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Editorial

Synergizing Regeneration and Pharmacology: Metformin-Loaded MSC Exosomes as a Biologically Intelligent Strategy for Myocardial Repair

Mostafa Akbariqomi [1], **Reza Heidari** [2*]

[1] Tissue Engineering and Regenerative Medicine Research Center, New Health Technologies Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[1] Cancer Epidemiology Research Center (AJA-CERTC), AJA University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Reza Heidari, Ph.D., Cancer Epidemiology Research Center (AJA-CERTC), AJA University of Medical Sciences, Tehran, Iran. Email: r-heidary@ajaums.ac.ir

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Despite remarkable advances in reperfusion strategies, antithrombotic therapy, and secondary prevention, myocardial infarction (MI) remains a leading cause of heart failure and cardiovascular mortality worldwide.[1] Among emerging regenerative approaches, exosome engineering has attracted considerable scientific interest. Exosomes are nano-sized extracellular vesicles secreted by nearly all cell types and are now recognized as highly organized mediators of intercellular communication. By transporting microRNAs, proteins, lipids, and signaling molecules, exosomes influence gene expression and cellular behavior in target tissues.[2,3] We argue that integrating metabolic modulators with engineered exosome delivery platforms represents not merely an incremental innovation but a paradigm shift in post-MI regenerative therapy.

Mesenchymal stem cell (MSC)-derived exosomes are particularly attractive for MI therapy because of their intrinsic anti-inflammatory, anti-apoptotic, anti-fibrotic, and pro-angiogenic properties. Experimental studies have shown that these exosomes can attenuate oxidative stress, suppress cardiomyocyte apoptosis, enhance endothelial repair, and improve ventricular function following ischemic injury. Importantly, exosomes exhibit lower immunogenicity, superior biosafety profiles, and greater stability during storage and administration compared with whole-cell therapies.[4]

However, native exosomes alone may not fully address the complex pathophysiological mechanisms underlying MI. This limitation has stimulated the development of engineered exosome platforms capable of delivering targeted therapeutic payloads.[4,5] Among these emerging approaches, the integration of exosome-based delivery systems with established cardiometabolic agents represents a particularly promising strategy.

A highly innovative therapeutic concept involves the use of metformin-loaded MSC-derived exosomes as a targeted regenerative approach for MI treatment.[6,7] Metformin, traditionally regarded as a first-line antidiabetic agent, has increasingly demonstrated pleiotropic cardioprotective effects independent of glycemic control. Experimental evidence indicates that metformin can reduce oxidative stress, activate AMP-activated protein kinase (AMPK), improve mitochondrial function, inhibit inflammatory signaling, and attenuate myocardial fibrosis. Nevertheless, systemic administration may fail to achieve sufficiently concentrated delivery to ischemic myocardial tissue, particularly during acute infarction.[8]

Dual-function therapeutic systems may amplify myocardial repair beyond what either therapy achieves independently. Metformin-loaded MSC exosomes may exert synergistic cardioprotective effects through multiple complementary pathways. First, exosomal cargo can suppress ischemia-induced cardiomyocyte apoptosis by modulating mitochondrial permeability and reducing reactive oxygen species generation. Second, metformin-mediated activation of AMPK signaling may improve cellular energy homeostasis in ischemic myocardium. Third, MSC exosomes can regulate macrophage polarization toward anti-inflammatory phenotypes, thereby limiting excessive inflammatory injury during post-infarction remodeling. In parallel, enhanced angiogenesis mediated by exosomal microRNAs may improve perfusion within peri-infarct regions and support tissue regeneration.[4]

Among the advantages of exosomes lies their targeted delivery potential. Engineered exosomal membranes can be modified with cardiac-homing peptides or ischemia-responsive ligands that selectively direct therapeutic cargo toward injured myocardial tissue. Such precision-targeted systems may substantially increase local drug

bioavailability while reducing systemic adverse effects.[9] This strategy represents a convergence of regenerative medicine, nanotechnology, and precision pharmacology.

Injectable hydrogels or cardiac patches incorporating metformin-loaded MSC exosomes may provide sustained local release within infarcted myocardium, thereby prolonging therapeutic exposure and enhancing tissue retention. Such approaches may also overcome their relatively short *in vivo* half-life.

Despite its considerable promise, this strategy remains in an early translational stage. Significant challenges must still be addressed before clinical implementation becomes feasible. Standardized methods for exosome isolation, metformin loading efficiency, dosage optimization, and large-scale good manufacturing practice (GMP) production are not yet fully established. Moreover, the heterogeneity of MSC sources may influence exosomal composition and therapeutic potency. Long-term safety evaluation also remains essential, particularly regarding biodistribution, immunogenicity, thrombogenicity, and unintended off-target signaling.

MI is a multifactorial disease involving intertwined pathways of ischemic injury, inflammation, oxidative stress, metabolic dysfunction, and fibrotic remodeling. Conventional single-target therapies often fail to adequately address this biological complexity. In contrast, engineered exosome systems offer a multidimensional therapeutic platform capable of simultaneously modulating several regenerative pathways.

The future of MI therapy may, therefore, depend not solely on reperfusion strategies but also on biologically intelligent repair systems capable of restoring tissue homeostasis after injury. Engineered exosomes represent one of the most promising examples of this next-generation regenerative paradigm and may ultimately emerge as central therapeutic agents in cardiovascular medicine.

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