulation and migrate to sites of injury. They express hematopoietic markers such as CD^{45} along with mesenchymal proteins, and they are capable of producing collagen and other ECM components [28]. In the post-MI setting, fibrocytes typically contribute less than 10% of the scar-forming cell population [29]. Their role may be more supportive, interacting with inflammatory cells and fibroblasts rather than serving as major collagen producers.

Pericytes and vascular smooth muscle cells (VSMCs) can also differentiate into matrix-secreting myofibroblast-like cells under stress conditions. Pericytes, normally supportive cells that stabilize capillaries, have been observed to migrate and acquire mesenchymal characteristics in ischemic injury [30]. Similarly, VSMCs from coronary vessels may contribute to the fibrotic response, though their quantitative impact is relatively small [31]. These populations may become more relevant in chronic remodeling or hypertension-associated fibrosis but remain secondary compared to fibroblasts and EndMT.

Figure 2: Sources of fibroblasts in post-myocardial infarction (MI) fibrosis.



Pie chart showing that resident fibroblasts are the main source for scar stability, while EndMT contributes ~10–30% of fibroblast-like cells, driving maladaptive fibrosis and endothelial loss. Smaller contributions arise from EMT, circulating fibrocytes, and pericytes/VSMCs.

Biology of EndMT in the Heart

EndMT is a form of cellular plasticity in which endothelial cells gradually lose their vascular identity and acquire mesenchymal characteristics. Although EndMT is essential during embryonic development and has been described in vascular diseases such as pulmonary hypertension and atherosclerosis, its role in MI is particularly significant and mechanistically distinct [32,33]. The combination of excessive fibrosis and vascular rarefaction makes EndMT uniquely maladaptive in post-infarction remodeling [34].

In the infarcted heart, endothelial cells undergoing EndMT downregulate classical endothelial markers such as VE-cadherin, PECAM-1 (CD[31]), and von Willebrand factor while gaining mesenchymal proteins including α-smooth muscle actin (α-SMA), vimentin, fibronectin, and collagen type I [32]. Morphologically, this corresponds to a transition from a cobblestone monolayer to an elongated spindle-shaped form with enhanced contractility and migratory capacity [33]. Many cells remain in hybrid states that co-express endothelial and mesenchymal markers, as shown in biopsies from human ischemic cardiomyopathy [35]. These intermediate phenotypes highlight that EndMT is not a discrete process but a continuum. This plasticity has profound therapeutic implications because cells in partial transition may still be reversible if interventions are applied during the right phase of infarct healing.

The timing and distribution of EndMT after MI emphasize its maladaptive role. It occurs predominantly during the proliferative phase, roughly one to three weeks after infarction, when fibroblast activity is peaking and the scar is consolidating [15,36]. Spatially, EndMT is concentrated in the border zone, where viable but stressed myocardium is exposed to hypoxia, inflammatory infiltration, abnormal mechanical strain, and progressive extracellular matrix stiffening. This is the very region where angiogenesis is most critically required to preserve surviving myocardium. By diverting endothelial cells toward a mesenchymal program, EndMT simultaneously adds to the fibrotic burden and undermines vascular repair, thereby shifting the process away from regeneration.

The infarct microenvironment provides a combination of signals that cooperate to induce EndMT. Inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, secreted by neutrophils and macrophages, together with

damage-associated molecular patterns released from necrotic cardiomyocytes, activate NF-κB signaling in endothelial cells [37]. NF-κB not only promotes inflammatory gene expression but also sensitizes endothelial cells to transforming growth factor-β (TGF-β), the canonical driver of EndMT. TGF-β is produced by activated fibroblasts, myofibroblasts, macrophages, and can also be released from latent stores in the extracellular matrix [37,41]. Notch ligands such as Jagged and Delta-like proteins, expressed on fibroblasts, immune cells, and stressed endothelial cells, activate endothelial Notch receptors, and release the Notch intracellular domain, which synergizes with Smads to reinforce mesenchymal differentiation [42]. Wnt ligands, including $Wnt^{3}a$ and $Wnt^{5}a$, are secreted by myofibroblasts, macrophages, and endothelial cells under hypoxic stress and bind Frizzled/LRP receptors, stabilizing β-catenin and facilitating its nuclear translocation where it partners with Smads to drive profibrotic transcription [43]. Hypoxia in the border zone stabilizes hypoxia-inducible factor-1α (HIF-1α), which directly induces transcription factors such as Snail and Twist [38]. At the same time, disturbed shear stress and cyclic strain are sensed by mechanosensory complexes composed of PECAM-1, VE-cadherin, $VEGFR^{2}$, and $Piezo^{1}$, which activate MAPK, $PI^{3}K$/ERK, and Rho/ROCK cascades [39]. As the scar matures, deposition and cross-linking of collagen stiffen the matrix; integrins and focal adhesions detect this stiffening and activate YAP/TAZ, which further reinforce mesenchymal gene expression [40]. MicroRNAs add another layer of regulation: miR-21, induced by TGF-β and inflammatory cues, suppresses $Smad^{7}$ and thereby amplifies $Smad^{2}$/3 activity; miR-29 normally restrains fibrosis by targeting collagen transcripts but is downregulated after MI; and endothelial-enriched miRNAs such as miR-126 and members of the miR-200 family help maintain vascular identity but are suppressed under hypoxia and inflammation, favoring EndMT [45].

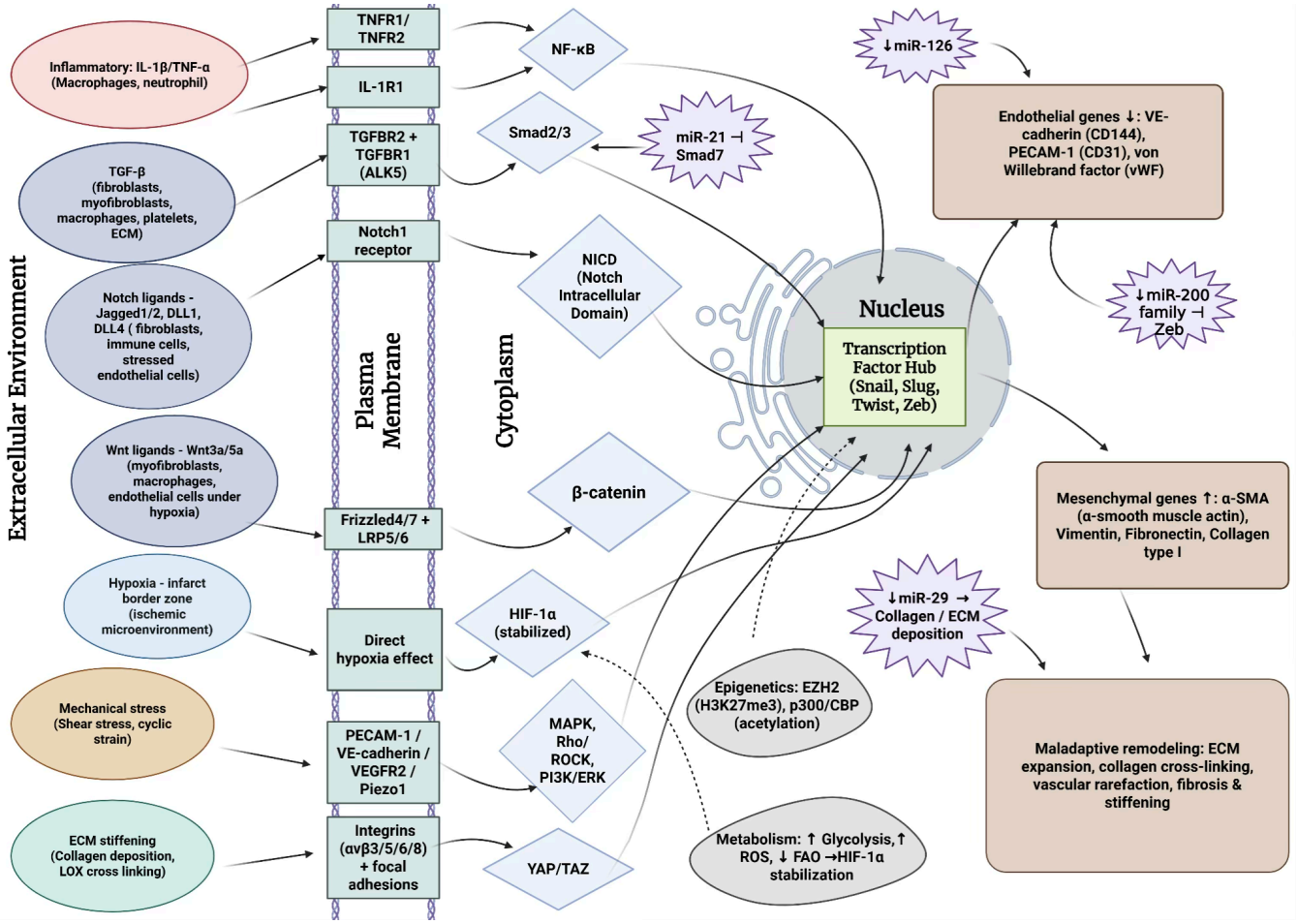
At the molecular level, these diverse inputs converge on a limited set of master transcription factors. The TGF-β/$Smad^{2}$/3 axis induces Snail, Slug, Twist, and Zeb, which directly repress endothelial genes and activate mesenchymal ones [41]. Notch and Wnt signaling cooperate with Smads to reinforce the transcriptional switch [42,43], while NF-κB and HIF-1α amplify inflammatory and hypoxic responses [37,38]. MAPK, $PI^{3}K$/ERK, and Rho/ROCK cascades remodel the actin cytoskeleton and drive motility [44]. Collectively, these signals establish a self-sustaining transcriptional network that decisively shifts endothelial cells toward the mesenchymal state.

The stability of this program is further reinforced by epigenetic and metabolic changes. Endothelial genes are silenced through promoter methylation and repressive histone modifications such as $H^{3}K^{27}$ trimethylation mediated by EZH^{2}, while mesenchymal loci are activated by histone acetylation through p^{300}/CBP [46]. Snail and Twist recruit these chromatin modifiers to enforce silencing of endothelial identity. Metabolically, endothelial cells shift from their typical reliance on glycolysis and fatty acid oxidation to enhanced glycolysis with reduced fatty acid oxidation. This metabolic reprogramming increases reactive oxygen species, which stabilize HIF-1α and further enhance TGF-β and Wnt signaling [47]. Together, these epigenetic and metabolic adaptations create a feed-forward loop that locks cells into a mesenchymal fate even after the initiating inflammatory triggers have subsided.

The tissue-level consequences of EndMT in MI are consistently maladaptive. EndMT-derived cells secrete collagens I and III, fibronectin, periostin, and other extracellular matrix proteins that expand the fibrotic matrix [48]. They promote collagen cross-linking through lysyl oxidase activity, which stiffens the ventricular wall [49], while the loss of endothelial cells reduces capillary density and leads to vascular rarefaction. This impairs oxygen delivery, exacerbates hypoxia, and sustains EndMT, creating a vicious cycle of fibrosis and ischemia. Thus, unlike fibroblast-driven scar formation, which is required to prevent rupture, EndMT-derived fibrosis adds stiffness without providing mechanical benefit and simultaneously undermines tissue perfusion, thereby accelerating progression from infarct healing to chronic heart failure.

A key therapeutic insight is that EndMT appears to be partially reversible. Studies in renal and pulmonary fibrosis show that bone morphogenetic protein-7 and other counter-regulatory signals can reverse TGF-β–induced EndMT and restore endothelial characteristics [52]. This raises the possibility that in the infarcted heart, EndMT-derived or hybrid cells could be rescued if targeted during the proliferative phase. Such interventions might prevent the generation of new mesenchymal cells while rescuing those in partial transition, preserving the vasculature and permitting fibroblast-driven scar stabilization to proceed. Unlike broad antifibrotic therapies that indiscriminately block fibroblast activation and risk destabilizing the scar, approaches directed at EndMT may provide specificity and reversibility. This makes EndMT not only a uniquely maladaptive process but also a uniquely targetable one, opening the door to therapeutic strategies that move beyond traditional antifibrotic approaches.

Figure 3: Molecular pathways driving EndMT after MI.



Signals from inflammation, TGF-β, Notch, Wnt, hypoxia, mechanical stress, and ECM stiffening converge on endothelial cells, activating transcription factors (Snail, Slug, Twist, Zeb) that repress endothelial genes and induce mesenchymal markers. EndMT-derived cells deposit ECM, promote fibrosis, and contribute to ventricular stiffening and heart failure, with regulation by microRNAs, epigenetic, and metabolic changes.

Clinical Consequences of EndMT in Myocardial Infarction

A major clinical consequence of EndMT in MI is diffuse fibrosis, which directly links to the growing burden of heart failure with preserved ejection fraction (HFpEF). EndMT-derived cells secrete collagens, fibronectin, and periostin, expanding the extracellular matrix in border and peri-infarct zones during the proliferative phase [4,7,48]. Unlike fibroblast-mediated fibrosis that stabilizes the scar, this redundant deposition stiffens the ventricle, impairs relaxation, and elevates filling pressures. Clinically, these structural changes manifest as dyspnea, pulmonary congestion, and exercise intolerance despite preserved systolic function-hallmarks of HFpEF. Imaging studies provide quantitative evidence: cardiac magnetic resonance with extracellular volume (ECV) mapping shows that each 1% increase in ECV corresponds to a measurable rise in risk for hospitalization and mortality among HFpEF patients [3,6,42]. Post-MI individuals with high ECV often develop diastolic dysfunction even when ejection fraction is maintained, highlighting how EndMT-driven fibrosis transforms an initially adaptive scar into a substrate for chronic dysfunction and a key driver of HFpEF progression [53].

Equally significant is microvascular rarefaction. By converting endothelial cells into mesenchymal phenotypes, EndMT reduces capillary density and limits oxygen delivery to viable myocardium [35]. The resulting hypoxia stabilizes hypoxia-inducible factor-1α, which further promotes EndMT, establishing a reinforcing cycle [38]. Animal models demonstrate that reduced capillary density correlates with ongoing cardiomyocyte apoptosis and expansion of replacement fibrosis [36]. Clinically, coronary microvascular dysfunction predicts poorer prognosis, impaired exercise capacity, and higher mortality [54]. Thus, EndMT drives both structural scarring and ischemic injury in viable tissue, accelerating the progression toward heart failure.

Beyond reducing vascular supply, EndMT further aggravates adverse remodeling by altering matrix quality. EndMT-derived cells increase collagen cross-linking through lysyl oxidase activity, raising matrix rigidity and compounding ventricular dysfunction [49]. In this way, vascular loss and fibrosis act synergistically, together driving the transition from adaptive

repair to pathological remodeling. Over time, the ventricle becomes progressively stiffened and underperfused, resulting in worsening diastolic dysfunction, reduced stroke volume, and symptomatic heart failure [41]. Imaging studies provide translational evidence of these processes: cardiac magnetic resonance imaging with ECV mapping detects diffuse fibrosis and correlates with outcomes [3,6,42], while fibroblast activation protein (FAP) positron emission tomography (PET) identifies sustained fibroblast activity, often persisting in patients who later develop adverse remodeling [55]. Together, these imaging modalities may indirectly capture ongoing EndMT activity and serve as early warning markers of maladaptive fibrogenesis.

Evidence from experimental and human studies reinforces the prognostic importance of EndMT. Zeisberg et al. demonstrated that up to one-third of fibroblast-like cells after MI arise from endothelial origins [24], and Hashimoto et al. showed that inhibiting TGF-β reduced endothelial-derived fibroblasts and attenuated fibrosis without compromising scar stability [50]. In humans, Evrard et al. identified endothelial–mesenchymal hybrid cells in ischemic cardiomyopathy, with their presence correlating to microvascular loss and poor clinical outcomes [35]. Single-cell RNA sequencing by Farbehi et al. confirmed that endothelial cells in post-MI myocardium occupy transitional states along the mesenchymal continuum, underscoring the clinical relevance of this process [51]. Collectively, these findings position EndMT not as a secondary contributor but as a central driver of pathological remodeling and poor prognosis in MI.

Current Therapeutic Approaches to Fibrosis and Limitations

Therapeutic efforts to reduce post-MI fibrosis have historically focused on broad suppression of profibrotic signaling pathways or on indirect modulation through conventional cardioprotective drugs. While some approaches have shown preclinical efficacy, translation to clinical benefit has been limited by a lack of selectivity, poor timing, and significant safety concerns.

The most direct antifibrotic strategies have focused on TGF-β, a central regulator of fibroblast activation and extracellular matrix deposition. In preclinical models, broad TGF-β blockade consistently reduced collagen accumulation, improved diastolic compliance, and attenuated remodeling [7,41]. However, these promising results have not been translated into human therapies because of what has been termed the “temporal paradox” of TGF-β inhibition. TGF-β is necessary during the early proliferative phase of healing, when fibroblast activation and matrix deposition are required to stabilize the infarct and prevent rupture. Global inhibition at this stage reduces scar tensile strength, predisposing the ventricle to thinning and catastrophic rupture [1,2]. Conversely, when TGF-β inhibition is delayed until the scar has matured, its impact is negligible, since collagen fibers are already cross-linked and resistant to remodeling [36]. Thus, TGF-β–directed therapies have failed because they cannot be administered without either undermining early survival or offering no meaningful late benefit.

Other molecular targets such as connective tissue growth factor (CTGF), lysyl oxidase, and matricellular proteins like periostin have also shown encouraging results in experimental models, where their inhibition reduces extracellular matrix deposition and attenuates fibrosis. Yet these approaches suffer from a lack of selectivity. CTGF, periostin, and lysyl oxidase play physiological roles in normal wound healing and tissue homeostasis; systemic inhibition risks slowing repair of surgical wounds, weakening host defense against infection, or disrupting extracellular matrix dynamics in other organs [41]. Because these proteins are widely expressed outside the heart, their blockade produces organ-specific toxicities and limits clinical feasibility.

Conventional post-MI pharmacotherapies provide indirect antifibrotic benefits but remain nonspecific. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce fibroblast activation through suppression of angiotensin II signaling, yet their antifibrotic effects are modest and secondary to hemodynamic unloading. β-blockers mitigate adrenergic drive and reduce oxygen demand but do not specifically target fibrogenic pathways. Mineralocorticoid receptor antagonists attenuate aldosterone-driven collagen synthesis but have systemic side effects, including hyperkalemia and renal dysfunction, that constrain dosing. Sodium-glucose cotransporter 2 inhibitors have recently been linked to reduced adverse remodeling, but their antifibrotic effects are indirect and mechanistically unclear [2,7,36]. While all of these drug classes improve survival and reduce heart failure progression, their ability to directly restrain maladaptive fibrosis is limited, diffuse, and nonspecific.

A final limitation that unites all of these strategies is the problem of systemic exposure. Broad antifibrotic drugs circulate throughout the body and cannot distinguish between adaptive fibroblast-mediated scar formation, which is necessary for survival, and maladaptive sources of fibrosis such as EndMT or pericyte activation. This nonspecific action risks interfering with essential repair processes in the heart while simultaneously producing toxicities in other organs including the lungs, kidneys, and skin. The absence of precision targeting explains why, despite decades of research, no antifibrotic drug has been successfully integrated into standard post-MI therapy.

Why Focus on EndMT?

The relative contribution of EndMT to fibrosis, estimated at 10–30% of fibroblast-like cells in lineage-tracing models [24,50], may appear modest compared to fibroblasts, but its clinical impact is disproportionately harmful. By converting endothelial cells into mesenchymal phenotypes, EndMT adds to the fibrotic burden while subtracting from vascular supply, creating a dual pathology: excessive fibrosis and vascular

rarefaction [35,38]. No other source of fibrosis simultaneously increases stiffness and decreases perfusion. Targeting EndMT therefore offers a unique opportunity to reduce both fibrotic load and microvascular loss, two key determinants of adverse post-MI remodeling.

Equally important, EndMT is governed by well-defined and targetable signaling pathways. Standard mediators such as TGF-β/Smad, Notch, Wnt/β-catenin, and HIF-1α converge on transcription factors including Snail, Slug, Twist, and Zeb, which repress endothelial genes and activate mesenchymal programs [41–44]. MicroRNAs such as miR-21 and miR-29 further modulate this process, creating opportunities for RNA-based therapeutics [45]. Because these pathways are distinct from those driving fibroblast activation, it is possible to design interventions that selectively block EndMT without impairing fibroblast-mediated scar formation. This separation of pathways provides the foundation for the safety advantage of EndMT-directed therapy.

Another reason to prioritize EndMT is its partial reversibility. Unlike terminally differentiated fibroblasts, EndMT-derived cells often remain in intermediate or hybrid states, co-expressing endothelial and mesenchymal markers [35,51]. Experimental studies have shown that such transitional cells can be coaxed back toward an endothelial phenotype by signals such as bone morphogenetic protein-7 (BMP-7), Notch modulation, or microRNA manipulation [52]. This plasticity suggests that therapeutic intervention could not only prevent the emergence of new mesenchymal cells but also restore vascular function by reprogramming hybrid cells. Clinically, this would translate into both reduced fibrosis and preserved microvascular density, a combination rarely achievable with current therapies.

Finally, focusing on EndMT aligns with the principle of precision medicine. Because EndMT activity peaks during the proliferative phase of MI healing (weeks 1–3) [36], therapies could be delivered within this defined window, guided by imaging and biomarker surveillance [3,6,55]. Such temporal and mechanistic specificity would overcome the general limitations of broad antifibrotic approaches. Instead of chronically suppressing fibroblasts, clinicians could intervene selectively and transiently against EndMT, achieving therapeutic benefit without jeopardizing scar integrity.

Table 1: Comparison of broad antifibrotic strategies versus EndMT-targeted therapy.

Therapy type	Mechanism	Pros	Cons	Timing / Safety
Pan–TGF-β blockers	Neutralizing antibodies, ligand traps, or receptor kinase inhibitors suppress global TGF-β signaling	Potent reduction of fibrosis in preclinical models	High risk of impaired wound healing, immune dysregulation, and cardiac rupture post-MI	Unsafe in early proliferative phase; systemic toxicity limits clinical translation
Collagen cross-linking inhibitors	Inhibit enzymes such as lysyl oxidase (LOX) to reduce collagen maturation and scar stiffening	Lower myocardial stiffness; potential benefit in chronic remodeling	Ineffective once fibrosis is established; risk of scar fragility	Narrow window, best late after MI; limited clinical benefit shown
ACEi / ARB / SGLT2i (indirect)	Neurohormonal modulation reduces fibroblast activation and interstitial fibrosis	Well-established safety; proven reduction in HF progression and mortality	Indirect, nonspecific antifibrotic effect; incomplete suppression of remodeling	Safe across MI timeline; cornerstone in current guidelines
Anti-EndMT therapies (e.g., miRNA modulation, pathway inhibitors, BMP-7, glycocalyx stabilizers)	Selectively block or reverse endothelial-to-mesenchymal transition by targeting TGF-β/Smad, Notch, Wnt/β-catenin, HIF-1α, or ncRNAs (miR-21, miR-29, MALAT^{1}, H^{19})	Spares essential fibroblast-driven scar formation; preserves endothelial pool and microvascular perfusion; partially reversible process allows rescue	Still experimental; delivery and specificity challenges; long-term safety untested	Best suited for proliferative phase (weeks 1–3 post-MI) when EndMT peaks; time-limited, precision-guided therapy

How to Detect Excessive Fibrosis and EndMT?

Translating EndMT into a clinical target requires reliable methods to detect when it is occurring at maladaptive levels after MI. Unlike fibroblast activation, which can be broadly inferred by fibrosis imaging or serum collagen markers, EndMT is more elusive because it represents a cellular fate transition rather than a single product. Nevertheless, converging advances in cardiac imaging, circulating biomarkers, and functional assessments now provide indirect yet clinically meaningful ways to detect excessive EndMT activity.

Imaging Approaches

Cardiac magnetic resonance imaging (CMR) is currently the standard for assessing fibrosis in vivo. Late gadolinium enhancement (LGE) identifies areas of focal scar but does not capture diffuse interstitial fibrosis, which is a hallmark of maladaptive remodeling. To overcome this, T1 mapping and extracellular volume (ECV) quantification are employed. These techniques measure the proportion of myocardium occupied by extracellular space, which expands as collagen accumulates. In patients after MI, persistently elevated ECV has been shown to correlate with collagen fraction on biopsy and to predict hospitalization, arrhythmias, and death [3,6,42,57,58]. In the context of EndMT, the key signal is when ECV rises out of proportion to infarct size, indicating that new collagen-producing cells are contributing to diffuse fibrosis outside the scar core. Repeated CMR over time adds an additional layer of insight: physiological scarring stabilizes after a few weeks, whereas continued expansion of ECV on serial scans suggests ongoing EndMT activity [59].

FAP-PET adds a functional dimension by detecting fibroblast activation. Fibroblast activation protein (FAP) is expressed by activated fibroblasts in healing myocardium, and PET tracers against FAP can visualize this activity in vivo. Normally, FAP uptake peaks during weeks 1–3 of scar formation and declines as fibroblasts enter a quiescent state [55]. However, in patients who later develop adverse remodeling, FAP uptake remains abnormally elevated well beyond the expected healing window, implying persistent fibroblast activation [60]. Because EndMT generates new fibroblast-like cells that join the activated pool, prolonged FAP signal is an indirect but powerful indicator of excessive EndMT. Even though FAP-PET cannot differentiate fibroblast origin, its persistence points toward a non-physiological source of ongoing activation, of which EndMT is a prime candidate. Combining FAP-PET with CMR in PET-MR protocols strengthens detection by linking fibrotic burden (ECV) with fibroblast activity (FAP uptake), providing a two-dimensional view of abnormal remodeling. Moreover, some novel tracers like experimental live-cell EndMT reporter systems have recently been developed to visualize endothelial–mesenchymal hybrid states. For example, a CNN1-Rep fluorescent construct allows real-time tracking of endothelial cells as they downregulate endothelial identity and acquire mesenchymal traits in 2D, 3D, and organ-on-chip platforms. While still experimental, such tracers hold promise for enabling molecularly specific detection of EndMT in physiologically relevant settings [61,62].

Circulating Biomarkers

Collagen turnover peptides (PICP, PINP, and PIIINP) are among the oldest serum markers of fibrosis. They represent fragments released during collagen synthesis and degradation. Elevated peptide levels after MI indicate that the myocardium is actively remodeling [36]. In cases where infarct size is stable but collagen peptides remain persistently high, this suggests a continued supply of fibrogenic cells beyond the normal fibroblast pool. EndMT is a plausible contributor to this abnormal signal, as it introduces new collagen-secreting cells even after the scar should have matured [63].

MicroRNAs (miRNAs) provide more mechanistic information about EndMT. miR-21 promotes EndMT by suppressing the inhibitory regulator Smad7, while miR-29 normally represses collagen transcripts but is downregulated after MI. Thus, a miR-21↑/miR-29↓ profile is characteristic of fibrogenic activity driven by EndMT [45,64]. Measuring these levels in circulation reflects not only the presence of active fibrosis but also its mechanistic basis. Adding miR-126, which is enriched in endothelial cells, further improves specificity: a fall in circulating miR-126 signals endothelial cell injury or loss, which aligns with the depletion of endothelial cells through EndMT [65]. Together, these signatures allow clinicians to infer that fibrosis is being driven not solely by resident fibroblasts, but also by endothelial-derived cells.

Beyond miRNAs, noncoding RNAs (ncRNAs) such as long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) are increasingly recognized as key regulators of endothelial plasticity [66]. Unlike miRNAs, which primarily repress gene expression post-transcriptionally, lncRNAs and circRNAs act through diverse mechanisms including miRNA sponging, scaffolding transcription factors, modulating chromatin states, and stabilizing specific mRNAs [66]. These regulatory functions allow them to adjust signaling pathways that drive endothelial cells toward a mesenchymal phenotype. Several lncRNAs have already been implicated in EndMT-related signaling. For instance, MALAT1 has been shown to promote EndMT by activating TGF-β/Smad signaling [70], while H19 can act as a competitive endogenous RNA (ceRNA) to sequester antifibrotic miRNAs, thereby enhancing mesenchymal transition [71]. CircRNAs often function as miRNA sponges, binding to pro- or anti-fibrotic miRNAs to alter the balance of gene expression. For example, circRNAs such as circACR have been linked to vascular remodeling and myocardial injury by regulating endothelial apoptosis, autophagy, and differentiation pathways [72]. Because lncRNAs and circRNAs are stable in circulation, circRNAs in particular resist exonuclease degradation due to their covalently closed loop structure, they represent attractive candidates for biomarker development [66]. Unlike collagen peptides, which reflect general matrix turnover, or miRNAs, which highlight a narrow regulatory axis, lncRNAs and circRNAs could provide multi-level insight into the transcriptional and post-transcriptional networks that sustain EndMT. Measuring their circulating levels could therefore extend current biomarker panels, improving specificity for endothelial-derived fibrosis and potentially distinguishing EndMT activity from fibroblast activation alone [66,70–72].

The most direct, but still experimental, approach for detecting EndMT activity is the identification of circulating endothelial–mesenchymal hybrid cells. These cells co-express

endothelial markers such as CD31 or VE-cadherin together with mesenchymal markers including α-smooth muscle actin (α-SMA) or vimentin, reflecting their transitional state. Early feasibility assays using multicolor flow cytometry have detected such dual-marker populations in peripheral blood samples, while more recent advances in single-cell RNA sequencing have confirmed their hybrid transcriptomic profiles in patients with ischemic cardiomyopathy [35,73]. Although not yet validated for clinical practice, these methods demonstrate that EndMT-derived cells can be directly traced in human circulation. If optimized for sensitivity and standardization, circulating hybrid cells could serve as a unique and specific biomarker of ongoing EndMT, distinguishing it from fibroblast activation and providing real-time insight into the dynamics of post-MI remodeling.

Clinical and Functional Indicators

Clinical phenotyping provides real-world evidence of excessive EndMT. Patients who develop ventricles that are disproportionately stiff compared to their infarct size, detectable with echocardiographic markers of diastolic dysfunction or invasive pressure–volume analysis, are showing signs of diffuse interstitial fibrosis [53]. When fibrosis extends beyond the infarct zone, ventricular compliance falls, filling pressures rise, and diastolic function deteriorates. This is the clinical manifestation of excessive EndMT: an expanded pool of fibroblast-like cells laying down diffuse extracellular matrix in regions that should remain compliant.

Another clue is the early appearance of heart failure with preserved ejection fraction (HFpEF) in post-MI patients who did not suffer large infarcts. HFpEF reflects a mismatch between preserved systolic function and impaired diastolic filling, often due to diffuse fibrosis and vascular rarefaction. Because EndMT both stiffens myocardium and reduces endothelial cell density, its signature phenotype is exactly this combination of compliance loss and perfusion impairment [54,68]. Longitudinal studies in HFpEF consistently show that patients with microvascular rarefaction and diffuse fibrosis have worse exercise capacity and prognosis [69]. In this way, functional testing is not specific for EndMT, but when combined with imaging and biomarkers, it highlights which patients have progressed beyond adaptive scarring to maladaptive fibrosis.

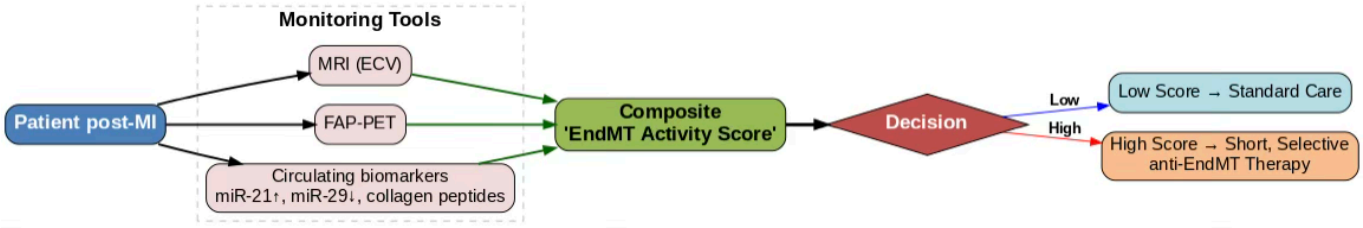
Toward an "EndMT Activity Score"

Individually, none of these methods definitively identify EndMT. Imaging captures structure and activity, biomarkers reflect molecular drivers, and clinical indices demonstrate physiological consequences. By integrating them, however, it becomes possible to construct an EndMT activity score that stratifies patients based on the likelihood of ongoing maladaptive remodeling. A prototypical high-risk patient would show an elevated ECV on CMR disproportionate to infarct size, persistent FAP-PET uptake beyond the expected healing phase, and a circulating profile of miR-21↑/miR-29↓ with reduced miR-126. This constellation strongly suggests excessive EndMT activity and would identify candidates for selective, short-term therapy during the proliferative phase (weeks 1–3 post-MI). Patients lacking this profile could avoid unnecessary treatment.

The strength of this framework lies in its structured integration of tools across different stages of clinical development. Validated clinical markers such as CMR-derived ECV and serum collagen peptides provide a robust framework that can already be implemented in routine care. Translational tools, including FAP-PET and circulating microRNA panels, add mechanistic specificity that connects imaging findings to the biological processes of EndMT. Finally, experimental approaches, such as tracers designed to identify endothelial–mesenchymal hybrids and noncoding RNA signatures, represent future refinements that could elevate the specificity of the score once standardized.

Unlike traditional fibrosis metrics that simply quantify scar size or global collagen burden, an EndMT activity score would offer a mechanism-based index that links structural remodeling with the molecular and cellular processes driving it. This approach would advance precision cardiology in two major ways: first, by providing clinicians with a decision-making tool to individualize treatment based on biology rather than anatomy alone; and second, by serving as a trial enrichment strategy to ensure that novel EndMT-targeted therapies are tested in the subset of patients most likely to benefit. By shifting from descriptive endpoints to mechanistically informed risk stratification, the EndMT activity score has the potential to transform post-MI care and accelerate the development of targeted antifibrotic interventions.

Figure 4: Translational framework for an EndMT Activity Score.



ECV mapping, FAP-PET imaging, and circulating biomarkers are combined into a composite score to stratify post-MI patients. High scores identify candidates for short, selective anti-EndMT therapy, enabling a precision medicine approach.

Future Directions

Precision Timing of Therapy

EndMT activity peaks during the proliferative phase of MI healing (weeks 1–3), coinciding with fibroblast expansion and extracellular matrix deposition [36]. Early suppression, before fibroblasts complete scar stabilization, risks rupture; late intervention, after collagen cross-linking, cannot reverse mature scar tissue [1]. The therapeutic window for EndMT is therefore narrow and defined. Monitoring tools such as CMR-derived extracellular volume, FAP-PET imaging, and circulating microRNAs [3,6,45,55] may allow clinicians to identify when EndMT activity is excessive, enabling time-limited therapies that intervene precisely during this window. Such biomarker-guided approaches would resolve the "temporal paradox" that has defeated global antifibrotic strategies.

Therapeutic Strategies

A range of therapeutic approaches has been proposed to selectively target EndMT. The most direct involve inhibition of canonical developmental pathways such as TGF-β/Smad, Notch, and Wnt/β-catenin, using small-molecule inhibitors, neutralizing antibodies, or ligand traps. While these interventions are mechanistically straightforward, their lack of specificity raises concerns about systemic side effects, as these pathways regulate a wide variety of tissues. More refined strategies focus on microRNA modulation. In particular, anti-miR-21 therapy or miR-29 replacement may restore balance within the regulatory axis that drives EndMT and fibrotic collagen deposition. Another promising line of investigation seeks to preserve or restore endothelial identity. Experimental interventions such as glycocalyx stabilizers, vascular endothelial growth factor analogues, and bone morphogenetic protein 7 (BMP-7) have demonstrated the ability to reverse EndMT and reestablish endothelial phenotype. Beyond suppression of mesenchymal transition, pro-endothelial and angiogenic strategies, including endothelial progenitor cell therapy and the delivery of angiogenic growth factors, aim to counteract the microvascular rarefaction induced by EndMT and restore tissue perfusion.

Delivery Systems and Localization

Because systemic blockade of pathways such as TGF-β and Wnt is likely to produce off-target effects, localized delivery systems are increasingly viewed as essential for safe and effective EndMT-directed therapy. Nanoparticle-based systems, injectable hydrogels, microneedle patches, and drug-eluting stents provide promising platforms. Hydrogels allow localized, sustained release of anti-EndMT agents directly into the infarct border zone, reducing systemic exposure. Microneedle cardiac patches can deliver small molecules, RNA therapeutics, or antibodies directly to the epicardial surface in a minimally invasive fashion. Similarly, bioresorbable stents coated with anti-EndMT compounds could modulate endothelial plasticity in coronary arteries while maintaining vascular patency. These approaches allow high local drug concentrations while minimizing systemic exposure, an important consideration given the multifunctional roles of these signaling pathways in development, immunity, and tissue homeostasis. The combination of localized delivery with biomarker-guided timing offers the potential to suppress EndMT only when and where it is pathogenic, thereby maximizing therapeutic efficacy while minimizing risk.

Biomarker-Guided Personalization

The integration of imaging, molecular, and clinical measures into a composite "EndMT activity score" may enable real-time personalization of therapy. Patients who exhibit persistently elevated extracellular volume on CMR, abnormal FAP-PET uptake beyond the expected healing window and circulating biomarkers consistent with a miR-21-high/miR-29-low profile could be classified as high risk for maladaptive EndMT. These individuals might then be considered candidates for short-course EndMT-targeted therapy delivered during the proliferative phase, while patients without this profile would be spared unnecessary intervention. This paradigm exemplifies precision cardiology, in which therapeutic decisions are guided not only by anatomy and symptoms but also by dynamic biomarkers that reflect ongoing cellular processes.

Research Priorities

Looking ahead, progress will require a clear roadmap that spans preclinical discovery to clinical application. Preclinical studies should focus on mechanistic dissection of key pathways (TGF-β, Notch, Wnt/β-catenin, mechanosensitive channels) and the validation of ncRNA regulators such as MALAT1, H19, and circRNAs as therapeutic targets. Translational efforts should then refine biomarker panels, including miR-21/miR-29, endothelial miRNAs, collagen peptides, and emerging lncRNAs/circRNAs, to identify reliable markers of EndMT activity in patients. Once validated, these biomarkers can be incorporated into early-phase clinical trials that test EndMT-directed therapies delivered through hydrogels, microneedle patches, or targeted nanoparticles. Finally, large-scale randomized trials can use the EndMT activity score both to select high-risk patients and to monitor response, ensuring that outcomes are tied directly to the biology of interest.

Conclusion

Fibrosis after myocardial infarction is crucial for scar stability yet becomes maladaptive when excessive, driving ventricular stiffening, impaired perfusion, and heart failure. Broad antifibrotic therapies have failed because they suppress essential fibroblast activity, whereas EndMT represents a non-essential, maladaptive source of fibrosis that simultaneously depletes vascular networks. Evidence from lineage tracing, human biopsies, and single-cell analyses confirms its role in adverse remodeling, while advances in imaging and circulating biomarkers now make its activity clinically measurable. With defined molecular drivers, partial reversibility, and a clear

therapeutic window, EndMT emerges as a uniquely targetable process. Selective, time-limited modulation of EndMT could reduce pathological scarring, preserve microvascular integrity, and shift post-MI care toward precision antifibrosis therapy.

Declarations

Conflict of Interest

The author declares no conflicts of interest.

Ethical Approval

Not applicable.

This review did not involve studies with human participants or animals.

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