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Editorial

Exosomes in Tissue Engineering and Regenerative Medicine: Unlocking their Therapeutic Potential as Biological Nanocarriers

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For decades, regenerative medicine has offered the promise of repairing, replacing, or regenerating damaged tissues and organs, and stem cell therapy has emerged as a cornerstone of this vision. However, despite decades of research, cell-based therapies have faced persistent challenges, including poor cell survival and homing, immunogenicity, tumorigenic risks, scalability limitations, and complex regulatory pathways. These obstacles have led to a fundamental paradigm shift from cell-based therapies to cell-free strategies. At the center of this evolution are exosomes.[1,2]

Exosomes are More Than Just Simple Vesicles

Exosomes are lipid bilayer extracellular vesicles, ranging in size from 30 to 150 nm, that are naturally secreted by almost all cell types. They are not cellular debris but rather complex communication vehicles that carry a rich cargo of bioactive molecules such as proteins, lipids, nucleic acids, and microRNAs. These vesicles deliver their molecular cargo to recipient cells, where they establish cellular connections that lead to the regulation and modulation of cellular function and changes in the microenvironment. What makes exosomes particularly attractive for regenerative medicine is their ability to convey many of the therapeutic potential of their parent cells, without the associated risks. For example, according to existing studies, mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as a pivotal therapeutic agent in this field as they have been shown to significantly mediate tissue repair through modulation and regulation of angiogenesis, immunoregulation, extracellular matrix remodeling, and re-epithelialization. They reduce apoptosis and inflammatory responses while facilitating repair in various organs. In skin regeneration in particular, MSC-Exos accelerate healing by polarizing macrophages from a pro-inflammatory M1 phenotype to a repair-promoting M2 phenotype, demonstrating their immunomodulatory potency.[3,4]

Exosome Engineering

While natural exosomes have intrinsic therapeutic potential, their clinical application has been limited by challenges such as specific targeting, cargo loading capacity, stability, and batch-to-batch compatibility. These limiting challenges have been overcome by engineering strategies that transform exosomes from passive biological particles into precision therapeutic platforms. Accordingly, cargo optimization, surface functionalization, genetic modification, and cellular preconditioning have all been employed to enhance exosome therapeutic efficacy.[5] For example, M2 macrophage-derived exosomes (M2-Exos) have been engineered to enhance targeting specificity, cargo retention, and microenvironment-responsive release kinetics, making them precise tools for inflammatory diseases and regenerative medicine.[6] Similarly, engineered exosomes carrying two ligands, WNT3A and RSPO1, have shown remarkable capacity to hyperactivate WNT signaling and stimulate efficient liver organoid growth, accelerating liver repair and regeneration in acute and chronic injuries.[7] These advances underscore the critical insight that exosomes are not simply drug carriers, but are programmable therapeutic agents themselves.

Exosomes as a Bridge Between Biology and Biomaterials

Perhaps the most transformative development in exosome-based regenerative medicine is their integration with advanced biomaterial scaffolds. Exosomes alone face significant limitations such as rapid clearance from the body and limited retention at sites of injury. Hydrogels, with their

high biocompatibility and porous structure, have emerged as ideal carriers, offering controlled release mechanisms that prolong exosome retention and enhance therapeutic efficacy. The combination of exosomes with hydrogels, including cell-free extracellular matrix hydrogels, alginate-based systems, and self-compatible dual network hydrogels, holds promise for advancing tissue repair strategies. Conductive scaffolds designed for electrically active tissues such as the heart and nervous system are even more complex. When exosomes are incorporated into these scaffolds, they exhibit synergistic therapeutic benefits in inducing angiogenesis, minimizing fibrosis, and improving function. This approach has shown particular efficacy in cardiac repair after myocardial infarction and in peripheral nerve regeneration, where both electrical and biochemical signals are essential for improved function. 3D bioprinted hydrogels, electrospun nanofibers, and 3D printed scaffolds are now being designed to provide controlled exosome release along with mechanical support for tissue regeneration.[8,9]

Exosomes and the Clinical Perspective

The expansion of exosome-based therapeutic approaches is expanding across all areas of regenerative medicine. In bone regeneration, exosomes deliver osteogenic proteins (BMP-2, RUNX2), angiogenic factors (VEGF, FGF-2), and immune regulatory molecules (miR-21, TGF-β) for complete healing.[10] In cartilage repair, human umbilical cord MSC-Exos have shown efficacy in reducing inflammation and promoting cartilage regeneration in osteoarthritis.[11] Heart repair with MSC-derived exosomes has shown promising progress, reversing ventricular remodeling and improving long-term cardiac function after acute myocardial infarction.[12] In neurological disorders, exosomes can cross the blood-brain barrier to deliver therapeutic molecules directly to the brain, offering a less invasive alternative to cell transplantation.[13] Clinical trials are now investigating the nasal administration of exosomes for Parkinson's disease and other neurodegenerative diseases.[14] Wound healing represents one of the most advanced clinical frontiers. A phase 1 trial is evaluating the safety of placental mesenchymal stem cell-derived exosomes for diabetic foot ulcers, while purified exosome products have been evaluated in phase 2 trials for diabetic foot ulcers and phase 1 trials for various wounds. Skin rejuvenation has entered clinical evaluation, in which adipose-derived MSC exosomes are being compared with platelet-rich plasma in combination with radiofrequency microneedling. Emerging applications include fertility restoration, autologous exosomes to reverse ovarian aging and promote neofolliculogenesis in premature ovarian failure and musculoskeletal disorders, where exosomes are a transformative paradigm for targeted and minimally invasive interventions.[15]

The Road Ahead: Challenges and Imperatives

Despite significant progress, the path to widespread clinical use faces challenges. Heterogeneity remains a major issue as exosome cargo and function vary significantly depending on the cell source, culture conditions, and isolation methods. Standardization of isolation and quality control protocols is urgently needed. Scalable production that meets GMP requirements at the clinical level while maintaining cost-effectiveness remains a major technical hurdle. Regulatory frameworks are still evolving, and there is no global consensus on specific guidelines for exosome-based therapies.[16,17] However, these challenges are likely to be overcome over time and as findings and technology advance. Of course, any emerging field will always have its challenges, but despite these limitations, exosomes can do something that synthetic nanoparticles cannot: the ability to regulate and modulate the body's communication system to coordinate the repair process. The integration of exosome biology with materials science, bioengineering, and precision medicine creates a new therapeutic paradigm, one that is cell-free, minimally invasive, and fundamentally regenerative.

Conclusion

We are at a pivotal time in the history of regenerative medicine. The limitations of cell-based therapies have revealed a path forward that is not a setback but a breakthrough, a move toward exosomes as biological nanocarriers. Exosomes, once overlooked as cellular debris, have emerged as the vanguard of a new therapeutic era. They offer the repair capacity of stem cells without the risks, the precision targeting of engineered nanoparticles without the toxicity, and the versatility to address conditions ranging from chronic wounds to neurological diseases. The question is no longer whether exosomes will revolutionize regenerative medicine; they are already revolutionizing it. The question is how quickly we can overcome the remaining hurdles to bring these exosome-based therapies to the patients who need them. With accelerating clinical development, advancing engineering capabilities, and increasing regulatory clarity, the prospect of exosomes in tissue engineering and regenerative medicine is not on the horizon; it is already here.

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