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The Bio-envelope revolution: Encapsulation strategies for stem cell-based therapies

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ABSTRACT

The encapsulation of stem cells within biocompatible biomaterials has revolutionized regenerative medicine by offering a means to enhance cell survival, functionality, and therapeutic efficacy. This strategy creates a protective, semi-permeable microenvironment—often engineered using hydrogels—that closely mimics the native extracellular matrix (ECM) while allowing essential exchange of nutrients, gases, and biochemical signals. Among the most widely studied are mesenchymal stem cells (MSCs), whose multipotent and immunomodulatory properties make them ideal candidates for encapsulated therapies. Encapsulation not only improves MSCs viability and engraftment but also mitigates challenges such as immune rejection and uncontrolled differentiation. A diverse range of natural and synthetic materials—including alginate, collagen, and polyethylene glycol (PEG)—have been developed to fabricate tunable delivery platforms that support cell function and targeted therapeutic action. This review explores the core principles behind cell encapsulation technologies, the pivotal role of hydrogels as ECM analogs, and the clinical advances enabled by these systems. It also addresses current limitations and future directions, including the incorporation of gene-editing tools and stimuli-responsive biomaterials to create intelligent, next-generation cell therapies.

Keywords: Stem Cell Encapsulation; Regenerative Medicine; Biocompatible Matrices; Extracellular Matrix; Immunomodulation; Controlled Release; Mesenchymal Stem Cells; Cell Viability.

1. Introduction

Cell-based therapies have emerged as a powerful tool in regenerative medicine, offering new possibilities for treating degenerative diseases and tissue injuries. However, a key challenge remains how to ensure the survival, function, and targeted activity of therapeutic cells once introduced into the body. One promising solution is cell encapsulation, a technique that embeds living cells within biocompatible, semi-permeable materials to protect and support them *(Bhujbal et al., 2014)*. Encapsulation forms a protective microenvironment that allows essential exchanges—like oxygen, nutrients, and signaling molecules—while shielding the cells from immune attacks and mechanical stress *(Freimark et al., 2010)*. This method is especially useful for stem cells, including MSCs, which are known for their ability to self-renew, differentiate into various tissue types, and modulate immune responses.

Among encapsulation strategies, hydrogel-based systems stand out. Hydrogels mimic the natural ECM, providing a three-dimensional (3D) scaffold that promotes cell survival and function. Materials like alginate, collagen, and PEG are commonly used to tailor the mechanical, chemical, and biological properties of these bio-envelopes. Through careful design, encapsulated MSCs can be protected while remaining active, capable of releasing therapeutic molecules and responding to environmental cues *(Zhao et al., 2022)*.

Encapsulation not only improves stem cell viability and therapeutic efficacy but also offers spatial and temporal control over their behavior. As research advances, smart biomaterials and gene-editing tools are being integrated into these systems, moving us closer to next-generation therapies that are responsive, precise, and clinically effective. This article explores the principles behind stem cell encapsulation, the materials used, and current

biomedical applications. We also examine the challenges ahead and the innovations shaping the future of this exciting field.

1.1. Study Objectives

The following are the main objectives of this study:

(i) To analyze the key properties of biomaterials used for stem cell encapsulation.

(ii) To describe the main types of stem cells used in encapsulation systems for biomedical applications.

(iii) To review current cell encapsulation methods and their impact on viability, differentiation, and cell functionality.

(iv) To evaluate the challenges and technical limitations of encapsulation systems in their transition to clinical applications.

(v) To identify future opportunities in the design of smart biomaterials to improve the therapeutic efficacy of encapsulated stem cells.

2. Cell Encapsulation

Cell encapsulation involves the immobilization of various cell types—including myoblasts, fibroblasts, MSCs, and embryonic stem cells—within a semi-permeable, biocompatible matrix *(Bhujbal et al., 2014)*. This strategy facilitates the diffusion of therapeutic molecules, allows the ingress of oxygen and nutrients, and supports the removal of metabolic waste *(Zhao et al., 2022)*. Encapsulation provides multiple advantages, such as preserving cell viability, enabling proliferation, supporting differentiation and self-renewal, and protecting the embedded cells from mechanical stress and immune system attacks *(Freimark et al., 2010)*. The primary goal of encapsulation is to create a selective barrier that restricts the passage of high molecular weight immune agents while allowing the controlled release of bioactive molecules with therapeutic potential *(Lopez-Mendez et al., 2021)*. Two main types of encapsulation systems are used, distinguished by the number of cells contained within each unit. Microencapsulation involves enclosing individual islets or small clusters of cells within tiny capsules. This format improves oxygen and nutrient exchange due to a high surface-area-to-volume ratio, but achieving a therapeutic dose often requires a large number of microcapsules. In contrast, macroencapsulation incorporates a larger number of cells into a single material or device. While this configuration has demonstrated therapeutic potential *in vivo*, it presents challenges such as limited nutrient and oxygen diffusion due to its lower surface-area-to-volume ratio *(Krishnan et al., 2024)*.

2.1. Methods of cell encapsulation

One of the most widely used methods for cell encapsulation involves the entrapment of cells within hydrogel beads—a simple, stable, and reproducible technique that remains relevant today. This is commonly accomplished by dispensing alginate hydrogel droplets into a calcium chloride solution, where ionic crosslinking solidifies the matrix. While alginate remains the most prevalent material, various ionic crosslinking strategies have been developed to fabricate encapsulation membranes with tailored properties *(Wu et al., 2022)*.

To enhance control over droplet formation and encapsulation uniformity, advanced methods such as coaxial air jet systems and liquid jet techniques have been introduced. Additional strategies—including macromolecular matrices composed of type I collagen, hollow fiber fabrication through injection and co-extrusion, and photopolymerization using UV light to minimize cell damage—have significantly contributed to the refinement of encapsulation technologies *(Wu et al., 2022)*. Many of these foundational approaches continue to be utilized, with ongoing innovations improving their effectiveness and broadening their biomedical applicability. In recent years, cutting-edge techniques such as micromolding, electrostatic droplet extrusion, microfluidics, and bioprinting have been extensively explored and optimized since their early conceptualization in 1958, collectively shaping the future of stem cell-based therapies *(Wu et al., 2022)*. The following section provides an overview of the most commonly employed methods (Figure 1) for stem cell encapsulation.

2.1.1. Extrusion

In tissue engineering, extrusion-based encapsulation is one of the most commonly employed techniques for cell microencapsulation, as it enables the formation of uniform hydrogel microspheres that protect cells and support their viability. This method involves dispensing a suspension containing both the precursor polymer and cells through a needle—either by gravity or under controlled pressure—into a cross-linking solution, where the droplets undergo rapid gelation to form stable capsules *(Hashemi & Kalalinia, 2015)*. The size and uniformity of the resulting microspheres are influenced by several critical parameters, including the density and viscosity of the polymer solution, the diameter of the extrusion needle, the flow rate, and the surface tension of the droplets *(Abbas et al., 2025)*. Optimization of these variables is essential to ensure consistent capsule formation and maintain the desired physiological conditions for encapsulated cells.

2.1.2. Emulsion

Emulsion-based encapsulation is a widely used technique for immobilizing bacteria, proteins, and living cells. This method involves dispersing a precursor polymer within a water-in-oil emulsion, creating an immiscible system. Gelation is subsequently initiated internally, typically stabilized through intermolecular hydrogen bonding, and the encapsulated structures are recovered by centrifugation *(Lee et al., 2021)*. Among its main advantages are process scalability and encapsulation efficiency, particularly for live cells and enzymes used in tissue engineering applications, as the method supports effective exchange of nutrients, oxygen, and metabolic products with the surrounding environment. However, this approach tends to produce a broad distribution of particle sizes and morphologies under varying process conditions, which can be a limitation when uniformity and reproducibility are required *(Sivan et al., 2022)*. Moreover, prolonged exposure to the oil phase and surfactants commonly used in emulsions has been reported to reduce cell viability *(Chan et al., 2013; Qu et al., 2021)*, highlighting a key challenge for clinical translation.

2.1.3. Microfluidics

Microfluidic cell encapsulation is increasingly employed for tissue repair and regeneration, as it allows the recreation of a stem cell-like microenvironment *(Utech et al., 2015)* and serves as a platform to study cell

interactions *(Soleymani et al., 2024)*. This technique involves the formation of uniform droplets containing stem cells, which are encapsulated within polymeric matrices using microchannel devices. The droplets are subsequently gelled to form stable microcapsules, followed by a demulsification process that transfers the encapsulated materials from the oil phase to the aqueous phase through cyclic centrifugation and re-dispersion steps *(An et al., 2020)*. One of the key advantages of microfluidic encapsulation is its ability to control and manipulate small volumes of fluids, enabling the production of monodispersed droplets and allowing precise cell allocation within each capsule *(Allazetta & Lutolf, 2015; Headen et al., 2014)*. These features make microfluidic encapsulation highly suitable for applications requiring high precision in cell delivery and uniformity in the encapsulation process.

2.1.4. Micromolding

Micromolding is an effective technique for cell encapsulation that allows precise control over the cellular microenvironment while encapsulating stem cells using specialized lithography equipment. The process involves fabricating micromolds, which are then immersed in a polymer solution containing suspended cells. Afterward, a prepolymer solution is poured into the molds, and upon solidification, the formed gel is extracted, resulting in uniform microcapsules with high reproducibility and versatility *(Kim et al., 2019)*. This highly controlled process enables the creation of complex architectures suitable for tissue regeneration applications. Moreover, the materials used in the fabrication of micromolds must exhibit high mechanical stability to ensure that the molds maintain their structural integrity throughout the process *(Costa et al., 2022)*.

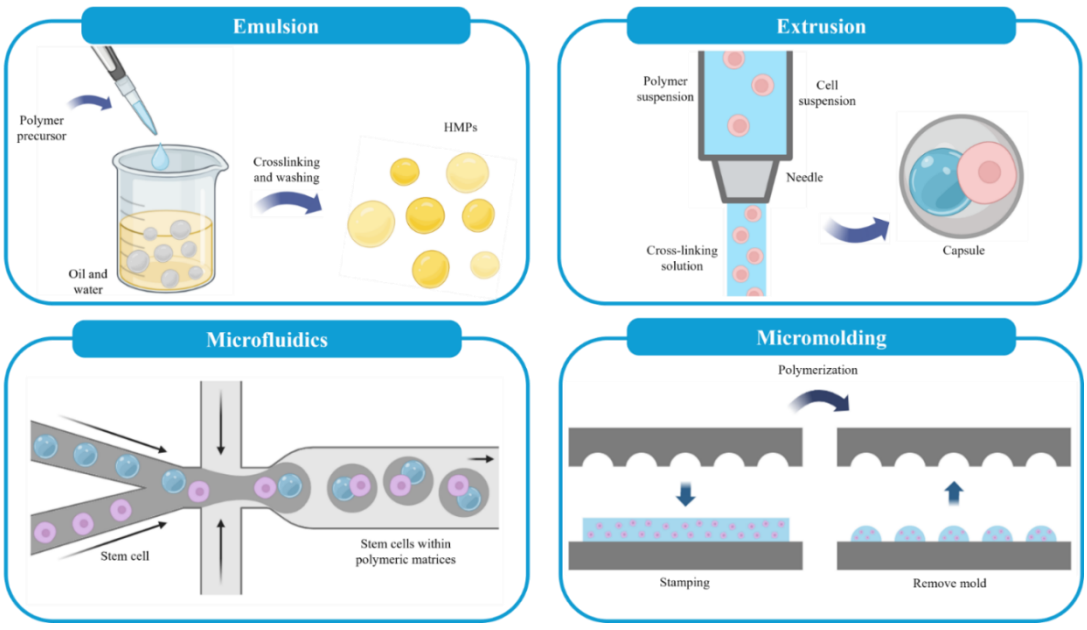

Figure 1. Stem cell encapsulation methods

2.2. Properties for cell encapsulation

An essential factor for successful cell encapsulation is the choice of materials used in the process, as these must ensure the desired functionality and applicability. Biocompatibility is a critical property; the material used for encapsulation must not negatively impact cell viability or provoke adverse immunological responses. Instead, it

must be compatible with living tissues, preserving both their biological and physical characteristics *(Saroia et al., 2018)*. Permeability is another key consideration, as the encapsulating polymer must facilitate the diffusion of essential nutrients and oxygen required for cell survival while also providing a protective barrier that prevents immune system activation. This protective layer acts as a steric barrier, blocking the recognition of non-self-antigens on the surface of transplanted cells by host T cells and preventing the binding of host antibodies to the transplanted cells *(Marikar et al., 2022)*. Furthermore, the mechanical properties of the encapsulating material are crucial to maintaining the structural integrity of the capsule during handling within the physiological environment. These properties ensure that the encapsulated cells remain protected from external mechanical stresses, preventing capsule rupture or deformation, which could otherwise compromise cellular viability *(P. Gupta et al., 2023)*.

3. Biomaterials

The development of biomaterials is not a recent field of study, with its origins dating back approximately half a century. Essentially, a biomaterial is any material specifically designed and adapted for medical applications. These materials can serve a passive role, such as in the case of heart valves, or they can be bioactive, actively interacting with biological systems *(Detsch et al., 2018)*. Biomaterials represent a distinct category of engineered substances, created to assume specific forms that, either independently or as part of more complex systems, influence therapeutic or diagnostic processes by modulating interactions with biological components.

3.1. Chemical classification

Biomaterials are typically classified according to their chemical composition, with common categories including metal, ceramic, polymer, and composite materials *(Chong et al., 2023)*.

3.1.1. Metal

Metallic biomaterials are designed to offer structural reinforcement to biological tissues and are commonly employed in applications such as joint replacements, dental implants, orthopedic fixations, and stents. While they provide essential support and durability, the widespread use of metallic biomaterials is often associated with various implant-related complications. These include inadequate integration with surrounding tissues, inflammation, mechanical instability, tissue necrosis, infections, and prolonged patient recovery times. Such complications can result in significant discomfort and functional impairment, sometimes necessitating additional surgical interventions or extended patient care *(Prasad et al., 2017)*. Consequently, while metallic biomaterials remain an essential part of medical devices, ongoing research focuses on improving their biocompatibility and reducing associated risks.

3.1.2. Ceramics

Ceramics are inorganic compounds primarily made up of metal and metalloid oxides, nitrides, sulfides, or carbides. Their exceptional physicochemical properties, such as high biocompatibility, hardness, and resistance to wear and corrosion, make them indispensable in the biomedical field. Ceramics are particularly valued for their compatibility with specific tissues in the human body, allowing them to integrate well with bone and dental

structures. The use of bioceramic materials, such as porcelain, in medical applications dates back to the 18th century, when they were first employed for dental crown restorations *(Punj et al., 2021)*. Over time, the range of bioceramics has expanded to include materials like hydroxyapatite and bioactive glass, which are now commonly used in orthopedic implants, bone grafts, and dental materials due to their ability to support tissue regeneration and promote osseointegration.

3.1.3. Polymeric

Polymeric biomaterials, which can be derived from either natural or synthetic sources, are specifically designed to interact with biological systems to promote the regeneration, restoration, or enhancement of tissues, organs, or bodily functions. These materials are highly versatile and can be tailored to mimic the natural ECM, providing a suitable microenvironment for cellular activities such as adhesion, proliferation, and differentiation. Natural polymers, such as collagen, chitosan, and hyaluronic acid, are prized for their inherent biocompatibility and ability to promote tissue healing. On the other hand, synthetic polymers, like polylactic acid (PLA), polyglycolic acid (PGA), and PEG, offer advantages such as customizable mechanical properties, degradation rates, and the ability to fabricate complex structures through advanced manufacturing techniques. These materials are employed in a wide range of applications, including drug delivery systems, wound healing, tissue engineering scaffolds, and implants, where they serve to support and enhance the body's natural healing processes *(Shanmugam & Sahadevan, 2018)*.

3.1.4. Composite materials

Composite materials are engineered by combining two or more distinct components or phases, which can be identified at either the microscopic or macroscopic level. These phases are typically chemically or physically different and are intentionally combined to leverage the unique properties of each component, enhancing the overall performance of the material. The term "composite" usually refers to materials where these phases are not uniformly mixed at the atomic level, but rather exist as distinct entities within the material. As a result, composite materials exhibit significantly altered properties, such as a higher elastic modulus, improved mechanical strength, toughness, or thermal resistance, compared to homogeneous materials *(Park & Lakes, 2007)*. By carefully selecting the constituent materials, composites can be designed to achieve a wide range of mechanical, thermal, and chemical properties tailored to specific applications, making them highly useful in industries such as aerospace, automotive, and biomedical engineering.

3.2. Source of biomaterials

Biomaterials are typically classified into three main categories: synthetic, natural, and semi-synthetic. Synthetic biomaterials are known for their well-defined composition, which allows for precise control over their mechanical and chemical properties. This level of control makes them highly adaptable for specific applications in tissue engineering and medical devices. In contrast, natural biomaterials, which have a more complex and less defined composition, possess intrinsic bioactivity. This bioactivity is largely attributed to the presence of native ECM components such as collagen, fibronectin, and laminin. These biomaterials offer important molecular cues,

including the Arginine-Glycine-Aspartic acid (RGD) motif, which promotes cell adhesion, migration, and signaling, supporting cellular functions necessary for tissue regeneration *(Yonesi et al., 2021)*. On the other hand, semi-synthetic biomaterials combine the advantages of both synthetic and natural materials. They are typically modified natural biomaterials designed to overcome the limitations of their naturally derived counterparts, offering a more controlled and tunable structure. For instance, synthetic polymers like polycaprolactone (PCL) and PLA provide highly reproducible structures and allow precise modulation of physical and chemical properties across multiple scales. This ability to fine-tune their properties makes synthetic biomaterials invaluable for creating scaffolds with tailored characteristics for various biomedical applications *(Yonesi et al., 2021).*

3.3. Mesenchymal stem cells encapsulated in hydrogels

Hydrogels are 3D polymeric networks formed through physical interactions (such as hydrogen bonding, hydrophobic interactions, or ionic associations) or via covalent chemical crosslinking between polymer chains. These highly hydrated matrices can be fabricated from natural polymers—including collagen, gelatin, alginate, chitosan, or hyaluronic acid—or from synthetic polymers such as PEG, polyvinyl alcohol (PVA), and PLA *(Kandilogiannakis et al., 2020)*. Their tunable mechanical properties, biocompatibility, and high water content make them ideal for encapsulating living cells, particularly MSCs, in tissue engineering and regenerative medicine. When encapsulated in hydrogels, MSCs are provided with a biomimetic microenvironment that promotes cell viability, proliferation, and differentiation while protecting them from mechanical stress and immune system recognition. Depending on the hydrogel's composition and crosslinking strategy, specific biological cues can be incorporated to direct stem cell fate and enhance functional integration with host tissue *(Kandilogiannakis et al., 2020)*. Figure 2 illustrates the wide range of biomedical applications explored in current research involving MSCs encapsulated within hydrogels and scaffold systems. These include applications in cartilage and bone regeneration, wound healing, cardiovascular repair, and drug delivery systems, demonstrating the versatility and therapeutic potential of hydrogel-based stem cell delivery platforms.

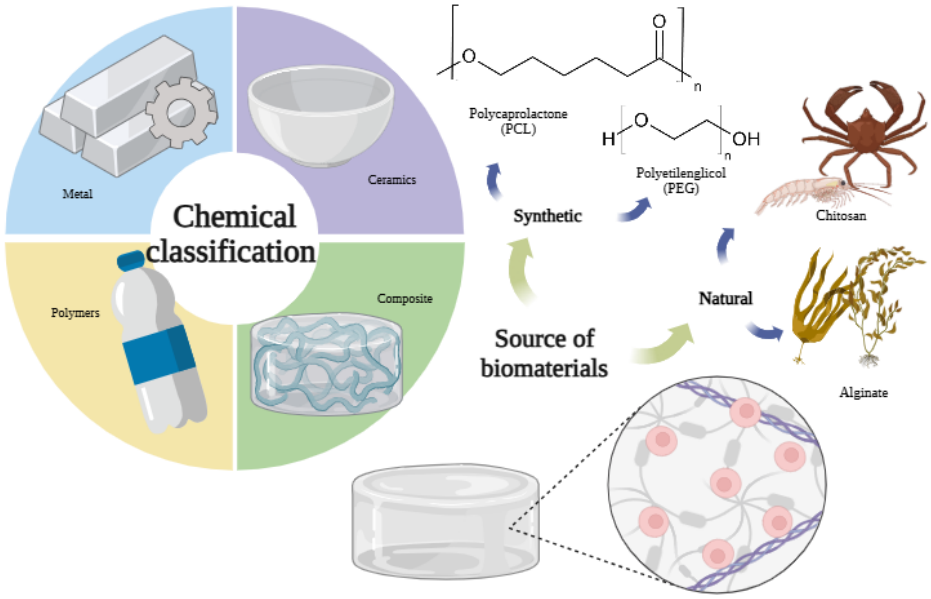

Figure 2. Applications of MSCs encapsulated in hydrogels and scaffold-based systems

Cell-based therapies, particularly those involving stem cell transplantation, have gained significant attention as innovative strategies for tissue regeneration and organ repair. Among the diverse types of stem cells, MSCs stand out due to their robust self-renewal capacity, ability to differentiate into multiple cell lineages (including osteogenic, chondrogenic, and adipogenic lineages), and the absence of ethical controversies that typically accompany embryonic stem cells. Furthermore, MSCs are characterized by low immunogenicity, reduced risk of teratoma formation, and the capacity to modulate immune responses, making them especially attractive for a wide range of regenerative medicine applications *(Kim et al., 2019)*. Encapsulation of MSCs within biomaterials—particularly hydrogels—has become a pivotal technique in tissue engineering, offering multiple functional advantages. This strategy enables the recreation of a 3D microenvironment that closely resembles the native ECM, enhancing cell viability, proliferation, and lineage-specific differentiation. Encapsulation also acts as a protective barrier, shielding the cells from host immune responses while still permitting the diffusion of critical biomolecules such as oxygen, nutrients, cytokines, and growth factors, which are essential for maintaining cellular functions and promoting tissue integration *(Z. Chen et al., 2024)*.

Table 1 provides a summary of representative studies involving the encapsulation of stem cells using different types of natural and synthetic polymers, highlighting their respective biomedical applications in areas such as cartilage regeneration, bone repair, and wound healing.

Table 1. Studies on stem cell encapsulation in hydrogels and scaffolds

Type of polymer (natural or synthetic)	Type of material	Characteristics	Application	Reference
Alginate	Hydrogel	3D hydrogel encapsulation has been shown to direct the differentiation of MSCs toward bipotent prechondro-osteogenic lineages and multipotent differentiation pathways, while simultaneously inhibiting their commitment to the smooth muscle cell lineage.	Cartilage and bone tissue engineering	*(B. Li et al., 2024)*
Chitosan and PCL	Hydrogel	An optimal biomimetic microenvironment was engineered to enhance the proliferation and chondrogenic differentiation of transplanted MSCs.	Osteoarthritis and focal cartilage defect repair	*(P. Li et al., 2021)*
PLGA blended in PLLA	Scaffolds	The retention and viability of MSCs were significantly enhanced within the engineered matrix, leading to improved engraftment efficiency and therapeutic outcomes.	Therapy for ischemic diseases	*(Czosseck et al., 2022)*
PEG-collagen	Hydrogel	The approach facilitated rapid epithelial wound closure and significantly minimized corneal scar formation, promoting enhanced tissue regeneration.	Burn-induced corneal injury	*(Na et al., 2021)*
Cellulose	Hydrogel	The proliferation of MSCs demonstrated a direct correlation with cellulose concentration.	Delivery vehicle for immunomodulatory MSCs	*(Flores et al., 2019)*

4. Advantages of cell encapsulation

4.1. Immune protection

Cell encapsulation has emerged as a highly effective strategy for protecting stem cells from immune system attacks, particularly in allogeneic cell therapies, where the transplanted cells are derived from genetically distinct donors. The encapsulating material acts as a semi-permeable barrier, preventing direct contact between the stem cells and the host's immune cells, including host dendritic cells, macrophages, and lymphocytes. This protective barrier effectively mitigates the risk of triggering immune responses, such as chronic inflammation or immune rejection of the transplanted material *(Kioulaphides & García, 2024)*. Unlike conventional approaches that rely on systemic immunosuppressants—which often come with a range of unwanted side effects—encapsulation provides localized immunoprotection while preserving the functionality and viability of the stem cells. Additionally, encapsulation serves as a physical shield that allows for the controlled exchange of essential biomolecules, including nutrients, oxygen, and signaling factors, while blocking the entry of cytotoxic immune cells and antibodies *(H. Wang et al., 2025)*. This advantage is particularly critical in applications such as pancreatic islet transplantation for type 1 diabetes, where encapsulation has been shown to prevent the autoimmune destruction of insulin-secreting cells *(Q. Zhang et al., 2022)*.

Furthermore, encapsulation allows for the use of stem cells in regenerative medicine without the need for genetic modifications to reduce their immunogenicity, thereby broadening their potential for application in translational therapies.

4.2. Support for cell differentiation

Encapsulation of stem cells in biomaterials plays a pivotal role in directing their differentiation into specific cell lineages, a process largely influenced by the microenvironment provided within the encapsulating material. The physical properties, chemical composition, and material of the capsule can modulate the biochemical and mechanical signals that guide stem cell differentiation *(Kim et al., 2019)*. For instance, biomaterials such as alginate and fibrin can be modified with bioactive peptides, growth factors, or other bioactive molecules that induce differentiation into specific cell types, such as osteoblasts, chondrocytes, or endothelial cells, depending on the intended tissue engineering application *(Andersen et al., 2015)*. Moreover, the mechanical properties of the encapsulating matrix, including its stiffness and flexibility, play a crucial role in regulating cellular responses to mechanical cues. These properties can influence gene expression, phenotypic behavior, and cellular morphology, which is particularly important in the context of cartilage and bone tissue repair, where precise stem cell differentiation is necessary for the functionality of the regenerated tissue *(Bicer et al., 2021)*.

Furthermore, encapsulation within a controlled 3D environment helps to prevent unwanted spontaneous differentiation, thereby maintaining stem cells' pluripotency until the appropriate signals for differentiation are provided. This controlled environment not only preserves the regenerative potential of stem cells but also optimizes their application in clinical therapies by ensuring that differentiation occurs in response to the right cues at the right time *(Caliari & Burdick, 2016)*.

4.3. Controlled release of bioactive factors

One of the key advantages of stem cell encapsulation is its ability to regulate the release of bioactive factors, thereby optimizing cell signaling and enhancing the therapeutic efficacy of regenerative therapies. As encapsulated stem cells secrete essential molecules such as cytokines, growth factors, and ECM proteins, the encapsulating material acts as a controlled release system, enabling the gradual and sustained diffusion of these bioactive agents into the surrounding tissue *(Huang et al., 2022)*.

This controlled release is crucial in regenerative medicine, as it prevents the potential adverse effects associated with uncontrolled release, such as excessive inflammation or fibrosis, which could impair healing and tissue function. Depending on the material composition, porosity, and structural characteristics of the capsule, the diffusion rate of these molecules can be finely tuned, ensuring that an optimal concentration is maintained at the implantation site over time *(L. Wang et al., 2018)*. Moreover, encapsulation facilitates the development of hybrid systems that combine stem cells with nanoparticles, biodegradable polymers, or other advanced materials, enabling the release of specific factors in response to physiological stimuli. This ability to design responsive systems significantly enhances the regenerative capacity of stem cells *(Y.-T. Chen et al., 2023)*. A notable example of this is the encapsulation of mesenchymal stem cells in vascular endothelial growth factor (VEGF)-functionalized hydrogels, which promotes controlled angiogenesis for ischemic tissue repair. This approach exemplifies how encapsulation can support localized and sustained delivery of bioactive factors, reducing the need for systemic administration of growth factors and minimizing the associated side effects *(Hwang et al., 2018)*. By providing a precise and controlled environment for the release of therapeutic molecules, encapsulation emerges as a powerful strategy in regenerative medicine, offering the potential to enhance tissue repair while mitigating risks related to systemic therapies.

5. Clinic applications

Stem cells are undifferentiated, pluripotent cells with the remarkable potential to differentiate into various specialized cell types, depending on their potency and origin. Embryonic stem cells (ES cells) are derived from human embryos, while adult stem cells are isolated from mature organs and tissues. In addition, stem cells can be harvested from the umbilical cord following childbirth, known as cord blood stem cells, or from amniotic fluid, referred to as amniotic fluid stem cells. Additionally, placental stem cells are obtained from the placenta *(D. R. Gupta & Singh, 2023)*.

Regenerative medicine is an emerging interdisciplinary field that integrates biology, healthcare, and engineering to repair, replace, or restore the function of damaged tissues and organs. A cornerstone of this field is stem cell therapy, which capitalizes on the self-renewal and multipotent differentiation abilities of stem cells to regenerate or repair compromised tissues. One of the most promising platforms in regenerative medicine is the use of hydrogels, which have become indispensable biomaterials in various biomedical applications, including targeted drug delivery, tissue regeneration, wound healing, biosensing, and as vehicles for the delivery of stem cells and bioactive molecules. Hydrogels are particularly valued for their versatile and highly customizable properties, such

as mechanical resilience, biocompatibility, and the ability to control their degradation rates. These unique attributes enable the precise tailoring of hydrogels to meet the specific needs of different therapeutic contexts, thereby optimizing their clinical efficacy and enhancing patient outcomes *(L. Liu et al., 2025)*. Table 2 presents a comprehensive overview of medical applications involving stem cells, highlighting their potential in transforming modern healthcare.

Table 2. Regenerative medicine applications using stem cells encapsulated in hydrogels

Hydrogel composition	Characteristics	Application	Reference
Hyaluronic acid and chitosan-grafted aniline tetramer	The hydrogel's excellent biocompatibility was evidenced by histological analysis in rat myocardium, which revealed significant upregulation of angiogenic factors and enhanced cellular interactions, indicating its potential to promote tissue regeneration and vascularization.	Cardiac tissue regeneration	*(Xue & Gao, 2024)*
Alginate, hyaluronic acid (HA) or HA/gelatin	This study demonstrated the successful differentiation of retinal pigment epithelium (RPE) cells from pluripotent stem cells, both independently and in combination with neural retina.	Retinal regeneration and the restoration of vision.	*(Hunt et al., 2017)*
Gelatin	MSCs encapsulated within the microporous hydrogel demonstrated rapid cell spreading and the formation of direct intercellular connections, which are essential for maintaining cellular communication and promoting tissue regeneration.	Bone tissue repair and wound healing	*(Edwards et al., 2024)*

5.1. Cell therapies

Stem cell-based therapies utilizing hydrogel encapsulation have emerged as a promising approach for tissue engineering and drug delivery. Hydrogels offer a versatile platform, providing a supportive microenvironment, which not only enhances stem cell viability but also protects them from immune rejection, facilitating their use in allogeneic therapies. Furthermore, hydrogels can be precisely engineered with bioactive molecules to optimize stem cell survival and functionality, promoting targeted differentiation into specific tissue types *(Choe et al., 2018)*. By incorporating biochemical and biophysical cues, these hydrogels guide stem cell fate, thereby improving therapeutic outcomes and advancing the field of regenerative medicine.

Stem cell therapy, particularly for wound healing, has gained considerable attention for its ability to stimulate angiogenesis, accelerate wound closure, reduce scar formation, and promote collagen remodeling. Among various stem cell populations, human adipose-derived stem cells (hADSCs) have shown remarkable potential due to their ability to facilitate dermal repair and tissue regeneration *(C. Hong et al., 2025)*. Despite these advances, challenges such as low cell survival, poor engraftment, and limited site-specificity continue to hinder the full clinical potential of stem cell-based therapies *(Lee et al., 2021)*.

6. Challenges and limitations

The encapsulation of stem cells within biomaterials presents significant potential for regenerative medicine, offering the possibility to enhance tissue repair and regeneration. However, several challenges and limitations remain that impede the full realization of its therapeutic promise. Among the most pressing hurdles are the precise regulation of stem cell differentiation and the efficient integration of engineered tissues with the recipient tissue. These challenges are closely intertwined with the physicochemical properties of the microenvironment, such as substrate stiffness, porosity, and biochemical cues, as well as the host's biological response, including immune rejection and tissue remodeling. Addressing these factors is crucial for optimizing stem cell-based therapies and improving their clinical efficacy.

6.1. Precise control of stem cell differentiation

One of the major challenges in the encapsulation of stem cells lies in effectively directing their differentiation into specific cell lineages. Although stem cells inherently possess multipotent and self-renewing capabilities, their fate is highly dependent on the precise modulation of their surrounding microenvironment *(Xu et al., 2019; Zakrzewski et al., 2019)*. Stem cell behavior is governed not only by biochemical cues—such as cytokines, morphogens, and growth factors—but also by the physical and mechanical stimuli transmitted through the ECM or synthetic scaffolds *(Smith et al., 2018)*. Among these biophysical cues, the stiffness of the encapsulating material plays a pivotal role in guiding stem cell fate decisions. Substrates with defined elastic moduli can mimic the biomechanical properties of target tissues, thereby promoting lineage-specific differentiation—for instance, softer matrices favor neurogenic pathways, whereas stiffer matrices support osteogenic or myogenic fates *(Bratt-Leal et al., 2011; Smith et al., 2018)*. Nevertheless, replicating such finely tuned mechanical environments in a fully 3D system remains technically challenging.

Modern biomaterials aim to emulate the complexity of native ECM by providing spatially and temporally regulated signals in 3D, a marked improvement over conventional two-dimensional (2D) culture systems that lack physiological relevance *(Xu et al., 2019)*. These advanced scaffolds are engineered to deliver morphogen gradients, present adhesion ligands, and respond dynamically to cellular activity, thus offering a robust platform for processes like morphogenesis and lineage specification *(Bratt-Leal et al., 2011)*.

Despite these innovations, the design of biomaterials tailored to specific stem cell types and therapeutic applications remains resource-intensive. Parameters such as porosity, biodegradability, surface chemistry, nano- and micro-topography, and even electrical conductivity must be finely controlled *(Martino et al., 2012)*. The

underlying molecular mechanisms through which these variables influence cellular fate are still not fully elucidated, complicating efforts to standardize scaffold design across different systems *(Bratt-Leal et al., 2011)*.

Moreover, cell–matrix interactions can modulate gene expression patterns and epigenetic landscapes, potentially altering the phenotype and functionality of the encapsulated cells. In this regard, encapsulation should be recognized not merely as a passive shielding strategy, but as an active and tunable modulator of cell behavior *(Kim et al., 2019)*.

While recent advances—such as microgel-based encapsulation—have shown considerable potential, several technical challenges persist. For example, photopolymerization methods commonly used for scaffold formation often rely on radical initiators that can compromise cell viability. Similarly, encapsulation techniques involving oil emulsions may disrupt cellular membranes and impair function. Therefore, it is critical to develop next-generation encapsulation strategies that minimize exposure to cytotoxic agents, reduce light intensity and exposure time, and eliminate the use of oil-based components *(Choe et al., 2018)*. Such efforts will be essential for achieving safe, efficient, and clinically translatable stem cell therapies.

6.2. Efficiency of tissue integration

Beyond the challenges of directing stem cell differentiation, a major limitation in stem cell-based therapies is the efficient and functional integration of engineered tissues into the host. Successful tissue integration hinges on achieving adequate vascularization at the implantation site, which is critical for ensuring sustained oxygen and nutrient delivery to the transplanted cells *(Di Nicola, 2019; Paez-Mayorga et al., 2020)*. In the absence of proper vascular support, implanted constructs are prone to hypoxia, resulting in cell death and eventual graft failure. Currently, many encapsulation strategies rely on invasive surgical implantation, which can limit their clinical applicability and increase procedural risks. Although less invasive alternatives, such as subcutaneous implantation, are under investigation, these sites often exhibit poor vascularization, further exacerbating the challenge of maintaining long-term cell viability *(Paez-Mayorga et al., 2020)*.

To address these limitations, advanced delivery systems are being developed to promote angiogenesis through the controlled and localized release of pro-angiogenic factors such as VEGF and fibroblast growth factor (FGF). Despite these efforts, achieving precise spatial and temporal control over growth factor delivery remains a major technological hurdle *(Kim et al., 2019)*. Stimulus-responsive hydrogels and core-shell microparticles have emerged as promising platforms, offering tunable release profiles in response to physiological cues. However, their successful application often requires complex fabrication protocols, stringent material optimization, and careful control of physicochemical properties *(Amirsadeghi et al., 2020)*.

Other strategies, including the use of biomimetic nano- and microstructured materials such as foams, electrospun fibers, and functionalized particles, have demonstrated potential to enhance vascular ingrowth and support early stages of tissue regeneration. Nevertheless, many of these constructs fall short in meeting the immediate and dynamic metabolic demands required during the critical early phases of graft integration *(Amirsadeghi et al., 2020)*. Moreover, the ECM composition, architecture, and mechanical properties vary significantly across

different tissue types. Consequently, a scaffold optimized for one application—such as skin regeneration—may not be appropriate for another, such as cartilage or myocardial repair *(Kim et al., 2019)*. This underscores the necessity for highly specific, customizable biomaterial platforms that can be precisely engineered to emulate the unique structural, mechanical, and biochemical characteristics of the intended target tissue. Tailoring scaffold properties in this way will be crucial for enhancing host-graft integration and improving the long-term success of stem cell-based regenerative therapies.

7. Future Perspectives

The future of regenerative medicine and gene therapy lies in the convergence of smart biomaterials with advanced gene-editing technologies. Among the most promising developments is the emergence of stimuli-responsive biomaterials that can adapt to external signals—such as changes in temperature, pH, light, or mechanical stress—to control therapeutic delivery and direct stem cell behavior with greater precision *(Amirsadeghi et al., 2020; Gelmi & Schutt, 2021)*. These smart materials have evolved to incorporate dynamic functionalities, including 3D and 4D engineered environments, capable of responding to internal and external cues to modulate the cell–material interface, a key element in successful tissue regeneration *(Ma et al., 2018; Wan et al., 2021)*.

Next-generation biomaterials are designed to closely mimic the native ECM, serving both as structural frameworks and as carriers for bioactive agents such as growth factors and stem cells. This dual role facilitates enhanced cell adhesion, proliferation, and differentiation—parameters critical for effective regenerative outcomes *(Wan et al., 2021)*. Recent studies have shown that stem cells are highly responsive to mechanical and biochemical signals from their environment, activating mechanotransduction pathways that govern cell fate decisions *(Crowder et al., 2016; K. Zhang et al., 2018)*. Additionally, bioresponsive polymers and nanoparticle-based scaffolds provide versatile platforms for delivering stimuli that influence the spatiotemporal behavior of stem cells during repair and regeneration *(Ma et al., 2018; Narkar et al., 2022)*. These technologies can actively modulate the stem cell niche *in vivo*, addressing longstanding challenges such as poor cell retention and viability by creating supportive, adaptive 3D microenvironments *(I.-S. Hong, 2022)*.

In parallel, the integration of these material platforms with gene-editing tools—particularly CRISPR-Cas9—is revolutionizing therapeutic approaches for genetic and acquired diseases. While viral vectors remain widely used due to their high transfection efficiency, they present limitations including immunogenicity, insertional mutagenesis, and limited scalability *(Bulcha et al., 2021; Dubey et al., 2022)*.

In contrast, biomaterials offer a safer, more versatile alternative, enabling improved transfection efficiency, minimized off-target effects, and customizable, tissue-specific delivery *(Dubey & Mostafavi, 2023; Mitragotri & Lahann, 2009; Riley & Vermerris, 2017)*. Biomaterial-based systems have demonstrated the capacity to effectively encapsulate and deliver CRISPR components—whether as plasmid DNA, mRNA, or ribonucleoprotein complexes—while overcoming key challenges related to stability, immune evasion, and intracellular delivery *(Dubey & Mostafavi, 2023; Han et al., 2022)*. By protecting gene-editing tools and directing them to specific tissues, these platforms are unlocking new possibilities for safe, targeted, and personalized gene therapies for both hereditary and infectious diseases *(Gaj et al., 2016; Dubey & Mostafavi, 2023)*. Ultimately, the synergy between

smart biomaterials and gene-editing technologies represents a paradigm shift from passive scaffolding systems to actively responsive therapeutic platforms. This integration holds immense potential to transform the treatment of complex diseases and usher in a new era of precision medicine *(Gaj et al., 2016)*. In Figure 3, a schematic representation of the use of smart biomaterials, such as hydrogels, integrated into advanced therapeutic strategies involving stem cells. These systems modulate the cellular microenvironment through biochemical and physicomechanical cues, enhancing cell viability, directed differentiation, and the overall effectiveness of regenerative therapies.

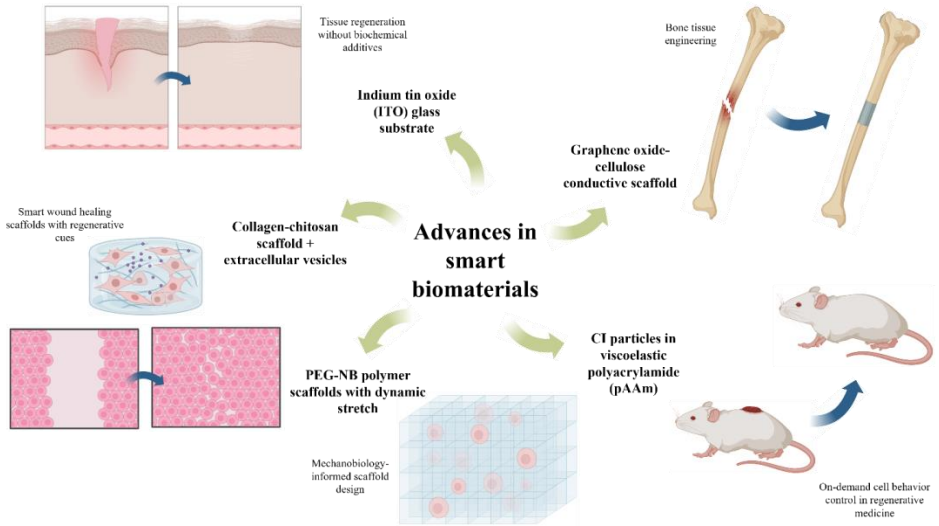

Figure 3. Smart hydrogels integrated with stem cells to enhance targeted regenerative therapies

Table 3 presents selected emerging examples of smart biomaterials and gene therapy-enabled platforms, with a focus on the interactions between stem cells (such as mesenchymal stem cells, pluripotent stem cells, and adipose-derived stem cells) and smart scaffolds. These advanced systems enhance cellular behavior, support tissue regeneration, and optimize therapeutic outcomes by offering precise control over stem cell differentiation, migration, and integration into the host tissue. These innovations are shaping the future of regenerative medicine by improving stem cell viability, reducing immune rejection, and enabling targeted gene delivery for personalized treatments.

Table 3. Advances in smart biomaterials and their role in future therapies

Scaffold	Cell Type/ Target	Stimulus/ Modulation	Response/ Outcome	Application/ Future potential	Reference
Indium tin oxide (ITO) glass substrate	Human mesenchymal stem cells (hMSCs)	Electrical stimulation	Exclusive osteogenic differentiation, without growth factors	Healing of various tissues, including nerve, bone, and cardiac tissue	*(Wechsler et al., 2016)*
Graphene oxide-cellulose conductive scaffold	Adipose-derived stem cells (ASCs)	Electrical stimulation	Increased proliferation and osteogenic differentiation	Bone tissue engineering; electrically responsive implants	*(J. Li et al., 2020)*

Colloidal inclusion particles in viscoelastic polyacrylamide (pAAm)	MSCs	Reversible mechanical stiffness control	Reversible control of MSC activity	Adaptive scaffolds for tissue engineering and wound healing.	*(Abdeen et al., 2016)*
Alginate, Arg-Gly-Asp -modified agarose/PEG hydrogels	Murine MSCs	Matrix stiffness	Adipogenesis and osteogenesis	Tissue engineering and regenerative medicine for skin, bone and cartilage	*(Huebsch et al., 2010)*
Collagen-chitosan hydrogel and extracellular vesicles	MSCs	Scaffold mechanics mimicking soft tissue	Enhanced collagen deposition and accelerated wound healing	Smart wound healing scaffolds with regenerative cues	*(Abolgheit et al., 2021)*
PEG-norbornene polymer scaffolds	MSCs	Dynamic strain application using a diaphragm pump	Modulated stem cell differentiation	Bone tissue regeneration	*(H. Liu et al., 2016)*

8. Conclusion

The Bio-envelope revolution marks a pivotal shift in regenerative medicine, positioning stem cell encapsulation as a cornerstone strategy for advancing therapeutic efficacy. By engineering protective microenvironments—particularly through hydrogel-based systems—encapsulation technologies offer critical solutions to long-standing challenges such as immune rejection, poor cell viability, and suboptimal integration into host tissues. These bio-envelopes, composed of evolving materials like alginate, collagen, and PEG derivatives, not only shield stem cells but also modulate their behavior through controlled biochemical and mechanical cues. As this field progresses, the convergence of encapsulation strategies with gene-editing technologies and the emergence of smart, stimuli-responsive biomaterials open new frontiers for precise, adaptive, and personalized therapies. However, significant hurdles remain, including fine-tuning material properties for specific applications, ensuring vascular integration, and scaling systems for clinical use. This work highlights the transformative potential of encapsulation in stem cell-based therapies and advocates for the continued development of bio-responsive scaffolds that serve as both protectors and active modulators of cellular function. Ultimately, advancing the design and implementation of these bio-envelopes will be key to unlocking the full regenerative capacity of stem cells and reshaping the future of personalized medicine.

9. Future Suggestions

The following are some future suggestions.

(i) To investigate the use of bioactive compounds acting as bifunctional cofactors in cell encapsulation systems.

(ii) To expand comparative studies between different types of biomaterials and encapsulation methods to identify the most promising ones according to the therapeutic application.

(iii) To explore the impact of microenvironment conditions (pH, inflammation, hypoxia) on the behavior of encapsulated cells in various pathological contexts.

(iv) To explore in greater depth the relationship between biomaterial composition and the functional response of encapsulated stem cells, considering both mechanical and biochemical factors.

(v) To conduct systematic reviews that integrate preclinical and clinical evidence on the efficacy of cell encapsulation systems.

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Authors' contributions

All the authors took part in literature review, analysis, and manuscript writing equally.

Availability of data and materials

Authors are willing to share data and material according to the relevant needs.

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