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RESEARCH ARTICLE

MOLECULAR MECHANISMS OF STEM CELL–DERIVED EXOSOMES IN MYOCARDIAL REGENERATION AND CARDIAC REMODELLING IN HEART FAILURE

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Abstract

Heart failure (HF) remains the terminal manifestation of diverse cardio vascular pathologies, including ischemic cardiomyopathy, hypertensive remodelling, diabetic cardiomyopathy, inflammatory myocarditis, and inherited dilated cardiomyopathies, and continues to impose a substanti al global health burden. Despite major advances in guideline directed p harmacotherapy targeting maladaptive neurohormonal activation—such as angiotensin receptor–neprilysin inhibition,mineralocorticoid receptor antagonism, β-adrenergic blockade, and sodium–glucose cotransporter-2 inhibition- current treatments do not restore lost cardiomyocytes or re verse established structural remodelling. The intrinsic regenerative inca pacity of the adult mammalian myocardium therefore remains the central biological obstacle to curative therapy.In this context, stem cell–derived exosomes (SC-Exos) have emerged as a highly promising, cell-free regenerative platform capable of orchestrating multidimensional reparative signalling within the injured and failing heart.SC-Exos are nano-sized (30–150 nm) lipid bilayer extracellular vesicles generated through endosomal multivesicular body pathways and enriched with selectively packaged bioactive cargo, including microRNAs, long non-coding RNAs, circular RNAs, messenger RNAs, proteins, lipids, and mitochondrial components. These vesicles function as intercellular communication mediators, reprogramming recipient cardiomyocytes, endothelial cells, fibroblasts, and immune cells at transcriptional, epigenetic, metabolic, and post-translational levels.

Accumulating preclinical evidence demonstrates that SC-Exos attenuate cardiomyocyte apoptosis through activation of PI3K/Akt, ERK1/2, and STAT3 survival cascades; enhance angiogenesis via HIF-1α–dependent miRNA enrichment and endothelial nitric oxide signalling; suppress fibrotic remodelling by inhibiting TGF-β/Smad-driven myofibroblast differentiation; modulate macrophage polarization toward reparative phenotypes; and restore

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mitochondrial integrity and bioenergetic capacity through regulation of mitochondrial dynamics and metabolic transcriptional networks such as PGC-1α and AMPK pathways. Importantly, therapeutic efficacy is influenced by source-specific heterogeneity among mesenchymal stem cell–, cardiac progenitor cell–, induced pluripotent stem cell–, and embryonic stem cell–derived exosomes, each exhibiting distinct proteomic and transcriptomic signatures. Environmental priming conditions—including hypoxia, inflammatory stimulation, and metabolic modulation—further shape exosomal cargo composition, underscoring the need for standardized manufacturing protocols. Advances in bioengineering, including surface targeting ligand modification, hydrogel-assisted myocardial retention, and precision cargo enrichment strategies, have significantly improved myocardial tropism and functional outcomes in preclinical models. Nevertheless, translational challenges persist, including limited large-animal validation, biodistribution uncertainty, dose standardization, long-term safety evaluation, and regulatory harmonization under Good Manufacturing Practice frameworks. This comprehensive review synthesizes current mechanistic insights into SC-Exo–mediated myocardial regeneration and cardiac remodelling in HF, integrating molecular signalling pathways, epigenetic reprogramming, metabolic restoration, and intercellular network dynamics. Furthermore, critical translational gaps are delineated, and a precision-engineered therapeutic roadmap is proposed that integrates multi-omics profiling, stage-specific intervention strategies, and advanced delivery platforms. By consolidating emerging mechanistic evidence with translational considerations, this review aims to provide a high-resolution conceptual framework for advancing stem cell–derived exosome therapeutics from experimental innovation toward clinically transformative myocardial repair.

Introduction:-

Heart failure (HF) represents the terminal common pathway of diverse cardiovascular insults including ischemic cardiomyopathy, hypertensive remodelling, diabetic cardiomyopathy, myocarditis, and genetic dilated cardiomyopathies [1–3]. Despite transformative pharmacological advancements targeting neurohormonal activation—such as angiotensin receptor–neprilysin inhibition, mineralocorticoid receptor antagonism, β-adrenergic blockade, and sodium–glucose cotransporter-2 inhibition—the fundamental inability of adult mammalian myocardium to regenerate lost cardiomyocytes remains the principal biological limitation in reversing disease progression [4–6]. Globally, HF continues to affect more than 64 million individuals and is associated with high hospitalization rates, progressive functional decline, and substantial mortality [1,2]. Myocardial infarction (MI) initiates a cascade of sterile inflammation, oxidative stress, cardiomyocyte apoptosis and necrosis, fibroblast activation, extracellular matrix deposition, ventricular dilation, and ultimately maladaptive remodelling [7–9]. The chronic phase is characterized by capillary rarefaction, mitochondrial bioenergetic failure, metabolic inflexibility, and persistent low-grade inflammation that perpetuates systolic and diastolic dysfunction [10–12]. Conventional therapies largely attenuate neurohormonal maladaptation but do not restore functional myocardium [4,5].Initial regenerative approaches centered on stem cell transplantation, including bone marrow–derived mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), and induced pluripotent stem cells (iPSCs) [13–15]. However, long-term follow-up studies demonstrated modest improvements in left ventricular ejection fraction (LVEF), limited engraftment, poor electrical integration, and potential arrhythmogenic risk [14–16]. Increasing mechanistic evidence suggests that the therapeutic efficacy of stem cells is primarily mediated through paracrine secretion rather than structural differentiation into cardiomyocytes [15–17]. Among paracrine mediators, extracellular vesicles (EVs)—particularly exosomes—have emerged as critical nano-scale biological effectors capable of orchestrating intercellular signalling [17–19].

List of Abbreviations

Abbreviation	Description
ACC	American College of Cardiology
AGO2	Argonaute-2
AHA	American Heart Association
Akt	Protein Kinase B
AMPK	AMP-Activated Protein Kinase
ATP	Adenosine Triphosphate
Bax	Bcl-2-Associated X Protein
Bcl-2	B-cell Lymphoma 2
circRNA	Circular RNA
circRNAs	Circular RNAs
CPC-Exos	Cardiac Progenitor Cell-Derived Exosomes
CPCs	Cardiac Progenitor Cells

DNA	Deoxyribonucleic Acid
Drp1	Dynamin-Related Protein 1
DSP	Downstream Processing
ECM	Extracellular Matrix
eNOS	Endothelial Nitric Oxide Synthase
ERK1/2	Extracellular Signal-Regulated Kinases 1 and 2
ESC	European Society of Cardiology
ESC-Exos	Embryonic Stem Cell-Derived Exosomes
ESCRT	Endosomal Sorting Complexes Required for Transport
ETC	Electron Transport Chain
EVs	Extracellular Vesicles
GMP	Good Manufacturing Practice
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIF-1α	Hypoxia-Inducible Factor-1 Alpha
hnRNPA2B1	Heterogeneous Nuclear Ribonucleoprotein A2/B1
IL	Interleukin
iPSC-Exos	Induced Pluripotent Stem Cell-Derived Exosomes
iPSCs	Induced Pluripotent Stem Cells
ISEV	International Society for Extracellular Vesicles
IV	Intravenous
JACC	Journal of the American College of Cardiology
LDH	Lactate Dehydrogenase
lncRNA	Long Non-coding RNA
lncRNAs	Long Non-coding RNAs
LVEF	Left Ventricular Ejection Fraction
Mfn2	Mitofusin-2
MI	Myocardial Infarction
MIFlowCyt-EV	Minimum Information for Flow Cytometry of Extracellular Vesicles
miRNA	MicroRNA
miRNAs	MicroRNAs
MISEV	Minimal Information for Studies of Extracellular Vesicles
mRNA	Messenger RNA
MSC-Exos	Mesenchymal Stem Cell-Derived Exosomes
MSCs	Mesenchymal Stem Cells
mtDNA	Mitochondrial DNA
MVBs	Multivesicular Bodies
NF-κB	Nuclear Factor Kappa B
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha
PI3K	Phosphatidylinositol 3-Kinase
PTEN	Phosphatase and Tensin Homolog
RES	Reticuloendothelial System
RNA	Ribonucleic Acid
SC-Exos	Stem Cell-Derived Exosomes
SEC	Size-Exclusion Chromatography
Smad	Mothers Against Decapentaplegic Homolog Proteins
SOP	Standard Operating Procedure
STAT3	Signal Transducer and Activator of Transcription 3
TFF	Tangential Flow Filtration
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumor Necrosis Factor Alpha
TSG101	Tumor Susceptibility Gene 101
USP	Upstream Processing

VEGF	Vascular Endothelial Growth Factor
VPS4	Vacuolar Protein Sorting-Associated Protein 4
YBX1	Y-box Binding Protein 1
α-SMA	Alpha-Smooth Muscle Actin
ΔΨm	Mitochondrial Membrane Potential

Stem cell–derived exosomes (SC-Exos) are lipid bilayer vesicles ranging from 30 to 150 nm in diameter that encapsulate a complex repertoire of regulatory nucleic acids, proteins, lipids, and mitochondrial components [18–20]. These vesicles function as intercellular communication vehicles capable of reprogramming recipient cardiac cells at transcriptional, translational, epigenetic, and metabolic levels [17–20]. Accumulating preclinical evidence indicates that SC-Exos exert cardioprotective effects by modulating apoptosis, angiogenesis, fibrosis, imune cell polarization, mitochondrial dynamics, and metabolic remodelling [11,12,18–20]. However, mechanistic heterogeneity, cargo variability, and translational limitations continue to impede clinical implementation [16–20].
This review comprehensively examines the molecular mechanisms through which stem cell–derived exosomes regulate myocardial regeneration and pathological remodelling in heart failure. Emphasis is placed on intracellular signalling cascades, epigenetic regulation, bioenergetic modulation, and source-specific heterogeneity, followed by a critical translational gap analysis and future precision-engineered therapeutic perspectives.

Exosome Biogenesis and Molecular Architecture:-

Exosome biogenesis originates within the endosomal pathway [21–23]. Early endosomes undergo inward budding of their limiting membrane, generating intraluminal vesicles within multivesicular bodies (MVBs) [21,24]. The formation of these vesicles is regulated by endosomal sorting complexes required for transport (ESCRT)-dependent mechanisms involving TSG101, Alix, VPS4, and associated accessory proteins [22–25]. ESCRT-independent mechanisms, mediated by ceramide-driven lipid raft formation and tetraspanin microdomains, also contribute to cargo sorting and membrane curvature [23,26,27].

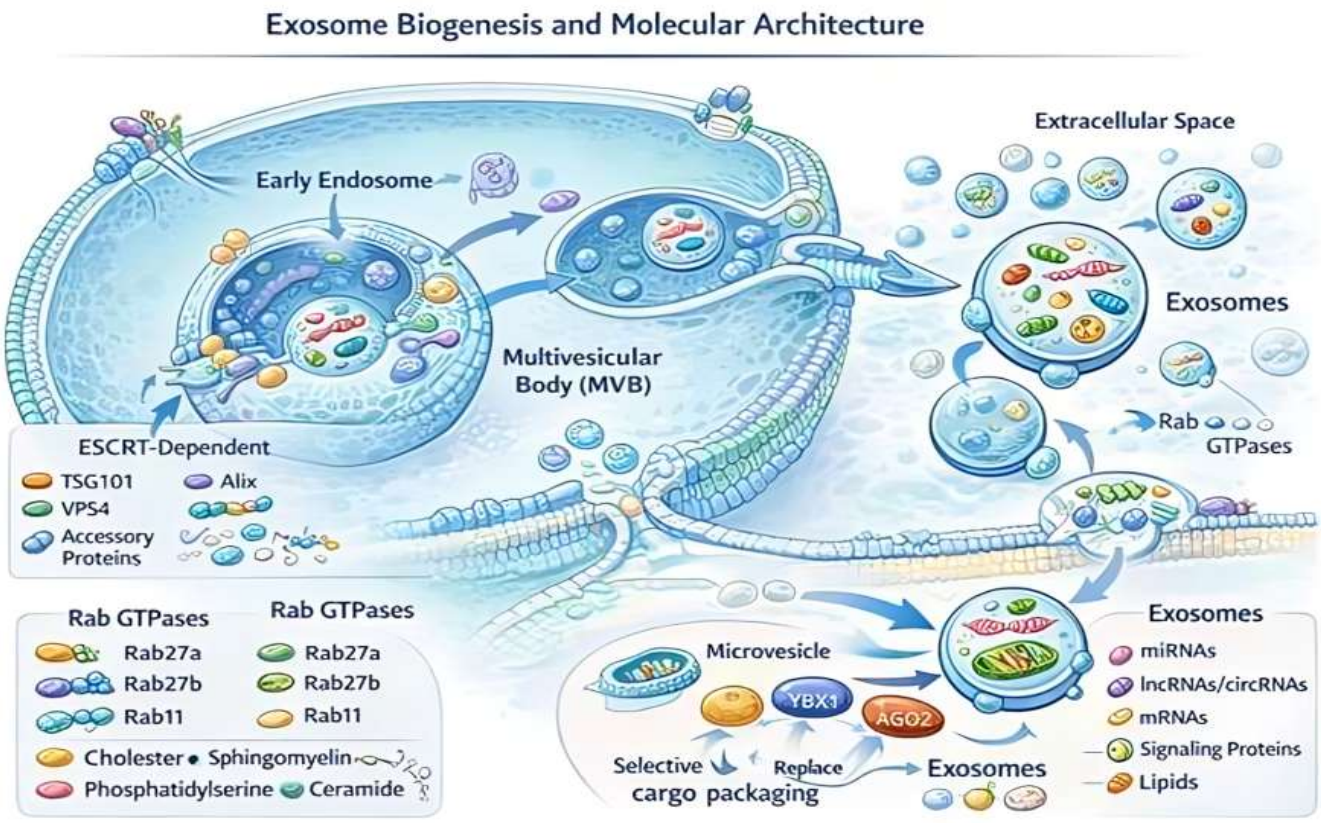

Figure 1. Biogenesis and molecular architecture of stem cell–derived exosomes. Exosomes form via ESCRT-dependent and -independent inward budding of endosomes into multivesicular bodies, with Rab GTPases mediating MVB trafficking and membrane fusion. Vesicles are enriched in cholesterol, sphingomyelin,

phosphatidylserine, and ceramide, and display canonical markers (CD63, CD81, CD9, Alix, TSG101). Selective cargo—regulatory RNAs, proteins, integrins, and bioactive lipids—is loaded via RNA-binding proteins (hnRNPA2B1, YBX1, AGO2) and modulated by microenvironmental cues such as hypoxia, inflammation, and metabolic stress.

Following MVB maturation, Rab GTPases—including Rab27a, Rab27b, and Rab11—regulate vesicular trafficking and fusion of MVBs with the plasma membrane, culminating in exosome release into the extracellular milieu [28–30]. The lipid composition of exosomes is enriched in cholesterol, sphingomyelin, phosphatidylserine, and ceramide, conferring structural stability and facilitating membrane fusion with recipient cells [23,27,31]. Stem cell–derived exosomes exhibit characteristic surface markers including CD63, CD81, CD9, Alix, and TSG101 [21,24,32]. However, their biological functionality is determined by cargo composition. SC-Exos are enriched with regulatory microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), messenger RNAs, signalling proteins, heat shock proteins, integrins, and bioactive lipids [26,31–34]. Importantly, cargo loading is not random but selectively regulated by RNA-binding proteins such as hnRNPA2B1, YBX1, and AGO2, which recognize sequence motifs directing nucleic acid packaging [33–36]. Environmental factors significantly influence cargo heterogeneity [37–40]. Hypoxic preconditioning enhances enrichment of angiogenic miRNAs such as miR-210 and miR-126 via HIF-1α–dependent transcriptional regulation [37,38]. Inflammatory priming alters exosomal immunomodulatory profiles [39]. Metabolic states, glucose availability, and oxidative stress similarly modulate cargo sorting, thereby influencing therapeutic efficacy [38–40].

Source-Specific Heterogeneity of Stem Cell–Derived Exosomes:-

The biological activity of SC-Exos is profoundly dependent on cellular origin [26,32,34]. Mesenchymal stem cell–derived exosomes (MSC-Exos) represent the most extensively studied subtype [32,37]. These vesicles demonstrate potent immunomodulatory, anti-apoptotic, and pro-angiogenic properties, largely mediated through miR-21, miR-146a, and miR-181b [33,37,39]. Cardiac progenitor cell–derived exosomes (CPC-Exos) exhibit enhanced cardiomyocyte-specific regenerative signalling, reflecting their lineage proximity [34,38]. CPC-Exos are enriched in miR-451, miR-133a, and cardiomyocyte survival–associated proteins, promoting contractile preservation and anti-fibrotic remodelling [34,38].

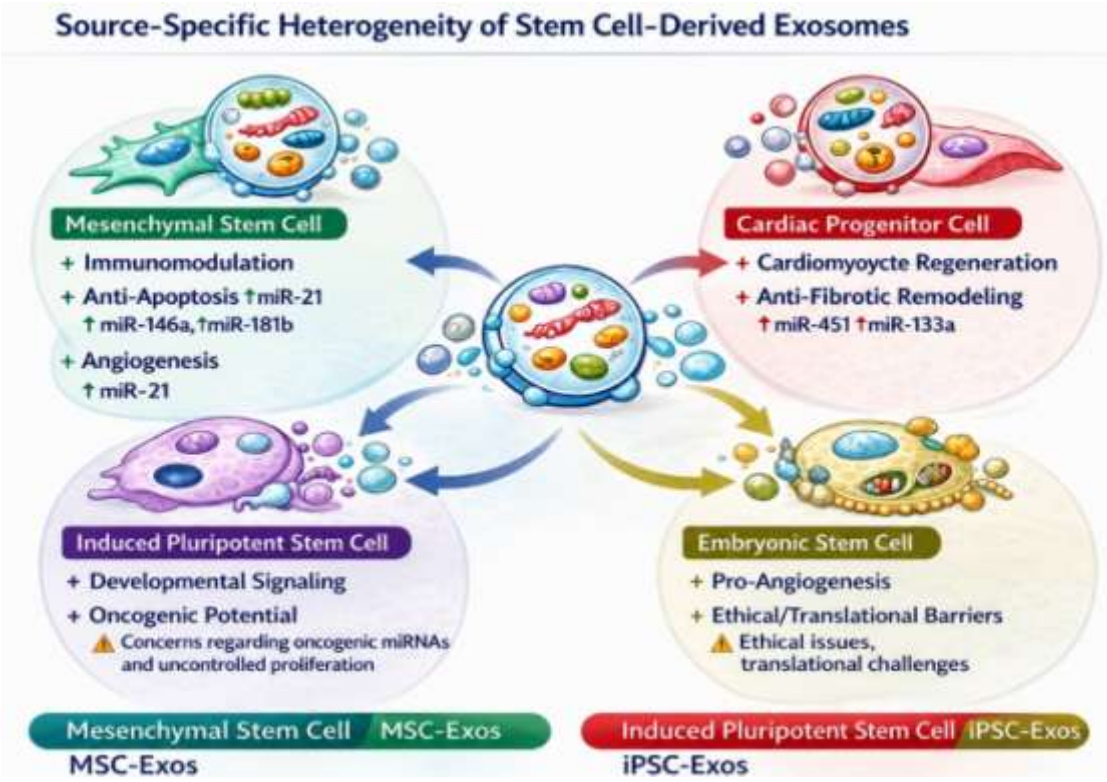

Figure 2.Source-specific heterogeneity of stem cell–derived exosomes (SC-Exos). Comparative schematic of MSC-, CPC-, iPSC-, and ESC-derived exosomes illustrating differential cargo profiles (miRNAs, proteins,

signaling molecules) and functional specialization in immunomodulation, cardiomyocyte regeneration, developmental signaling, and angiogenesis, highlighting origin-dependent therapeutic potential and translational considerations.

Induced pluripotent stem cell–derived exosomes (iPSC-Exos) display broader regenerative plasticity, with cargo capable of activating developmental signalling pathways including Wnt/β-catenin and Notch [35,40]. However, concerns regarding oncogenic miRNA enrichment and uncontrolled proliferative signalling warrant caution [35,40].Embryonic stem cell–derived exosomes (ESC-Exos) demonstrate robust angiogenic capacity but face ethical and translational barriers [36]. Comparative proteomic and transcriptomic analyses reveal significant divergence in cargo profiles between these exosome populations, underscoring the need for standardized head-to-head evaluation in identical experimental models [31,36,40].

Cellular Uptake Mechanisms and Intracellular Targeting:-

Following systemic or local administration, SC-Exos interact with recipient cardiac cells via multiple mechanisms [41–45]. Surface integrins and tetraspanins facilitate binding to extracellular matrix components and cell surface receptors [41,46]. Uptake occurs through clathrin-mediated endocytosis, caveolin-dependent internalization, micropinocytosis, phagocytosis, or direct membrane fusion [42–47]. Cardiomyocytes, endothelial cells, fibroblasts, and resident immune cells internalize exosomes differentially [43,48]. Integrin expression patterns influence tissue tropism, suggesting potential for targeted surface modification [44,49]. Once internalized, exosomal cargo escapes endosomal compartments and interacts with cytosolic or nuclear machinery, modulating gene expression and signalling cascades [45,50]. Emerging data suggest that exosomes may deliver intact mitochondrial fragments or mitochondrial DNA, contributing to restoration of bioenergetic function in damaged cardiomyocytes [46,51–53]. This mitochondrial transfer hypothesis represents a frontier area requiring deeper mechanistic clarification [47,54].

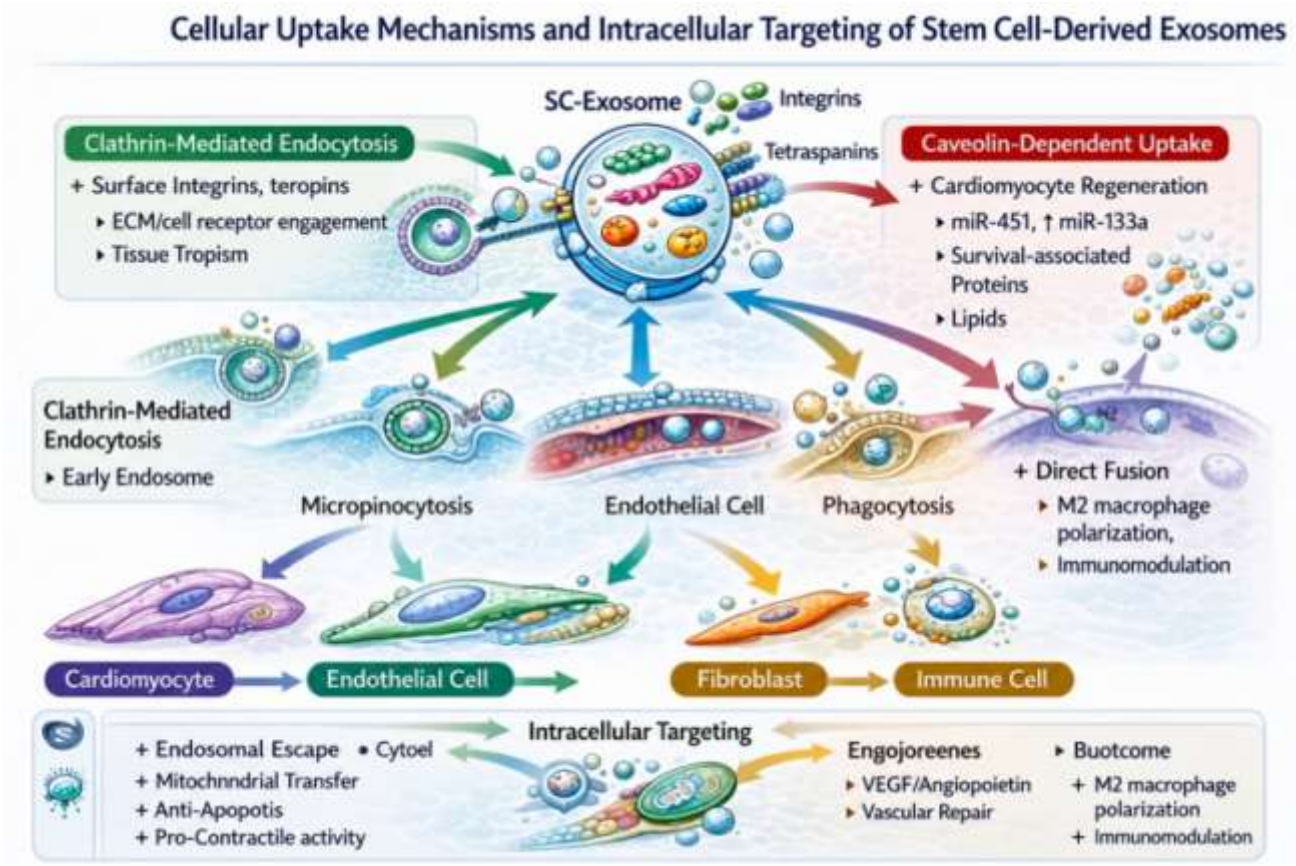

Figure 3:SC-Exos internalization in cardiac cells via endocytosis, fusion, or micropinocytosis, enabling cytosolic/nuclear cargo delivery and mitochondrial transfer for regenerative modulation.

Table 1:SC-Exos uptake pathways, recipient cell specificity, and intracellular targeting mechanisms driving cardiac repair and signaling modulation

Aspect	Mechanism / Feature	Functional Implications	References
Binding & Recognition	Surface integrins, tetraspanins	ECM/cell receptor engagement, tissue tropism	[41,46,49]
Internalization Pathways	Clathrin-mediated endocytosis, caveolin-dependent uptake, micropinocytosis, phagocytosis, direct membrane fusion	Multi-route uptake enhancing cellular delivery efficiency	[42–47]
Cellular Targets	Cardiomyocytes, endothelial cells, fibroblasts, immune cells	Differential internalization; cell type-specific functional outcomes	[43,48]
Intracellular Trafficking	Endosomal escape, cytosolic/nuclear targeting	Modulation of gene expression, signaling cascades	[45,50]
Mitochondrial Transfer	Delivery of mitochondrial fragments / mtDNA	Restoration of cardiomyocyte bioenergetics; emerging therapeutic avenue	[46,51–54]

Anti-Apoptotic and Pro-Survival Signalling Cascades:-

Cardiomyocyte apoptosis constitutes a central mechanism in both acute ischemic injury and chronic HF progression [55–57]. SC-Exos attenuate apoptosis primarily through activation of thephosphatidylinositol-3-kinase (PI3K)/Akt pathway [55,58]. Exosomal miR-21 suppresses PTEN expression, relieving inhibition of Akt phosphorylation and enhancing downstream pro-survival signalling [56,59].

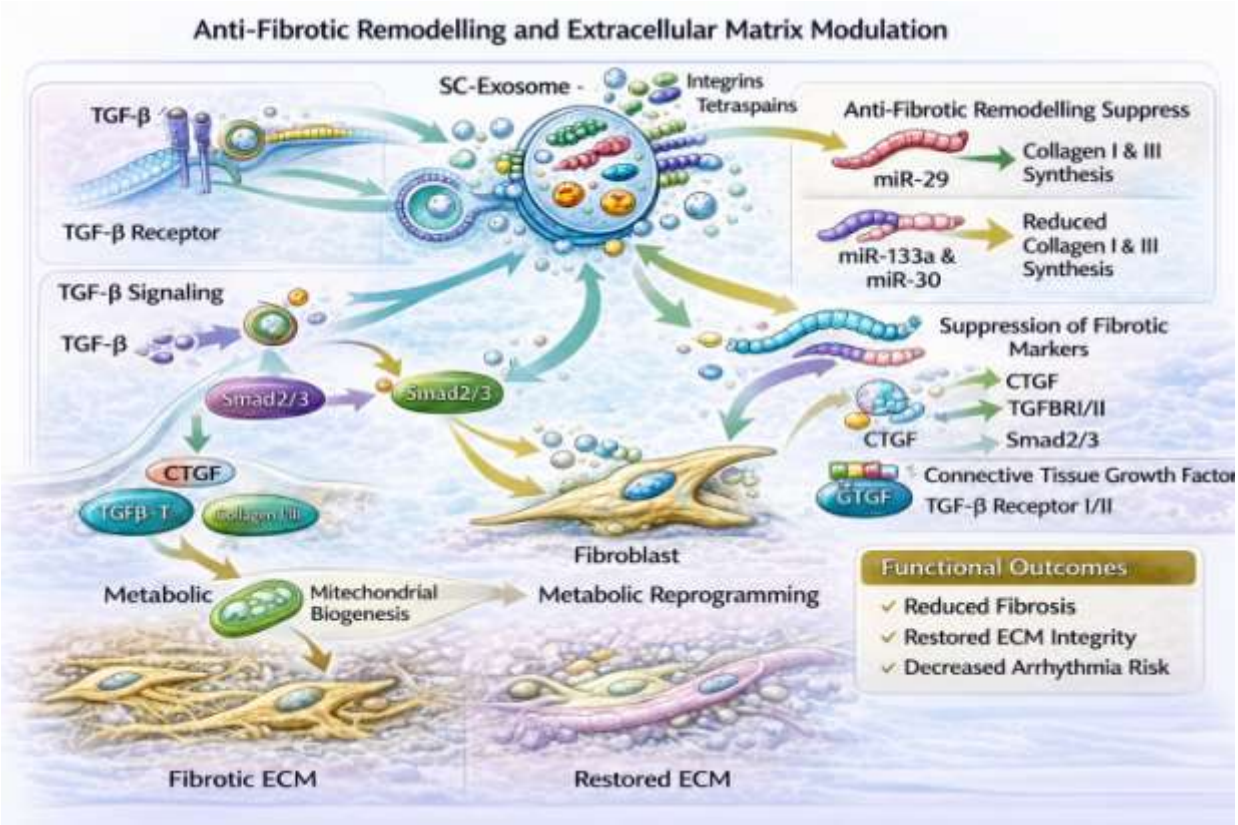

Figure 4:SC-Exos–mediated anti-apoptotic signaling in cardiomyocytes. Exosomal miR-21 inhibits PTEN, activating PI3K/Akt and downstream suppression of Bad/Bax and cytochrome c–caspase-9/3 signaling, with

concurrent ERK1/2 and STAT3 activation. Reduced ROS generation, enhanced antioxidant enzymes, and mitochondrial membrane stabilization collectively promote cardiomyocyte survival following ischemic injury.

Activated Akt phosphorylates and inactivates pro-apoptotic factors such as Bad, while upregulating anti-apoptotic Bcl-2 expression [57,59]. Concurrent suppression of Bax translocation and inhibition of cytochrome c release prevent caspase-9 and caspase-3 activation [58,60]. Additionally, exosomal cargo modulates ERK1/2 and STAT3 signalling, further promoting cellular survival [55,60]. Oxidative stress reduction constitutes another critical mechanism [55,58]. SC-Exos decrease reactive oxygen species generation, enhance expression of antioxidant enzymes including superoxide dismutase and catalase, and stabilize mitochondrial membrane potential [56,57,59]. These effects collectively preserve cardiomyocyte viability and attenuate infarct expansion [55,60]. Importantly, the anti-apoptotic efficacy of SC-Exos appears dose-dependent and influenced by timing of administration relative to ischemic insult [55,58]. Early post-MI delivery enhances cardiomyocyte salvage, whereas late-stage administration primarily modulates remodelling processes [56,59].

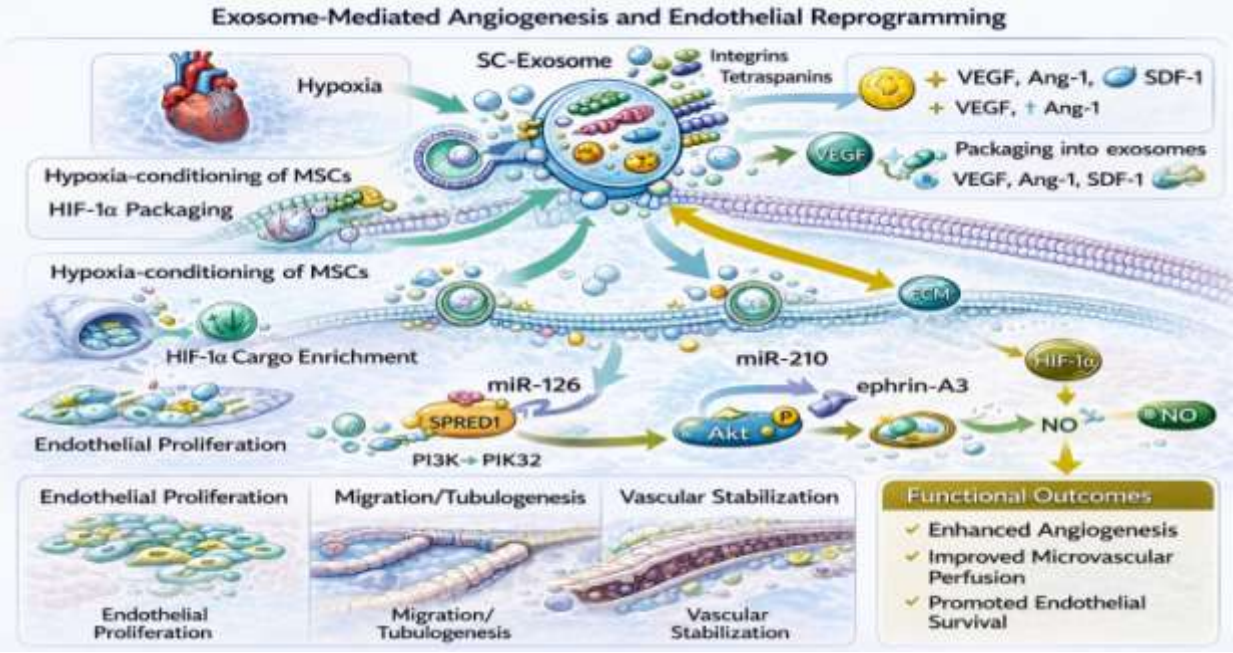

Figure 5: Exosome-mediated angiogenesis and endothelial reprogramming in post-ischemic myocardium. Stem cell–derived exosomes (SC-Exos) enriched in pro-angiogenic microRNAs (miR-126, miR-210) and proteins (VEGF, angiopoietin-1, SDF-1) activate PI3K/Akt/eNOSsignaling, suppress SPRED1 and PIK3R2, and enhance nitric oxide bioavailability. Hypoxia-conditioned parental cells augment HIF-1α–dependent cargo loading, amplifying endothelial proliferation, migration, and tubulogenesis, thereby promoting microvascular regeneration and perfusion recovery following myocardial injury.

Exosome-Mediated Angiogenesis and Endothelial Reprogramming:-

Impaired microvascular perfusion constitutes a central determinant of progressive ventricular remodelling following myocardial infarction and in chronic heart failure [61–64]. Capillary rarefaction exacerbates hypoxia, perpetuates cardiomyocyte apoptosis, and promotes fibrotic remodelling [61,65]. Restoration of microvascular density therefore represents a critical therapeutic objective [62,66]. Stem cell–derived exosomes (SC-Exos) exert potent pro-angiogenic effects through coordinated modulation of endothelial proliferation, migration, and tube formation [63,67]. Exosomal microRNAs play a dominant regulatory role in endothelial reprogramming. miR-126, enriched in mesenchymal stem cell–derived exosomes, enhances angiogenesis through suppression of SPRED1 and PIK3R2, leading to augmented PI3K/Akt signalling and endothelial nitric oxide synthase (eNOS) activation [64,68]. Increased nitric oxide bioavailability promotes vasodilation, endothelial survival, and anti-thrombotic signalling [65,69]. Similarly, miR-210, frequently upregulated under hypoxic preconditioning of stem cells, enhances endothelial cell survival through modulation of ephrin-A3 and regulation of mitochondrial metabolism [66,70].

Hypoxia-inducible factor-1α (HIF-1α)–dependent cargo enrichment significantly amplifies angiogenic potency [67,71]. Exosomes derived from hypoxia-conditioned MSCs demonstrate superior vascular regenerative capacity

compared to normoxic counterparts, reflecting selective packaging of angiogenic transcripts and proteins [68,72]. This suggests that environmental priming of parental stem cells may be strategically employed to tailor exosomal therapeutic profiles [69,73].

Beyond micro RNA-mediated regulation, exosomal proteins such as VEGF, angiopoietin-1, and stromal cell–derived factor-1 contribute to endothelial chemotaxis and vascular stabilization [70,74]. Importantly, exosomal integrins influence endothelial tropism and extracellular matrix interactions, potentially enhancing site-specific vascular repair [71,75]. However, angiogenesis must be tightly regulated. Excessive or aberrant vascular proliferation may lead to unstable neovascular networks [72,76]. Therefore, understanding dose-dependent and temporal regulation of exosome-mediated angiogenesis remains essential for translational optimization [73,77].

Anti-Fibrotic Remodelling and Extracellular Matrix Modulation:-

Cardiac fibrosis represents a maladaptive response characterized by fibroblast activation, differentiation into myofibroblasts, and excessive extracellular matrix (ECM) deposition [74,78]. Persistent activation of the transforming growth factor-β (TGF-β)/Smad pathway drives collagen I and III synthesis, leading to ventricular stiffening and diastolic dysfunction [75,79].

Stem cell–derived exosomes attenuate fibrotic remodelling through multiple molecular mechanisms [76,80]. Exosomal miR-29 directly targets collagen transcripts, reducing ECM deposition [77,81]. miR-133a and miR-30 suppress connective tissue growth factor and TGF-β receptor expression, thereby attenuating Smad2/3 phosphorylation and nuclear translocation [78,82]. Reduced expression of α-smooth muscle actin (α-SMA) limits myofibroblast differentiation [79,83].Beyond microRNA-mediated effects, exosomal cargo modulates fibroblast metabolic reprogramming [80,84]. Activated fibroblasts exhibit glycolytic shift and enhanced mitochondrial biogenesis [81,85]. Emerging evidence suggests that SC-Exos may restore metabolic quiescence in cardiac fibroblasts by suppressing pro-fibrotic transcription factors including myocardin-related transcription factor and serum response factor [82,86]. Importantly, fibrosis is not solely a structural phenomenon but also an electrical substrate contributing to arrhythmogenesis [83,87]. By attenuating interstitial fibrosis, exosomes may indirectly improve electrical conduction and reduce arrhythmic risk [84,88].

Despite these promising findings, the stage-specific impact of exosomes on established chronic fibrosis versus early post-infarct remodelling remains insufficiently characterized [85,89]. Long-standing scar tissue may be less amenable to reversal, highlighting the importance of therapeutic timing [86,90]. myofibroblast differentiation [79,83].Beyond micro RNA-mediated effects, exosomal cargo modulates fibroblast metabolic reprogramming [80,84]. Activated fibroblasts exhibit glycolytic shift and enhanced mitochondrial biogenesis [81,85]. Emerging evidence suggests that SC-Exos may restore metabolic quiescence in cardiac fibroblasts by suppressing pro-fibrotic transcription factors including myocardin-related transcription factor and serum response factor [82,86]. Importantly, fibrosis is not solely a structural phenomenon but also an electrical substrate contributing to arrhythmogenesis [83,87]. By attenuating interstitial fibrosis, exosomes may indirectly improve electrical conduction and reduce arrhythmic risk [84,88]. Despite these promising findings, the stage-specific impact of exosomes on established chronic fibrosis versus early post-infarct remodelling remains insufficiently characterized [85,89]. Long-standing scar tissue may be less amenable to reversal, highlighting the importance of therapeutic timing [86,90].

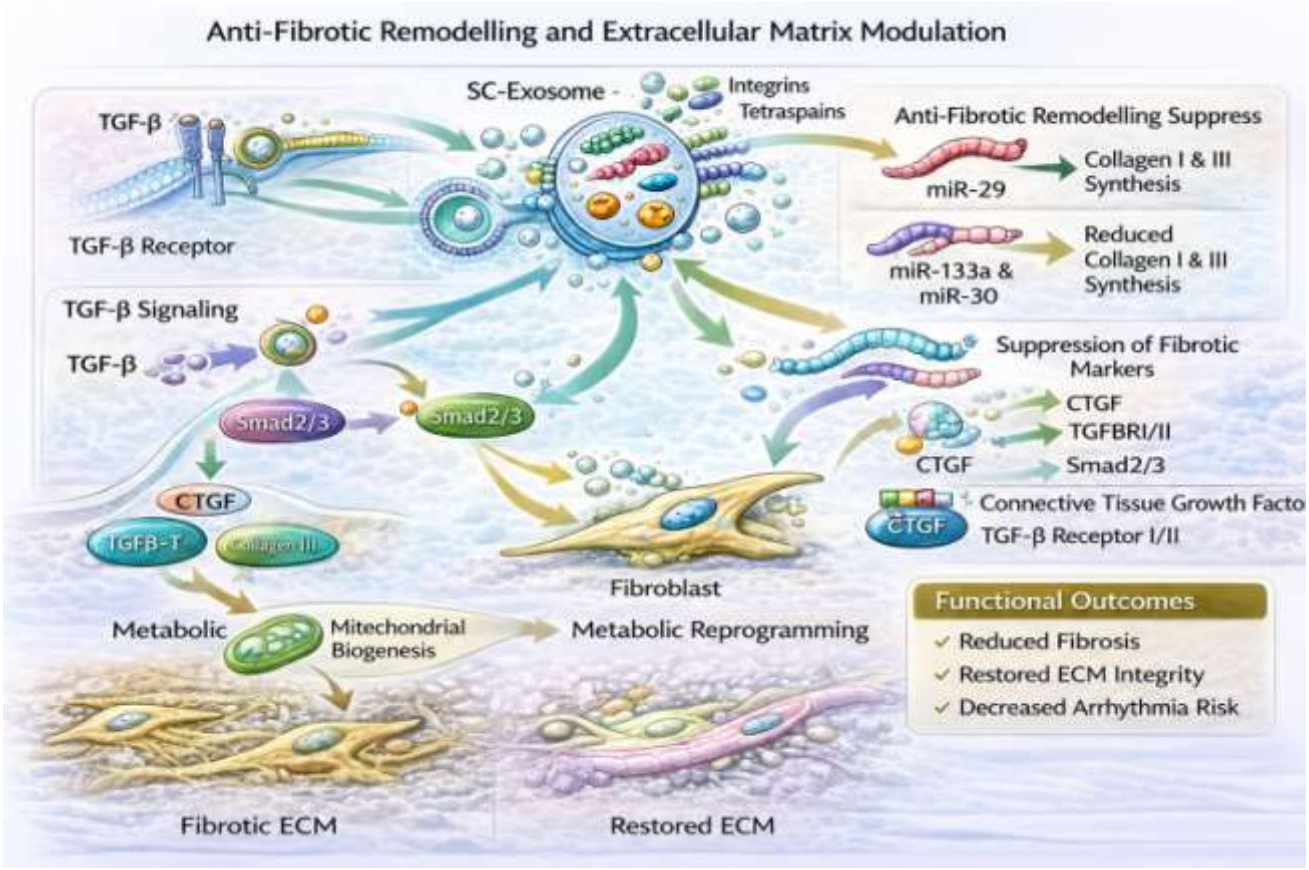

Figure 6:Exosome-mediated attenuation of cardiac fibrotic remodeling. Stem cell–derived exosomes suppress TGF-β/Smad2/3 signaling via delivery of anti-fibrotic microRNAs (miR-29, miR-133a, miR-30), downregulating collagen I/III synthesis, CTGF, TGF-β receptor expression, and α-SMA–dependent myofibroblast differentiation. Concurrent modulation of fibroblast metabolic reprogramming restores extracellular matrix homeostasis, limits ventricular stiffening, and reduces arrhythmogenic substrate formation.

Immunomodulation and Macrophage Polarization

The inflammatory response following myocardial injury is biphasic, consisting of an initial pro-inflammatory phase dominated by M1 macrophages, followed by a reparative phase characterized by M2 macrophage polarization [87,91]. Persistent M1 activation contributes to adverse remodelling and ventricular dilation [88,92]. Stem cell–derived exosomes exert immunomodulatory effects by influencing macrophage phenotype [89,93]. Exosomal miR-146a and miR-181b suppress Toll-like receptor signalling and inhibit NF-κB nuclear translocation, thereby reducing pro-inflammatory cytokine production including TNF-α, IL-1β, and IL-6 [90,94]. Concurrently, enhanced expression of arginase-1 and IL-10 promotes M2 polarization and tissue repair [91,95].

In addition to macrophages, SC-Exos influence T-cell activation and dendritic cell maturation [92,96]. Reduction in antigen-presenting cell activation may attenuate chronic immune activation observed in advanced heart failure [93,97]. However, excessive immunosuppression could impair host defence, necessitating balanced modulation [94,98]. Recent single-cell RNA sequencing analyses suggest that exosome-mediated reprogramming extends to cardiac resident macrophages and fibroblast–immune cell crosstalk [95,99]. These intercellular communication networks represent a complex and underexplored dimension of exosome biology [96,100].

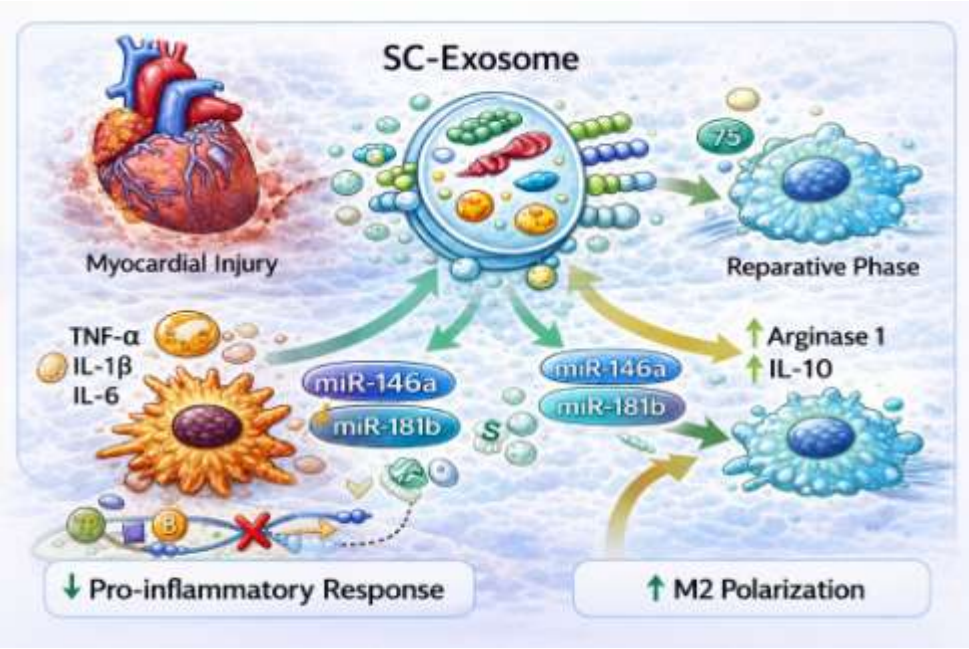

Figure 7:SC-Exosome–mediated macrophage reprogramming. Exosomal miR-146a and miR-181b inhibit TLR/NF-κB signalling and pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6), while promoting arginase-1 and IL-10 expression to drive M2 polarization and resolution of post-infarct inflammation.

Mitochondrial Transfer and Bioenergetic Restoration:-

Mitochondrial dysfunction is a defining feature of failing myocardium [97,101]. Reduced oxidative phosphorylation, impaired electron transport chain activity, increased reactive oxygen species production, and disrupted mitochondrial dynamics collectively contribute to contractile failure [98,102]. Emerging evidence indicates that SC-Exos modulate mitochondrial integrity through both indirect and potentially direct mechanisms [99,103]. Exosomal microRNAs regulate expression of genes governing mitochondrial fusion and fission, including mitofusin-2 and dynamin-related protein-1 [100,104]. Restoration of mitochondrial membrane potential and reduction of cytochrome c release have been observed in experimental models [101,105].

A particularly intriguing hypothesis involves exosome-mediated mitochondrial transfer [102,106]. Although full organelle transfer remains debated, mitochondrial DNA fragments and metabolic enzymes have been identified within exosomal cargo [103,107]. These components may integrate into recipient cardiomyocytes, facilitating metabolic recovery [104,108]. Furthermore, SC-Exos enhance expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a master regulator of mitochondrial biogenesis [105,109]. Upregulation of PGC-1α promotes replication of mitochondrial DNA, increases oxidative phosphorylation capacity, and restores ATP synthesis [106,110]. Given that metabolic inflexibility is a hallmark of chronic heart failure, the capacity of exosomes to reprogram bioenergetics represents a highly promising therapeutic avenue [107,111].

Table 2:Restoration of Bioenergetics - The integrated effect results in a shift from metabolic inflexibility to efficient oxidative phosphorylation

Component	Transition in Failing Heart	Post SC-Exo Treatment
Dynamics	Excessive Fission (Drp1↑)	Enhanced Fusion (Mfn2↑)
Biogenesis	Reduced Mitochondrial Mass	PGC−1α driven replication
Energy Output	Disrupted ETC / Low ATP	Restored Oxidative Phosphorylation
Cell Survival	Cytochrome c release / Apoptosis	Membrane Potential (ΔΨm) Stability

Metabolic Reprogramming in the Failing Myocardium:-

Healthy adult cardiomyocytes primarily rely on fatty acid oxidation for ATP production [108,112]. In heart failure, a metabolic shift toward glycolysis occurs, accompanied by reduced mitochondrial efficiency and accumulation of toxic lipid intermediates [109,113]. Stem cell–derived exosomes appear capable of restoring metabolic flexibility [110,114]. Exosomal cargo modulates AMP-activated protein kinase (AMPK) signalling, enhancing fatty acid oxidation and reducing lipotoxic stress [111,115]. Activation of sirtuin-1 and downstream deacetylation pathways further promotes mitochondrial efficiency [112,116].Exosomal long non-coding RNAs have also been implicated in metabolic regulation [113,117]. For example, lncRNA H19 influences glucose uptake and glycolytic enzyme expression, potentially stabilizing metabolic homeostasis [114,118]. The interplay between metabolic reprogramming and structural remodelling remains incompletely understood [115,119]. Whether metabolic restoration precedes functional recovery or occurs secondary to reduced apoptosis and fibrosis requires systematic temporal investigation [116,120].

Epigenetic and Transcriptomic Reconfiguration:-

Exosome-mediated gene regulation extends beyond direct mRNA suppression [81–82]. Exosomal microRNAs and long non-coding RNAs influence epigenetic landscapes by modulating DNA methyltransferases, histone acetyltransferases, and chromatin remodelling complexes [81,83]. Altered chromatin accessibility within cardiomyocytes may facilitate re-expression of fetal gene programs associated with survival and stress adaptation [82,84]. Additionally, circRNAs transported via exosomes function as competing endogenous RNAs, modulating microRNA availability and expanding regulatory complexity [83,85]. High-throughput transcriptomic and proteomic analyses demonstrate widespread reprogramming of recipient cardiac cells following exosome exposure [84,86]. However, integration of multi-omics datasets remains limited, hindering comprehensive systems-level understanding [85,87].

Intercellular Network Reorganization in the Cardiac Niche:-

The myocardium functions as an integrated multicellular ecosystem comprising cardiomyocytes, endothelial cells, fibroblasts, immune cells, and pericytes [86,88]. Exosomes serve as communication nodes within this network [81,82]. SC-Exos not only target cardiomyocytes but also modulate endothelial–fibroblast cross-talk, immune–fibroblast signalling, and paracrine feedback loops [83,84]. Network-level modelling suggests that exosome-mediated signalling may rebalance pathological remodelling circuits toward regenerative trajectories [85,86]. Despite these insights, spatial mapping of exosome biodistribution within cardiac tissue remains technically challenging [87,88]. Advanced imaging and labelling technologies are required to elucidate cell-specific uptake dynamics [81,88].

Delivery Strategies and Bioengineering Approaches for Enhanced Therapeutic Precision:-

Despite compelling mechanistic evidence, therapeutic translation of stem cell–derived exosomes (SC-Exos) is constrained by delivery inefficiencies [82,83]. Systemic administration results in rapid clearance through the reticuloendothelial system, with predominant accumulation in the liver, spleen, and lungs [84,85]. Limited myocardial retention substantially reduces therapeutic bioavailability. Consequently, optimization of delivery platforms represents a pivotal determinant of clinical success [86,87]. Intramyocardial injection improves local concentration but is invasive and clinically impractical for repeated dosing [88]. Intracoronary infusion offers less invasive myocardial targeting but risks microvascular obstruction if vesicle aggregation occurs [81,82]. Therefore, engineering strategies aimed at enhancing tissue tropism, sustained release, and cellular uptake are under intensive investigation [83,84].

Hydrogel-based delivery systems have emerged as promising adjuncts [85,86]. Injectable biomaterials composed of alginate, collagen, or decellularized extracellular matrix scaffolds can entrap exosomes and facilitate controlled release within infarcted myocardium [87]. Such systems prolong local retention, attenuate washout, and synchronize vesicle release with reparative phases of remodelling [88]. Preclinical models demonstrate improved ejection fraction and reduced fibrosis when exosomes are delivered within biodegradable hydrogels compared to bolus injection [81,82]. Surface modification of exosomes offers another translational strategy [83,84]. Genetic engineering of parental stem cells to express targeting ligands, such as cardiomyocyte-specific peptides or integrin-binding domains, enhances selective myocardial uptake [85,86]. Conjugation of ischemia-targeting moieties to exosomal membranes further increases infarct homing capacity [87]. However, these approaches require rigorous safety validation to exclude unintended off-target effects [88].

Cargo engineering constitutes a particularly promising frontier [81,82]. CRISPR-based editing and microRNA overexpression strategies allow enrichment of cardioprotective miRNAs within exosomes [83,84]. For example, selective enrichment of miR-126 or miR-21 amplifies angiogenic and anti-apoptotic potency, respectively [85,86]. Conversely, depletion of oncogenic or pro-fibrotic cargo reduces potential adverse signalling [87]. The challenge lies in achieving reproducible, scalable, and regulatory-compliant manufacturing of engineered vesicles [88].

Nanotechnology-assisted hybrid systems are also being explored [81,82]. Fusion of exosomes with synthetic nanoparticles may enhance stability, targeting precision, and cargo loading efficiency [83,84]. Such hybrid vesicles combine biological compatibility with engineering versatility, although immunogenic and regulatory concerns remain [85–88].

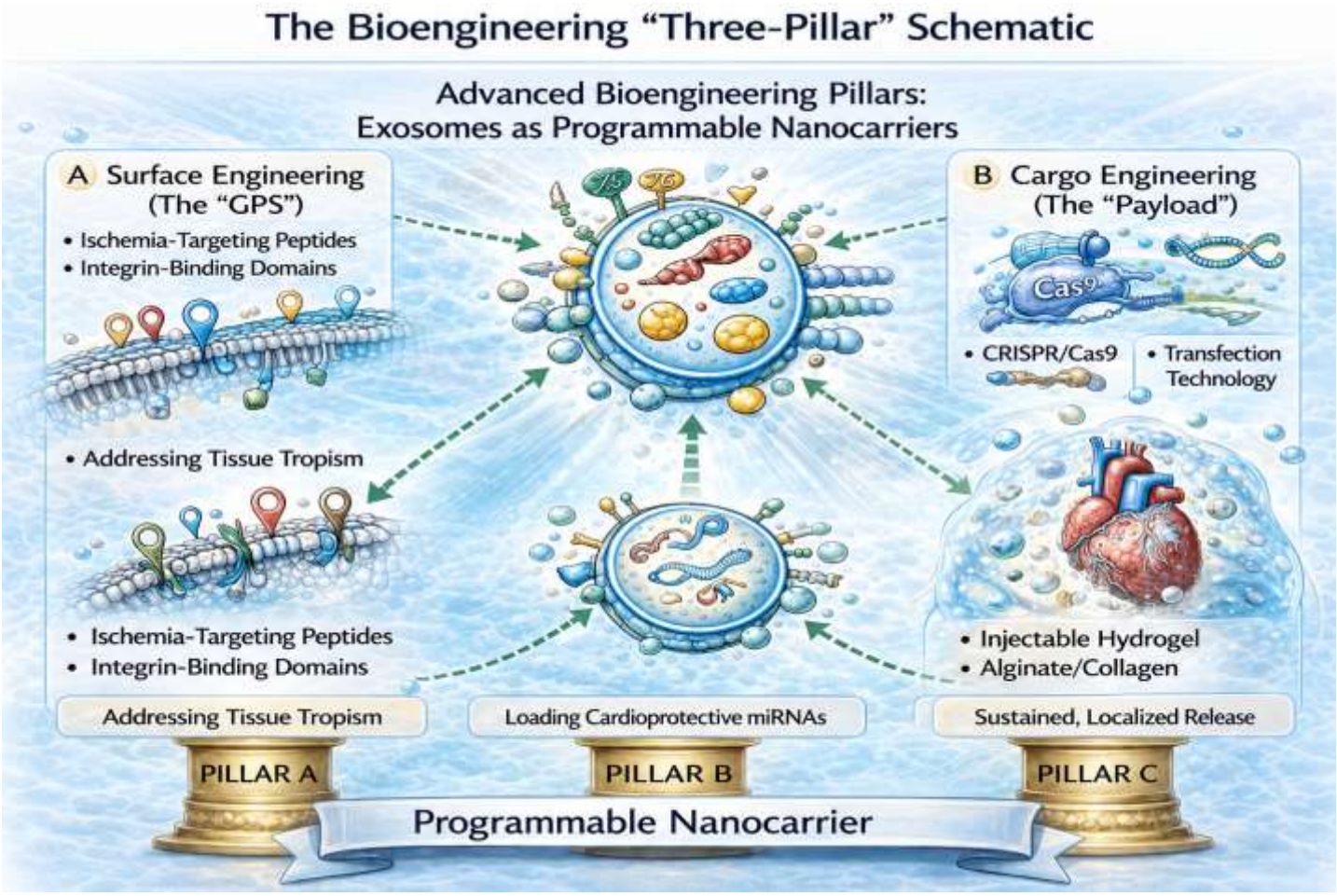

Figure 8:Bioengineered exosomes as programmable nanocarriers.Surface modification with ischemia-targeting peptides and integrin-binding domains enhances tissue tropism (Pillar A), CRISPR/Cas9- or transfection-mediated enrichment of cardioprotective miRNAs (miR-126, miR-21) optimizes therapeutic payload (Pillar B), and injectable alginate/collagen hydrogels enable sustained, localized myocardial delivery (Pillar C).

Table 3:Comparative Analysis of Delivery Route - This table summarizes the trade-offs between conventional administration methods

Delivery Route	Retention Level	Invasiveness	Clinical Risk/Constraint	Optimization Strategy
Systemic (IV)	Very Low	Low	Rapid clearance by liver/spleen (RES)	Surface modification with targeting ligands
Intracoronary	Moderate	Medium	Risk of microvascular obstruction/aggregation	Dilution protocols; high-purity isolation
Intramyocardial	High	High	Highly invasive; risk of arrhythmia/tissue damage	Guided catheter delivery
Hydrogel Scaffold	Superior	Medium	Variable biodegradation rates	Controlled-release biomaterials

Manufacturing, Standardization, and GMP Compliance:-

Large-scale production of clinical-grade exosomes presents formidable challenges [89–90]. Ultracentrifugation, the most commonly used isolation technique in experimental settings, lacks scalability and reproducibility [91]. Alternative methods such as size-exclusion chromatography, tangential flow filtration, and immunoaffinity capture provide improved consistency but require validation under Good Manufacturing Practice (GMP) conditions [92–93]. Batch-to-batch variability in exosomal cargo composition remains a critical obstacle [94]. Variations in donor characteristics, passage number, culture conditions, oxygen tension, and nutrient availability significantly influence vesicle content [95]. Without standardized upstream protocols, therapeutic reproducibility cannot be ensured [96]. Quantification metrics also lack consensus [97]. Exosome dosing may be defined by protein concentration, particle number, or functional bioactivity assays [98]. However, these parameters do not necessarily correlate linearly with therapeutic potency [99]. Functional potency assays evaluating angiogenesis, apoptosis inhibition, or macrophage polarization may ultimately provide more clinically relevant quality control benchmarks [100].

Furthermore, storage stability poses additional challenges [101]. Freeze–thaw cycles may compromise membrane integrity and cargo functionality [102]. Lyophilization and cryoprotectant strategies are under investigation to preserve bioactivity [103]. Regulatory frameworks for extracellular vesicle therapeutics remain evolving [104]. Whether exosomes are classified as biological products, cell-derived therapies, or advanced therapy medicinal products varies by jurisdiction [105]. Harmonization of regulatory guidelines is essential to accelerate clinical translation [106].

Table 4: Clinical Translation Framework for GMP-Compliant SC-Exo Manufacturing

Manufacturing Dimension	Critical Challenges & Obstacles	Technical Strategies for Optimization	Regulatory/Standardization Benchmark
Isolation & Scalability (DSP)	Ultracentrifugation lacks reproducibility and industrial scalability; risks vesicle damage.	Transition to Tangential Flow Filtration (TFF) and Size-Exclusion Chromatography (SEC) for high-purity, large-volume yields.	Validation of process consistency under GMP conditions; removal of non-vesicular protein contaminants.
Upstream Variability (USP)	Batch-to-batch heterogeneity due to donor age, passage number, oxygen tension (O2), and media composition.	Implementation of standardized bioreactor systems; use of chemically defined, serum-free media; specific donor selection criteria.	Established Standard Operating Procedures (SOPs) for cell culture and harvest timing.
Quantification & Dosing	Lack of correlation between total protein/particle count and actual biological therapeutic potency.	Development of functional potency assays (e.g., tube formation for angiogenesis or LDH release for anti-apoptosis).	Shift from "dosage by volume" to "dosage by bioactivity units" (Functional Benchmarks).
Storage & Stability	Membrane rupture during freeze-thaw cycles; loss of	Utilization of lyophilization (freeze-drying) and advanced	Stability testing and shelf-life validation at -80°C vs. 4°C; monitoring of

	miRNA or protein cargo functionality over time.	cryoprotectants (e.g., trehalose) to maintain structural integrity.	membrane potential (ΔΨ).
Regulatory Framework	Ambiguous classification (Biological product vs. Cell-derived therapy); jurisdictional variance.	Active participation in International Society for Extracellular Vesicles (ISEV) guidelines and harmonization efforts.	Compliance with MIFlowCyt-EV and MISEV reporting standards; safety data to exclude off-target effects.

Clinical Translation and Emerging Human Studies:-

Although preclinical evidence is substantial, clinical data remain limited [107–108]. Early-phase trials investigating extracellular vesicle–based therapy in cardiovascular diseases are ongoing, focusing primarily on safety and feasibility [89,90]. Preliminary findings suggest favourable safety profiles, with minimal immunogenicity and no significant arrhythmogenic events reported thus far [91,92]. However, robust randomized controlled trials evaluating long-term functional outcomes are lacking [93,94]. Standardized patient selection criteria, stratification by HF phenotype (HFrEF vs HFpEF), and timing relative to myocardial injury remain unresolved variables [95,96]. Moreover, optimal dosing frequency and route of administration require systematic investigation [97]. Importantly, chronic heart failure represents a heterogeneous syndrome [98]. Personalized approaches integrating biomarker profiling, imaging parameters, and molecular signatures may be required to identify patients most likely to benefit from exosome-based interventions [99,100].

Gap Analysis: Mechanistic and Translational Limitations:-

Despite rapid progress, substantial gaps persist that must be addressed to elevate SC-Exos from experimental promise to clinical standard [101–102]. First, mechanistic redundancy and pleiotropy complicate definitive pathway attribution [103]. Many studies report activation of PI3K/Akt, ERK1/2, and STAT3 signalling; however, causal hierarchy among these pathways remains unclear [104]. Systems-level modelling integrating phosphoproteomics and transcriptomics is necessary to delineate dominant signalling nodes [105]. Second, the spatial and temporal dynamics of exosome uptake in vivo remain insufficiently characterized [106]. Advanced imaging techniques such as super-resolution microscopy, single-vesicle tracking, and radiolabelled biodistribution studies are required to quantify myocardial retention and cellular specificity [107].

Third, inter-individual variability in stem cell donors may influence therapeutic consistency [108]. Age, comorbidities, metabolic status, and inflammatory background of stem cell donors may alter exosomal cargo [89]. Comparative studies evaluating autologous versus allogeneic exosomes are urgently needed [90]. Fourth, the long-term safety profile of repeated exosome administration remains uncertain [91]. Although immunogenicity appears low, cumulative effects on immune surveillance, fibrosis, or unintended angiogenesis require longitudinal assessment [92]. Fifth, comparative efficacy between MSC-, CPC-, and iPSC-derived exosomes has not been rigorously evaluated in standardized head-to-head trials [93]. Direct comparison within identical large-animal models would provide critical clarity [94].

Sixth, stage-specific therapeutic windows remain poorly defined [95]. Acute ischemic injury may require anti-apoptotic and pro-angiogenic emphasis, whereas chronic HF may necessitate anti-fibrotic and metabolic reprogramming strategies [96]. Precision stratification based on remodelling stage could substantially improve outcomes [97]. Seventh, integration of multi-omics datasets remains fragmented [98]. Proteomics, transcriptomics, lipidomics, and metabolomics analyses are often conducted independently [99]. Comprehensive integrative modelling could reveal synergistic cargo interactions and predictive biomarkers of response [100].Finally, ethical, regulatory, and manufacturing challenges continue to limit scalability [101]. Without harmonized international standards, translation will remain heterogeneous and slow [102].

Table 5: Key Translational Gaps and Strategic Opportunities in Engineered Exosome-Based Therapy for Cardiovascular Disease

Gap Area	Current Status	Opportunity for Review
Cargo Loading	Electroporation/extrusion ↑ efficiency but damages integrity; genetic mods complex.	Framework for Cargo–Mechanism matching (e.g., miR for fibrosis vs. peptides for homing).

Targeting/Delivery	Peptides/hydrogels improve retention; two-step strategies promising but preclinical.	Target Paradigm: Compare ligands (CSTSMLKAC vs. others) for HF vs. MI; clinical scalability.
Standardization/Safety	Heterogeneity in production; poor half-life, immunogenicity risks.	GMP protocols, zeta optimization, long-term HF trials.
Clinical Translation	Rodent data strong; human data sparse, no Phase II+ for engineered exosomes.	Precision Therapy Roadmap: Integrate multi-omics for patient-specific cargo.

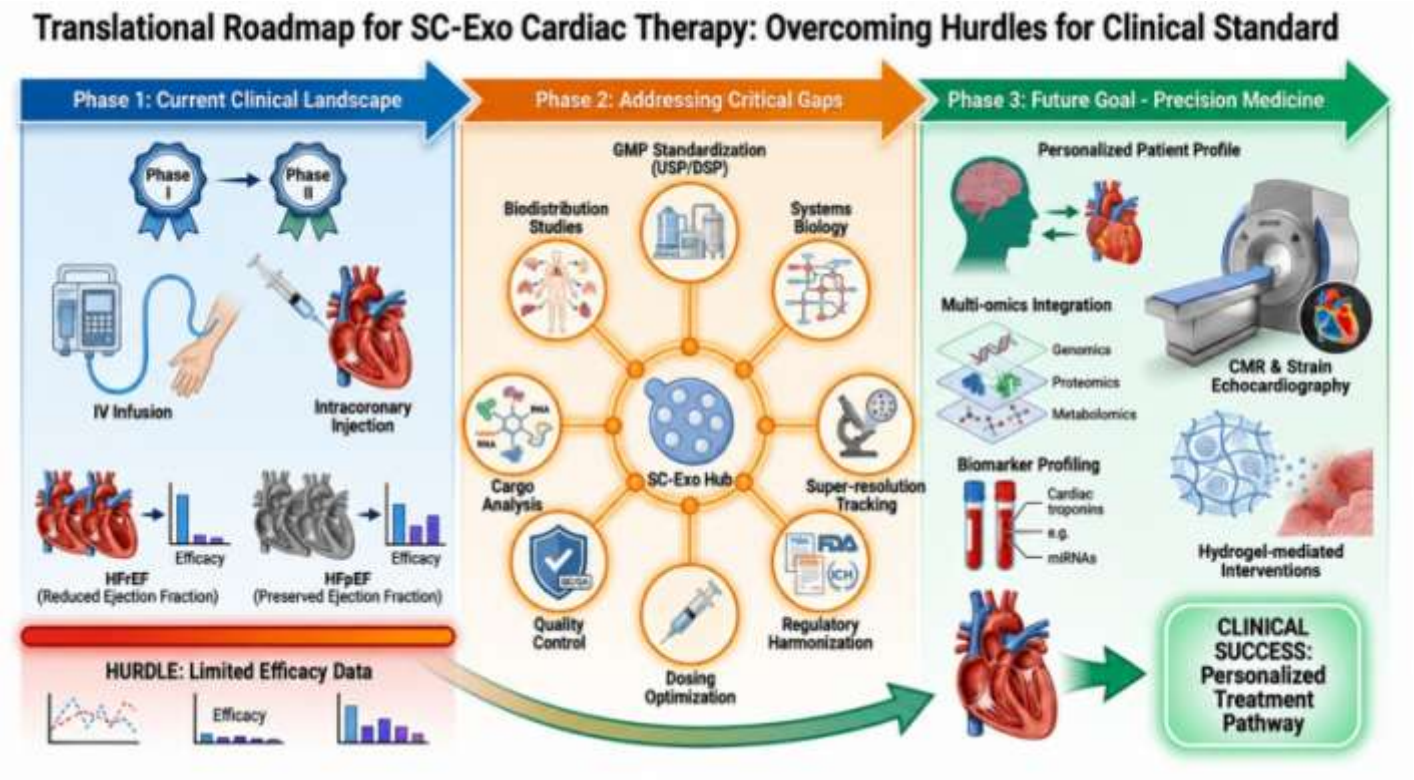

Figure 9. Translational Roadmap for SC-Exo Cardiac Therapy: Overcoming Hurdles for Clinical Standard. This graphical abstract depicts the three-phase translational pathway for stem cell-derived exosome (SC-Exo) therapies in cardiac repair. Phase 1 illustrates the current clinical landscape, including early-phase trials, delivery routes (IV vs. Intracoronary), and patient stratification (HFrEF/HFpEF), with a critical hurdle of limited efficacy data. Phase 2 identifies eight major research and manufacturing barriers: GMP standardization (USP/DSP), systems biology integration, super-resolution tracking, and regulatory harmonization (FDA/EMA/ISEV). Phase 3 envisions the future precision medicine approach, integrating multi-omics, biomarker profiling, and advanced cardiac imaging (CMR/Strain) to optimize hydrogel-mediated interventions for personalized cardiac regeneration.

Conclusion:-

Stem cell–derived exosomes represent a transformative paradigm in cardiovascular regenerative medicine. Unlike cell-based therapies, exosomes offer a cell-free, minimally immunogenic, and mechanistically versatile platform capable of orchestrating complex reparative signalling networks within the failing myocardium. Through coordinated modulation of apoptosis, angiogenesis, fibrosis, immune polarization, mitochondrial dynamics, and metabolic reprogramming, SC-Exos address multiple converging mechanisms that underlie pathological cardiac remodelling.

The mechanistic sophistication of exosome-mediated therapy lies in its systems-level influence. Rather than targeting a single receptor or signalling pathway, exosomes deliver multiplexed regulatory cargo capable of

reprogramming gene expression, epigenetic architecture, and cellular metabolism simultaneously. This multidimensional capability distinguishes exosome therapeutics from conventional pharmacological interventions.
Nevertheless, translation into clinical practice demands resolution of substantial mechanistic and logistical challenges. Standardization of isolation techniques, cargo profiling, dosing strategies, and delivery systems is imperative. Precision engineering approaches—including targeted surface modification, cargo enrichment, and biomaterial-assisted release—may significantly enhance myocardial retention and therapeutic potency. Furthermore, stage-specific and phenotype-guided treatment paradigms must be developed to address the heterogeneity inherent in heart failure syndromes.

Future research should prioritize multi-omics integration, large-animal validation, longitudinal safety assessment, and rigorously designed randomized clinical trials. Collaboration between bioengineers, molecular cardiologists, translational scientists, and regulatory authorities will be essential to establish standardized frameworks for therapeutic development. In summary, stem cell–derived exosomes embody a promising frontier in myocardial regeneration. With strategic refinement, precision bioengineering, and systematic translational validation, exosome-based therapeutics have the potential to redefine the treatment landscape of heart failure and shift the paradigm from symptomatic management toward genuine myocardial repair.

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