BIOTECH BLUEPRINT

BIOMATERIAL APPLICATIONS FOR STEM CELL-DERIVED EXOSOME THERAPY

doi: 10.35493/medu.48.20
AUTHORS:
GRACE HUR[1], IAN KIM[2], & ATTA YAZDY[3]
[1] Bachelor of Health Sciences (Honours Biomedical Discovery and Commercialization), Class of 2027, McMaster University
[2] Bachelor of Science (Honours Life Sciences), Class of 2028 McMaster University
[3] Bachelor of Science (Honours Kinesiology), Class of 2026, McMaster University

ARTIST:
YUEWEN GAO[4]
[4] Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

ABSTRACT

Stem cell-derived exosomes (SC-Exos) continue to emerge as a prominent and versatile cell-free therapy for promoting tissue regeneration and bioactive signalling. However, clinical translation is limited by challenges in targeted delivery, stability, and short circulation lifespans. To address these barriers, biomaterials that can protect exosomal integrity and allow for controlled release have been increasingly explored as effective delivery platforms. Understanding how such biomaterials can influence the outcomes of exosomal therapy is critical for advancing clinical applications and optimizing therapeutic potential.

SC-EXOS THERAPY

Like all other cells in the human body, stem cells release exosomes, which are membrane-bound vesicles that enable cell-to-cell communication. Exosomal nucleic acids and proteins have shown therapeutic potential, inheriting the beneficial attributes of parental cells, such as anti-inflammatory signals and tissue regeneration.[1] Once exosomes reach the recipient cell, the bioactive cargo gets released into the cytoplasm to mediate cellular and tissue responses, and molecular signalling pathways such as Wnt/β-catenin, MAPK, and JAK/STAT.[2-4]

SC-Exos therapy has shown therapeutic potential across various disciplines, including orthopedics, neurosurgery, cardiology, and wound healing. For instance, exosomes from adipose-derived stem cells have demonstrated improvement in skin wound healing by inducing macrophage polarization, activating cytokine IL-33 release, and promoting collagen formation.[5] SC-Exos are commonly administered through intravenous, intranasal, and subcutaneous routes, which can influence distribution rate in the body.[6] Unlike stem cells, exosomes cannot self-replicate, thereby presenting a lower risk of tumour formation compared to stem cell transplants.

Furthermore, exosomes can be biochemically modified through drug loading and surface modification to improve their therapeutic effects. A recent study developed an exosome-based drug delivery system by engineering the exosomal membrane with thrombopoietin-mimic peptides to achieve targeted delivery to acute myeloid leukemia (AML) cells.[7] A drug cargo of daunorubicin was selected for encapsulation within the exosomes for clinical efficacy and further tested in a mouse AML model.

DIFFERENT BIOMATERIALS AND COMPARISONS

One major challenge in SC-Exos therapy is targeted specificity. Different biomaterials have been used to ensure that the method of delivery is both highly specific and effective. Hydrogels, polymeric nanoparticles, and three-dimensional scaffolds are currently the most commonly used biomaterials, each offering distinct advantages and limitations in terms of exosome retention, bioactivity, and clinical applicability.[8]

Hydrogels, such as hyaluronic acid or alginate, excel at releasing exosomes in a controlled and sustained manner. They also possess mechanical properties that enable them to closely match native tissue, supporting biocompatibility and stable integration.[9] Their high water content also helps preserve exosome integrity and allows for minimally invasive delivery methods such as injections.[10] However, their degradation rates and crosslink densities require careful regulation to prevent premature bursting of exosomes during release.[11]

Polymeric nanoparticle carriers instead excel at tunable, multi-stage releases and provide the greatest support in stabilizing exosomes during systemic circulation. These carriers can also be hybridized with exosomal membranes to further improve cellular targeting and reduce immune recognition, increasing therapeutic precision and efficiency.[12,13] However, there is a potential health concern with the polymer residue these hydrogels leave behind, along with significant logistical obstacles in reproducibility, costs, and quality control due to their manufacturing complexity.[8,14]

Similarly, scaffolds focus on combining structural support and biological cues, an optimal method for localized retention of exosomes within target tissues. The mechanical stability that this technique provides also allows for a controlled microenvironment where the scaffolding material can facilitate sustained exosome delivery and cellular communication to influence behaviours such as adhesion, migration, proliferation, and differentiation.[15] Yet, their clinical translation remains limited with challenges remaining in complex fabrication methods, sensitivity to sterilization, and batch-to-batch variability.

THERAPEUTIC APPLICATIONS

SC-Exos have strong immunomodulatory, anti-inflammatory, and regenerative properties, making them strong candidates for wound healing.[16,17] However, the short life span of stem cells in conjunction with the low stability of their derived exosomes is a key limitation to their applicability.[16] Research has shown that the use of biomaterials can enhance

the delivery and longevity of SC-Exos, as exemplified by a study on the use of macroporous hydrogels. This study also found that HucMSC-Exos carry miRNAs that regulate fibroblasts, vascular endothelial cells, and macrophages, which are implicated in healing.[18,19]

In addition to its effects on wound healing, SC-Exos are an emerging potential treatment for bone defects such as fractures, osteoporosis, and bone metastases.[15] Current treatments to address bone defects face concerns of immunogenicity and stability; SC-Exos address these concerns by offering a cell-free approach.[15] SC-Exos are thought to deliver miRNAs, lncRNAs, proteins, and DNA to effectively stimulate osteoblasts, chondroblasts, osteoclasts, angiogenic factors, and immune cells, thereby increasing osteogenesis and angiogenesis while regulating the immune response.[15] However, these exosomes on their own face issues of low retention and lack of sustained release at their target tissue. Fortunately, engineered scaffolds made of metallic, synthetic, natural, or inorganic materials can be loaded with exosomes and delivered to target tissues while attenuating concerns of release or retention.[15] For example, one study investigated the effect of titanium scaffolds delivering human dental pulp SC-Exos (hDPSC-Exos) for bone regeneration.[20] The authors were able to effectively stimulate osteogenesis in hDSPCs through upregulating miRNAs which target osteogenic pathways.[20] This led to cell-free bone regeneration within ten weeks of delivery, addressing concerns of immunogenicity.[20]

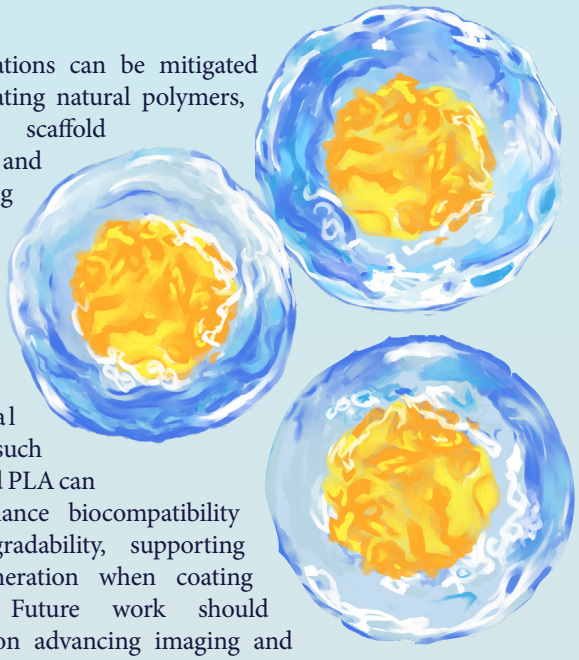
Overall, SC-Exos have been proposed as a promising treatment for both wound healing and bone repair. However, they face several limitations centred around stability and lifespan. The current literature underscores the effectiveness of biomaterials as a protective mechanism for delivering SC-Exos to the target site, ensuring their stability, and increasing lifespan.

LIMITATIONS AND FUTURE DIRECTIONS

Recent biomaterial applications using hydrogels, nanoparticles, and engineered scaffolds in SC-Exos therapy have proved to enhance the effectiveness of the therapy by improving the controlled release and targeted drug distribution. Despite the advancement of this stem cell therapy, numerous challenges remain for its clinical implementation.

Despite hydrogels being a promising biomaterial as delivery vehicles for SC-Exos, issues with gel stiffness, complexities in the production process, and gelation times must be addressed. It is also challenging to achieve homogeneous exosome incorporation into hydrogels while ensuring a controlled release. Although slow release can be accomplished through scaffold-based SC-Exos, consistent stability of release has yet to be achieved.[21] Further studies are required on the scalable manufacturing of the biomaterial.[14]

Scaffolds can also be tailored to specific microenvironments including ocular and nervous tissues as well as bone, cartilage, and skin. Each of these possess unique mechanical and vascular properties that can make scaffold optimization complex. From an engineering standpoint, scaffold design constraints must also achieve a balance between mechanical strength and biocompatibility, while minimizing degradation and ensuring controlled exosome release.[22]



These limitations can be mitigated by manipulating natural polymers, adding scaffold materials, and introducing synthetic polymers. Synthetic polymers that have tunable mechanical properties such as PLGA and PLA can further enhance biocompatibility and biodegradability, supporting tissue regeneration when coating SC-Exos.[23] Future work should also focus on advancing imaging and tracking technologies to monitor exosome distribution and retention in vivo. This could involve the use of biofluorescent materials or nanoparticles. Notably, inorganic nanoparticles loaded into exosomes can enhance imaging depth using MRI. Further development is also necessary to optimize scaffold design for exosome stability and sustained delivery. A quality control system is imperative for the therapy to align with good manufacturing practice standards to ensure reliable and consistent SC-Exos products. As current research is limited to small animal models, studies could expand to large animal models and clinical trials to assess scalability, biosafety, and therapeutic efficacy.[14]

CONCLUSION

In summary, integrating SC-Exos with biomaterial platforms represents a promising cell-free approach to tissue regeneration. By providing structural support and controlled delivery, biomaterials enhance the therapeutic efficacy of exosomes across diverse applications. This approach not only replicates the regenerative signaling of stem cells but also overcomes the limitations of direct exosome administration. As biomaterial design advances toward smart, responsive, and tissue-specific formulations, this strategy has strong potential to translate regenerative medicine into clinically viable therapies for complex tissue injuries and degenerative diseases.

REVIEWED BY: DR. ERIC SEIDLITZ (PHD)

Dr. Eric P. Seidlitz is an assistant professor in the Department of Anesthesia at McMaster University. He is also an instructor in the Honours Health Sciences Program at McMaster University. Dr. Seidlitz completed his PhD in 2009 in bone cancer pain research, and has previously lectured about exosome mechanisms.

EDITED BY: ADELE FENG & KUMKUM ANUGOPAL