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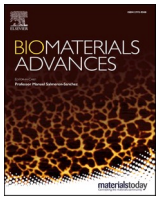

Review

Biomaterial engineering for cell transplantation

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ABSTRACT

The current paradigm of medicine is mostly designed to block or prevent pathological events. Once the disease-led tissue damage occurs, the limited endogenous regeneration may lead to depletion or loss of function for cells in the tissues. Cell therapy is rapidly evolving and influencing the field of medicine, where in some instances attempts to address cell loss in the body. Due to their biological function, engineerability, and their responsiveness to stimuli, cells are ideal candidates for therapeutic applications in many cases. Such promise is yet to be fully obtained as delivery of cells that functionally integrate with the desired tissues upon transplantation is still a topic of scientific research and development. Main known impediments for cell therapy include mechanical insults, cell viability, host's immune response, and lack of required nutrients for the transplanted cells. These challenges could be divided into three different steps: 1) Prior to, 2) during the and 3) after the transplantation procedure. In this review, we attempt to briefly summarize published approaches employing biomaterials to mitigate the above technical challenges. Biomaterials are offering an engineerable platform that could be tuned for different classes of cell transplantation to potentially enhance and lengthen the pharmacodynamics of cell therapies.

1. Introduction

Cumulated pre-clinical evidence suggests the potential therapeutic usage of transplanted cells to recover lost functionality in tissues and enhance tissue regeneration [1–3]. The clinical translation of cell therapy is hampered by technical challenges, including excessive mechanical tension on cells during cell transplantation and target residence, loss of cell function due to inadequate cell adhesion to the surrounding tissue microenvironment, and the immunological barriers posed by the host tissue microenvironment [4,5]. Moreover, limited access to oxygen, nutrients, and growth factors compromises the viability and lineage commitment of cells after transplantation [6]. The optimum cell quality attributes for effective transplantation and tissue regeneration are also not fully known yet [7–10].

Biomaterials have been employed to mitigate issues associated with cell transplantation. Engineered biomaterials provide structural frameworks tailored to the microenvironment of the native tissue to better recapitulate the host's physiological features at the transplantation site. Moreover, the incorporation of cells into designed biomaterials can protect the transplanted cells from hypoxia, stress, and immune attack, promoting long-term survival and maintenance [11–13]. Therefore, biomaterials' characteristics, including bioactivity, biocompatibility, and biochemical properties, are required to be tuned to a fit-for-purpose strategy for effective transplantation and protection against host insults.

In this review, we divided the transplantation process into 3 steps of pre-transplantation, during the transplantation procedure, and post-transplantation. We reviewed research challenges associated with each step, and biomaterials application as a mitigative strategy, overcoming technical and translational barriers for each step. (Fig. 1). In the pre-transplantation step, we discussed the importance of biomaterial choice and formulation for a superior cell therapy. There have been recent reviews about biomaterials types, characteristics, and their regulatory landscape [14–17]. Since many of the current biomaterials are hybridized with chemical conjugations that could impact biomaterials

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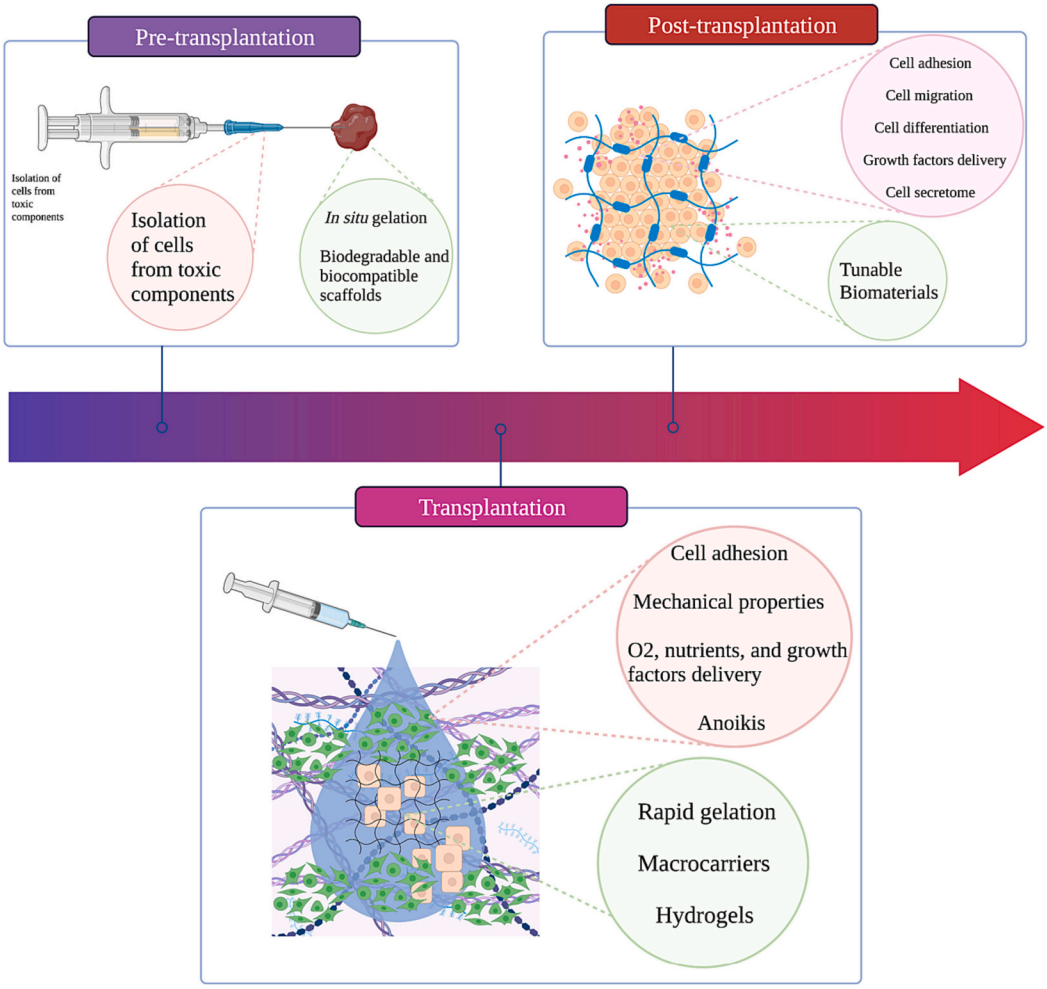

Fig. 1. Challenges in cell-biomaterial formulations at different stages of transplantation. In the pre-transplantation phase, cell exposure to cytotoxic encapsulation reagents could be mitigated by postponing the gelation to the transplantation stage by developing *in-situ* forming hydrogels. During the transplantation, rapid gelation could be achieved by *in-situ* forming hydrogels. Engineered biomaterials have been developed to address other challenges in the transplantation step, including lack of cell adherence to the extracellular matrix, detrimental mechanical forces cells experience, and lack of nutrients for cell survival and function. Upon completion of the cell transplantation procedure, major obstacles to the graft function are retaining cell adhesion after transplantation and promoting cell survival and differentiation in some cases. Some studies have addressed these issues by developing biomaterials with tunable properties like rigidity and viscoelasticity.

clinical translation, we briefly reviewed available cross-linking technologies with an eye toward their clinical translation. For the transplantation step, we reviewed biomaterials advantages in mitigating host's insults on the transplanted cells including mechanical forces, lack of functional integration, and immunological rejections of the transplant. Finally, we reviewed biomaterials benefit to support long-term survival and function of the transplanted cells in the post-transplantation section.

Results from recent studies indicate that engineered biomaterials hold great potential for ameliorating observed constraints in pre-clinical cell transplantation studies toward the clinical translation of cell therapy in the future.

2. Step 1: Pre-transplantation

Prior to the transplantation stage, cells generally need to be collected, purified, expanded, and prepared for administration. Upon isolation and/or maturation of cells to a transplantable stage, factors including shear stress may compromise the cell health and function. Biomaterials could be utilized to improve cell quality and retention during these processes. Before transplantation, engineering approaches could regulate the biodegradability of scaffolds [18,19]. Biomaterials applied in the transplant site may face stress, such as hydrolytic cleavage, and produce by-products that can be toxic to the host tissue and elicit immune responses. Thus, it is vital to design and engineer a biomaterial that would lead to safe by-products [12,20].

Based on the cell therapy product type, biomaterial choice and formulation play a critical role for a superior cell therapy. There have been recent reviews about biomaterials types, characteristics, and their regulatory landscape [14,16,21] that readers are encouraged to review. Biomaterial product is required to be biocompatible and biodegradable, which affects the outcomes of the pre-transplantation step (Figure 2). Along with ISO 10993 guidelines that regulatory bodies have required sponsors to follow, various methods have been proposed to assess the biocompatibility of biomaterials to promote cell survival and reduce post-transplantation complications [22–26]. Apart from the biomaterial choice, the formulation is the next critical consideration for product development. For example, cross-linking mechanisms may contain cytotoxic reagents or produce detrimental by-products during degradation, which affect cell survival or function. Eliminating or reducing the exposure of cells to such reagents and non-physiological conditions can alleviate the adverse effects on cell viability in pre-transplantation. One strategy could be to postpone gelation to the transplantation stage, in which dual barrel syringes separate cells in one barrel and cross-linking reagents in another [8], as depicted in Figure 2. Besides mitigating exposure to cross-linkers, it is necessary to use precursor

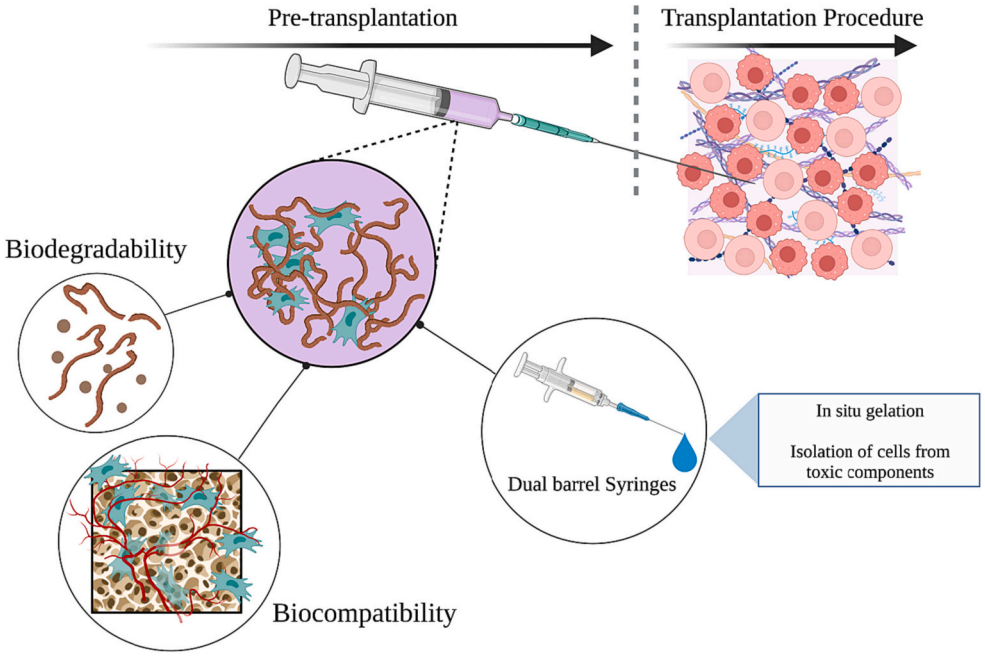

Fig. 2. Mitigating strategies for a successful cell transplantation during the pre-transplantation phase. Reducing long-term exposure to cross-linking agents before transplantation and using biodegradable and biocompatible biomaterials to avoid toxic by-products.

materials with suitable stability, low degradation rate, and lack of functional group deactivation before the start of *in-situ* gelation [27].

Developing injectable and *in-situ* forming hydrogels by *in-situ* gelation method reduces the exposure of cells to cross-linking agents. Furthermore, using *in-situ* forming double network hydrogels with this method reduces the degradation rate of the cell transplant to promote cell retention and provide support for differentiation of transplanted cells [28]. Two physical cross-linking mechanisms develop the double network hydrogel. The first step of cross-linking is intended to prepare a weak gel to encapsulate cells within itself, protecting them from the shear forces during injection. The second step of cross-linking occurs after injection *in-situ* to prolong the degradation of the hydrogel network, thereby promoting cell retention and differentiation after transplantation. Since the cross-linking is an evolving landscape in the biomaterials field, and affects the outcomes of biomaterial-cell transplantation, we briefly reviewed cross-linking technologies and commercial cross-linked biomaterial products in the following section.

2.1. Importance of cross-linking reaction

Cross-linking chemistry plays a pivotal role in *in-situ* gelation since cross-linking chemistry with suitable reaction kinetics contributes to the

Table 1
Comparison of different click chemistries for cross-linking in biomedical applications.

Cross-linking reaction	Relative gelation rate	Pros	Cons	Ref
CuAAC	Very fast	Occurring across a broad range of pH and temperatures Bioorthogonal	Cytotoxicity of Copper Not reversible at physiological pH	[33–36]
SPAAC	Fast	No need for copper as a catalyst Suitable mechanical strength Bioorthogonal	Longer gelation time compared to CuAAC Not reversible at physiological pH	[33,37,38]
Diels-Alder	Very slow	Bioorthogonal No need for a catalyst Highly stable	Slow reversibility	[33,39,40]
Aldehyde-hydrazide	Fast	No need for a catalyst Reversible gelation	Non-bioorthogonal Local toxicity induced by aldehyde groups at high concentration	[33,41–43]
Hydrazide-ketone	Slow	No need for a catalyst Reversible gelation Bioorthogonal No local toxicity induced by ketones	Slower gelation time due to lower reactivity between hydrazide and ketone	[33,44]
Thiol-Michael	Very fast	Fast gelation Possibility of using various functional groups	Non-bioorthogonal Typically occurring at basic pH	[33,45,46]
Disulfide	Very slow	Degradability in a reductive environment	Non-bioorthogonal Low selectivity	[33,47,48]
Imine Ligation	Fast	No need for a catalyst Responsive to shear and pH	Non-bioorthogonal Limited hydrolytic stability Toxicity by release of free glutaraldehyde	[33,49–53]
Oxime Ligation	Slow	Predecessor functional groups exhibit greater stability when compared to thiols and imines. Negligible protonation under physiological pH conditions	Non-bioorthogonal	[33,54–57]

Table 2
FDA applications on cross-linked hydrogels using the mentioned click chemistries.

Product name	Polymers	Cross-linking method	Gel form	Proposed application	Applicant	Administration	Product code	Status and year
Chitogel	Chitosan, dextran	Imine ligation	Gelled by mixing with water	Optimized wound healing after sinus surgery	Chitogel Ltd	Sinus Cavity	Class 1	510 K pre-market notification submitted (K172179) Substantially equivalent (2017)
Actamax	Dextran aldehyde and multi-arm PEG-amine	Imine ligation	*In-situ* gelation	Adhesion barrier following surgery	Actamax Surgical Materials LLC	Surgical	NCT03450421	Investigational device exemption (IDE) issued (2018)
Zyplast	Collagen cross-linked with glutaraldehyde	Imine ligation	Pre-gel	Dermal age correction	Allergan, Inc.	Injection	Class 3	Pre-market approval (PMA, P800022) (2003)
Cosmoplast	Collagen	Imine ligation	Pre-gel	Soft tissue contour deficiencies	Allergan, Inc.	Injection	Class 3	Pre-market approval (PMA, P800022 S050) (2003)
TenoGlide	Collagen, glycosaminoglycan	Imine ligation	Pre-gel	Protection of tendon injury in case of negligible loss of tendon tissue	Integra LifeSciences Corporation	Implant	Class 2	510 K pre-market notification submitted (K053655) Substantially equivalent (2006)
NeuraGen® 3D Nerve Guide Matrix	Collagen, glycosaminoglycan	Imine ligation	Pre-gel	Mid-gap nerve regeneration	Integra LifeSciences Corporation	Implant	Class 2	510 K pre-market notification submitted (K163457) Substantially equivalent (2017)
INFUSE Bone Graft	Collagen	Imine ligation	Pre-gel	Encapsulating rhBMP-2 for degenerative disc repair	Medtronic Sofamor Danek USA, Inc.	Implant	Class 3	510 K pre-market notification submitted (P000054) Substantially equivalent (2004)
Permvia	Hyaluronan, PEG diacrylate, gelatin	Thiol-Michael addition	Gelled by mixing with water	Wound healing	BioTime, Inc	Topical and surgical	KGN (Wound Dressing With Animal-Derived Material)	510 K pre-market notification submitted (K134037) Substantially equivalent (2014)
BioGlue	Bovine serum Albumin (BSA)	Imine ligation	*In-situ* gelation	Adhesive	CryoLife Inc.	Surgical	Class 3	510 K pre-market notification submitted (P010003) Substantially equivalent (2001)
ProGel	Human serum albumin	NHS-modified PEG	*In-situ* gelation	Sealing air leaks in both open and minimally invasive thoracic surgery	Neomend Inc.	Surgical	Sealant (NBE) Class 3	PMA P010047 approval (2010)
Tridyne	Human serum albumin	NHS-modified PEG	*In-situ* gelation	Reinforcing aortic anastomoses and control of bleeding	Neomend Inc.	Surgical	Sealant (NBE) Class 3	PMA P150016 Approval (2016)
PreveLeak	Bovine serum Albumin (BSA)	Imine ligation	*In-situ* gelation	Sealant for vascular and cardiac reconstruction	Baxter Healthcare Corp.	Surgical	Sealant (NBE) Class 3	PMA P100030 Approval (2017)

ultimate goal of attaining biocompatible biomaterials. In this regard, lack of interaction between the cross-linking reaction and biological components as well as tuning the speed of cross-linking for achieving uniform cell encapsulation and homogenous dispersion are considered in addition to conducting cross-linking reactions under physiological conditions with no toxic side products.

Using stepwise cross-linking chemistries, native or pre-anchored functional groups on one polymer chain must react with their corresponding groups. Click chemistry, first introduced by Sharpless and colleagues in 2001, has significantly evolved hydrogels by providing more methodologies to synthesize hydrogels and making hydrogels more accessible for bioengineering researchers [29]. Step-growth cross-

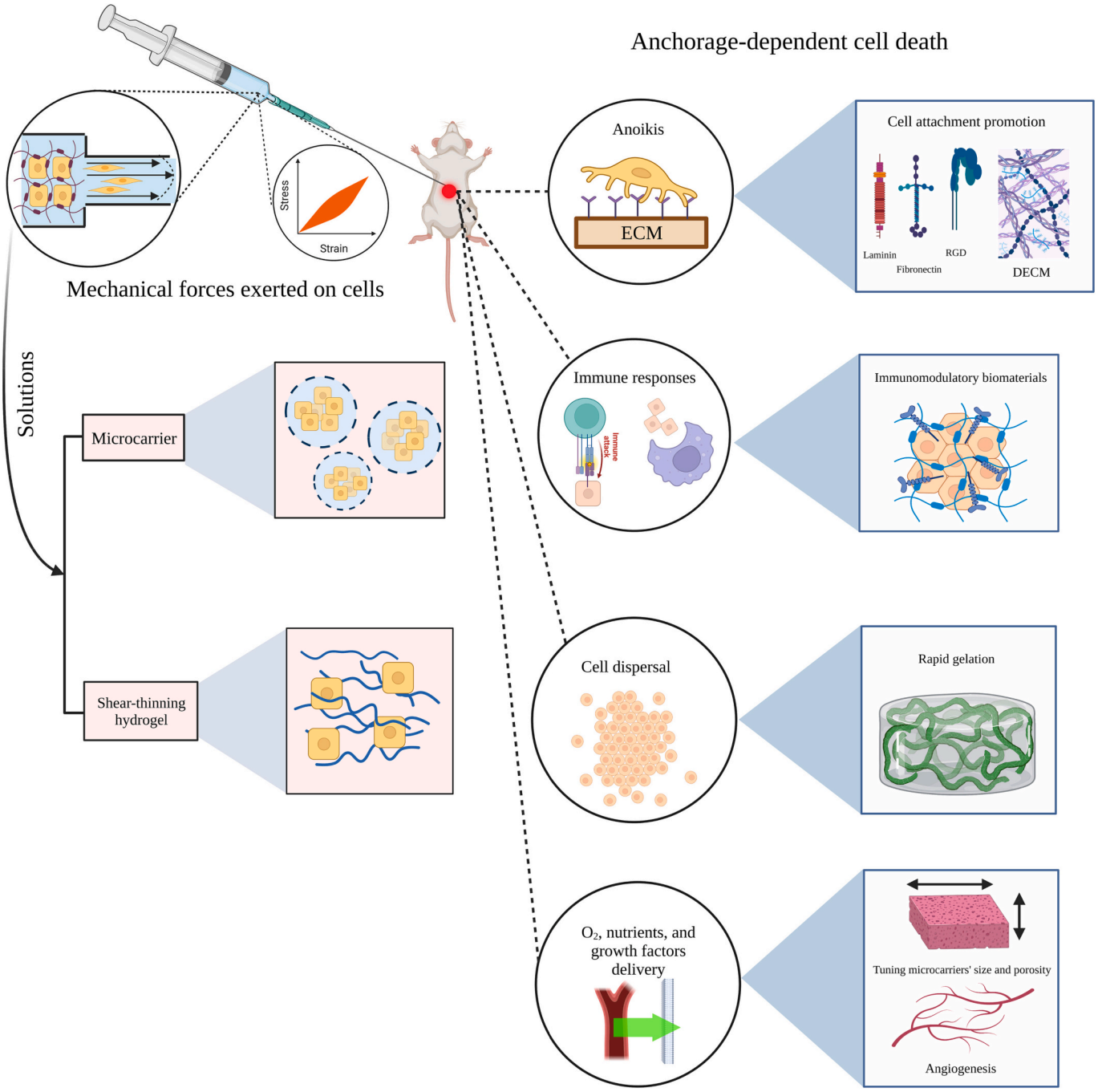

Fig. 3. Stress on transplanted cells could be mitigated by tuning biomaterial properties. Mechanical forces exerted on transplanted cells from the adjacent tissues can lead to membrane rupture and reduced cell viability or functionality after transplantation. This issue is addressed by developing microcarriers or shear-thinning hydrogels to ameliorate such forces. Lack of adherence to ECM can also result in anoikis. Developing hydrogels by incorporating cell-binding motifs such as laminin, fibronectin, collagen, or RGD onto biomaterials provides the integrin ligands necessary for attachment to the ECM. Also, decellularized ECM has been used to develop bioinks and hydrogels for cell encapsulation. Avoiding gelation in the pre-transplantation phase and rapid gelation in this phase results in preventing cell dispersal after transplantation. Providing a sufficient supply of oxygen and other nutrients, like growth factors, as an essential element to maintain cell viability in this phase is achieved by tuning the hydrogel or microcarriers' size and porosity.

linking is one of the main underlying concepts of click reactions for hydrogel formation. Based on that, various reactions proposed for hydrogel formation can be attributed as step-growth reactions and then categorized as bioorthogonal or non-bioorthogonal reactions.

Bertozzi and co-workers first developed bioorthogonal reactions to conjugate biomacromolecules [30,31]. This category of reactions progresses with high selectivity, avoiding any side reactions and ensuring that they do not interfere with the existing biological components. Bioorthogonal reactions have garnered attention to fabricate hydrogels for cell encapsulation purposes due to their attractive features, including providing highly compatible hydrogels without toxic by-products and proceeding under physiological conditions [32].

Widely used cross-linking reactions in the scientific literature as well as their gelation rates, advantages, and disadvantages have been showcased in Table 1. Also, the FDA applications relevant to these reactions are summarized in Table 2. As can be seen, each of the

Table 3
Most recent studies on microcarriers for cell delivery.

Platform	Delivered cell or growth factor	Type of study	Outcome	Reference
Nucleus pulposus cells (NPCs)-derived microcarriers	Adipose-derived stem cells (ADSCs)	*In vitro* & *In vivo*	NPC cells were first cultivated and aggregated into pellets and then decellularized to obtain their ECM as a microcarrier. Then, ADSCs were loaded into the prepared microcarriers and evaluated for differentiation *in vitro* and Nucleus pulposus regeneration in a rabbit model. The injectable microcarrier showed higher differentiation compared to ADCSs cultured in pellets, showing the elevated expression of NP-specific markers and increased matrix synthesis.	[81]
poly(L-lactic acid) (PLLA) nanofibrous microspheres	Human bone marrow mesenchymal stem cells (hBMSCs)	*In vitro* & *In vivo*	PLLA microcarriers were coated with Fe_3O_4@SiO_2 to evaluate the capability of guided release of cells at the transplantation site. The average size of the microcarriers was between 40 and 50 μm prepared by using the EDC/NHS modification method. The fabricated platform showed excellent biocompatibility and biodegradability, capable of storing cells and controlled release of cells under a magnetic field. Moreover, the *in vivo* studies showed the release of cells into tissue from injected microcarriers.	[82]
Conjugated hyaluronic acid methacryloyl (HAMA) to Fibronectin (FN)	Adipose-derived stem cells (ADSCs)	*In vitro* & *In vivo*	The fabricated microcarrier promoted biocompatibility and regulatory function through using HAMA and FN, respectively. In addition, multiple growth factors, such as Vascular endothelial growth factor (VEGF), Hepatocyte growth factor (HGF), and Fibroblast Growth Factor 2 (FGF2), were released to accelerate the migration and angiogenesis of HUVEC cells. The use of these microcarriers showed accelerated diabetic wound healing with enhanced collagen deposition, neovascularization, and follicular rejuvenation in type I diabetic mice.	[83]
Core-shell capsules made from co-extrusion of alginate and Matrigel	Human pluripotent stem cells (hPSCs)	*In vitro*	Core-shell microcapsules were developed by microfluidics to encapsulate hPSCs. By attaining the optimum size of the microcapsules (205 μm ± 39 μm), the supply of nutrients to cells was not limited, and significant enhancement in viability and maintaining pluripotency was observed.	[84]
Hyaluronic acid methacryloyl (HAMA)	Exosomes derived from Human umbilical cord mesenchymal stem cells (hUCMSCs)	*In vitro* & *In vivo*	Excellent biocompatibility and controlled release of exosomes were achieved owing to the biocompatibility and semi-permeable properties of HAMA. *In-situ* transplantation of the microcarriers showed prolonged restoration of ovarian function and enhanced fertility observed in chemotherapy-induced premature ovarian failure (POF) mice.	[85]
Polylactic acid (PLA) hydrogel	Bovine serum albumin (BSA) and Fibroblast growth factor (FGF)	*In vitro*	Micromolding was used to fabricate PLA hydrogels loaded with growth factors. *In vitro* studies showed sustained release of these growth factors for up to 2 weeks, resulting in promoting fibroblast proliferation.	[86]
Gelatin methacryloyl (GelMA)/ chitosan microspheres (GCMSs)	Retinal pigment epithelia (RPE) cell line, ARPE-19	*In vitro* & *In vivo*	Microspheres with a diameter of 120 μm fulfill both the criteria of accommodating a substantial number of ARPE-19 cells on their surface area and meeting the typical size requirements for injection. The microcarriers were completely degraded after 10 days and were biocompatible.	[87]
Light-weight polycaprolactone (LPCL)	Human mesenchymal stromal cells (MSC)	*In vitro* & *In vivo*	Microcarriers based on light-weight polycaprolactone were fabricated for large-scale production of MSCs in a stirred bioreactor. The microcarriers incorporating cells were stirred in the bioreactor at 40 rpm for 7 days. The optimized conditions for seeding cells were determined by *in vitro* studies to attain efficient proliferation and chondrogenic differentiation after 21 days. Evaluation of the implanted microcarriers in a rabbit model after 5 months following transplantation showed good healing outcomes, paving the path for further studies on its application for critically-sized cartilage defects.	[88]

crosslinking reactions have advantages and disadvantages compared to each other. Depending on the type of gel form shown in Table 2 and type of application, one of these reactions becomes superior for crosslinking. According to FDA applications so far, imine ligation is one of the prevalent types of cross-linking reactions for pre-gel or *in-situ* gelation.

3. Step 2: Transplantation

During transplantation, cells are required to maintain their viability and function. Various approaches have been proposed to maintain the viability of cells during cell transplantation. In what follows, we will review how biomaterials could tackle transplantation challenges, including mechanical forces, anchorage-dependent cell death, lack of growth factors, and immediate host response.

3.1. Mechanical forces exerted on cells during the transplantation process

Cells are often subjected to shear forces during syringe pass-through, which is exerted *via* Newtonian fluids, particularly with less viscous solutions such as saline and culture medium. There is a flow resistance near the interface of the syringe and the fluid, leading to extensional forces. Because of this resistance, the flow velocity at the center of the pass-through differs from the interface of the syringe and liquid adjacent to the syringe's internal surface. The more the difference in diameters between the syringe and the needle, the more shear forces will be exerted on cells during injection [58–60]. This shear stress could lead to cell membrane ruptures, reduced viability of transplanted cells *via* necrosis, and might impact the therapeutic transcriptome landscape of the cells. For example, force could induce apoptosis in cells, which results in cell death after cell transplantation. Biomaterials such as shear-thinning ones are proposed to limit the induction of unwanted shear stress on

cells during cell transplantation. In what follows, we will review microencapsulation as well as shear thinning strategies (Figure 3).

3.1.1. Microcarriers

Microcarriers are often described to range from 2 μm to 2 mm, and could be in the form of spherical microparticles with a porous matrix, allowing for essential molecules to diffuse inwards and outwards the encapsulated cell. In addition to protecting cells from shear forces during injection, microcarriers have several benefits for cell therapy, including a high enough surface area to volume ratio to allow molecules timely diffusion, protection of cells against host immune response, and encapsulation of large quantities of cells within [61].

Despite the promising potential of microcarriers, clinical translation of these platforms is still in the early steps and requires further research. For instance, the optimal size of the microcarriers is subject to debate and needs validation. Smaller microcarriers are considered to be less immunogenic, preferred for superior diffuse-ability of molecules, easier transplantation procedures such as laparoscopy, which might be more preferred by patients [62], and suitable sustained release of therapeutic molecules from the encapsulated cells. [63]. In contrast, encapsulating cells within thicker and larger microcarriers can enhance implant stability with easier extraction of the implant if needed [64], while resulting in insufficient transport of nutrients and wastes to maintain cell viability after injection [64,65]. In addition, microcarriers with a thin or too thick membrane can result in mechanical instability, cell leakage, and lack of protection against immune cells. Hence, a well-designed and optimized size should be developed and validated for desired clinical outcomes.

Besides the optimal size, the chemical composition of the microcarriers could impact the function of encapsulated cells *in vivo* [66,67]. Wilson et al. examined the impact of alginate composition and coating on embryonic stem cells (ESCs) differentiation [68]. They found that encapsulation of ESCs within alginate containing a high concentration of mannuronic acid promoted stem cells differentiation, whereas a high concentration of guluronic acid led to the lowest differentiation among the four studied compositions. In another study, alginate microbeads with a diameter < 200 μm were fabricated to enable subcutaneous injection of encapsulated adipose stem cells, which demonstrated acceptable viability over 2 months post transplantation [69].

Injectable microbeads made of fibrin hydrogel were developed to incorporate human umbilical cord mesenchymal stem cells. The fabricated microbeads were facilely degradable, resulting in macropores inside the microbead to maintain a consistent delivery of nutrients to the encapsulated cells and promote viability. Such pores further allowed the migration of cells out of the microbeads, enhancing myogenic differentiation for muscle tissue engineering. Several other studies have also investigated the impact of degradable injectable microbeads, cell density, and microbead composition on the viability and differentiation of encapsulated cells [61,70–74].

The methods used for encapsulating cells in microcarriers are typically based on emulsification and extrusion [75]. One of the major drawbacks of these two approaches is the shear force applied during microbeads fabrication [61,76]. In addition, thermal shock to incorporated cells after the emulsification process, the use of chemical solvents affecting biocompatibility, and lack of sufficient control on size distribution are other challenges in the use of the mentioned methods. Recently, microcarriers have been developed using microfluidic technology, offering better control over the size and geometry of microcarriers. However, the use of microfluidics is associated with several challenges as well, such as low density of encapsulated cells, high cost of fabrication devices, and cross-linking. Studies have established novel microfluidic platforms to lower the costs of this method and increase the loading density of cells with suitable cross-linking [77–80]. Overall, it is anticipated the optimum material, size, and shape of biomaterials need to be validated at least in the pre-clinical stage, which might vary for different cells or different therapeutic paradigms. Some of the most recent studies conducted on the application of microcarriers have been summarized in Table 3.

3.1.2. Shear-thinning hydrogels

Shear-thinning hydrogels are another biomaterial class that are developed to prevent mechanical shear. These biomaterials are pre-formed hydrogels that can become pseudo-liquid under the syringe shear forces and can be injected into the transplantation site. This type of hydrogel has advantages for cell transplantation since the cross-linking of the pre-formed hydrogel is less prone to be affected by the transplantation environment [89]. Additionally, shear-thinning hydrogels can return to their original elastic modulus faster than other hydrogels after removing shear stress [90]. Hydrogen bonds, hydrophobic, and electrostatic interactions result in cross-linking in shear-thinning biomaterials without any covalent bonding, obviating concerns with biocompatibility and the use of chemical cross-linkers in microcarriers fabrication [91]. In the context of cell injection, shear-thinning biomaterials can reduce the shear forces exerted on cells by providing an equal velocity all over the syringe tube, including walls. This plug flow diminishes mechanical stress on cells and promotes cell viability [92]. Shear thinning biomaterials reduce the mechanical forces on cells during injection and improve cell viability [93–95]. Gaffey et al. developed an injectable shear-thinning hydrogel for direct delivery of endothelial progenitor cells for myocardial infarction treatment. The shear-thinning attribute of the fabricated hyaluronic acid (HA) hydrogel resulted in a higher cell viability and contributed to vascularization and cellular retention at the site of transplantation [96].

Shear-thinning hydrogels have also been studied for controlled co-delivery of cells and growth factors as a necessary step toward clinical translation. A hybrid hydrogel was developed based on polyethylene glycol (PEG) and protein for the co-delivery of endothelial cells derived from human-induced pluripotent stem cell-derived (hiPSC) and vascular endothelial growth factors (VEGF). The shear-thinning hydrogel retained cell viability significantly compared to cell injection by saline, provided integrins to maintain endothelial cells adhesion, and enabled sustained co-delivery of growth factors and cells [97]. In a recent study, composite bioinks were developed with methacrylated alginate and human bone particles. The results showed enhanced shear-thinning after the addition of bone particles. The viability of cells remained around 90 % for 28 days after bioprinting, and enhanced osteogenesis was observed [98]. Overall, shear-thinning materials have offered an innovative approach to cell/biomaterial transplantation with the goal of transplanting cells with minimal surgical procedures. Table 4 represents recent studies performed on fabricating shear-thinning hydrogels.

3.2. Anchorage-dependent cell death and lack of growth factors

Excluding non-adherent cell types, other cells need to adhere to extracellular matrix (ECM) components *via* their integrins to activate cell survival pathways. Cell death due to the lack of adhesion to the ECM surface, known as anoikis, is a major challenge when cells are detached from the culture plate for encapsulation and after cell injection, resulting in poor cell viability. Some solutions have been proposed to overcome this issue in cell transplantation, which are summarized in what follows.

3.2.1. Use of biomaterials functioning as integrin-ligands

Cell death caused by anchorage-dependent mechanisms can be prevented with biomaterials containing integrin ligands, such as collagen, laminin, fibronectin, or HA [21]. In a recent study, silk, collagen, and laminin proteins were used to develop a hydrogel for neural stem cell (NSC) delivery toward spinal cord injury treatment in rats [104]. The fabricated hydrogel protected cells from mechanical forces during the injection, promoted the viability of NSCs through adhesion to the hydrogel matrix, and enhanced their migration and differentiation.

Table 4
Recent studies on shear-thinning hydrogels for cell delivery.

Hydrogel	Cell	Type of study	Outcome	Reference and year
Cellulose nanocrystals (CNCs)-modified alginate	Immortalized chondrocytes (TC28a2)	*In vitro*	Incorporating CNCs (1 % and 2 % (*w/v*)) into alginate hydrogels (1 % (*w/v*)) enhances shear-thinning behavior and improves mechanical stability. The inclusion of CNCs (up to 1 % (w/v)) does not appear to impact the performance of the polymeric systems. The existence of CNCs does not appear to have an impact on the viability of immortalized chondrocytes (TC28a2), which remain viable over a seven-day period post-encapsulation.	[99] (2023)
2,2,6,6-tetramethylpiperidine 1-oxyl-oxidized cellulose nanofiber (TOCNF) and chitosan nanofiber (CsNF)	Human hepatocellular carcinoma cells (HepG2)	*In vitro*	TOCNF carboxylates and amines of CsNF were directly cross-linked through EDC/NHS chemistry. The fabricated injectable hydrogels showed excellent viscoelastic features with a storage modulus of 1234 Pa ± 68 Pa, rendering them suitable for cell culture. The prepared biodegradable hydrogels encapsulating cells are anticipated to mimic the cellular microenvironment, offering the potential for bioadaptive 3D cell cultures.	[100] (2023)
Collagen hydrogel reinforced with surface-modified cellulose nanocrystals (CNCs)	Mesenchymal stem cell (MSC)	*In vitro* & *In vivo*	Following extrusion *in vitro*, MSCs showed high cell viability. Gelation occurred rapidly under physiological conditions (37 °C, pH 7.4), and the hydrogel demonstrated enhanced elastic modulus, quick shear-thinning, and self-healing properties. Subcutaneous injection of MSCs encapsulated in the hydrogel to mice exhibited enhanced implant integrity and increased cell retention.	[101] (2020)
Gelatin	Stem-cell-derived cardiomyocytes	*In vitro*	Gelatin was functionalized with complementary association domains, wherein their physical interaction could be disrupted with mild shear force and rapidly reformed upon force removal. The integration of β-cyclodextrin (CD) and adamantane (AD) moieties onto the gelatin backbone allows for the straightforward development of physically cross-linked hydrogel biomaterials with adjustable mechanical properties.	[102] (2020)
Methacrylate-Kappa-carrageenan (KaMA)-dopamine functionalized graphene oxide (GOPD)	Fibroblast	*In vitro*	KaMA-GOPD hydrogels exhibited shear-thinning behavior and injectability due to the interaction of active catechol groups of dopamine with other moieties in the hydrogel structure. Furthermore, these interactions enhanced the mechanical properties of the hydrogels, with the extent depending on the GOPD content. The reinforcement of KaMA with 20 wt% GOPD led to increased fibroblast proliferation (2.5 times) and spreading (5.7 times) after 5 days of culture.	[103] (2019)

3.2.2. *Developing bioinks and hydrogels for cell encapsulation from decellularized matrices*

In addition to the crucial role of ECM structure to mimic the physiological characteristics in prepared cell transplants, proteins in ECM are also vital for successful cell transplantation. Since proteins like collagen, laminin, and HA have proven to be effective in better cell adhesion and viability upon transplantation, the use of decellularized ECM as bioinks have been studied. Bae et al. transplanted an NSC-laden brain-derived ECM in the rat brain. The shear-thinning property of the bioink protected cells during injection and the adherence to the bioink retained NSCs on the implantation site. Also, the encapsulated neural stem cells differentiated into neurons successfully [105]. In another study, decellularized ECM of kidney mixed with alginate was proposed as an injectable hydrogel for progenitor cells delivery to kidney defect. The hybrid hydrogel provided better space for the adhesion of cells and proliferation [106].

3.2.3. *RGD sequences to enhance cell attachment*

Promoting integrin-mediated cell adhesion by arginine–glycine–aspartic acid (RGD) peptide is another approach to alleviate cell death due to lack of proper attachment in transplantation. RGD ligands, along with integrins on the cell surface that bind to them are key components of cell adhesion. Known as an attachment site on cells, the RGD peptide is recognized by ECM and proteins on the cell surface. Synthetic peptides containing the RGD sequence can mimic the integrin-binding activity of adhesion proteins [107,108]. In this regard, numerous research has been conducted on RGD peptides to enhance cell attachment and mitigate anoikis [109–111]. In a recent study, a hydrogel was functionalized with RGD peptide for cardiac progenitor cell delivery. The addition of RGD to the hydrogel improved integrin binding to the fibrillar network, enhanced interactions between the cell and the network, and enabled progenitor cells migration throughout the hydrogel [112].

In addition to the mentioned approaches, co-delivery of cells and growth factors and growth factor immobilization have also shown satisfying results in promoting cell adhesion to the matrix and enhancing proliferation after injection [94,113,114]. In the delivery of growth factors, it is vital to strike a balance between cell survival and side effects caused by prolonged exposure to growth factors. Tuning biomaterials can provide control over the release of growth factors to avoid burst release, resulting in unfavorable consequences like hyperplasia and tumorigenesis [115–117]. For instance, using chemical cross-linking or mixing physical and chemical interactions to immobilize growth factors in the delivery platform has shown sustained release of growth factors to preclude the burst release.

In a study by Wang et al., dopaminergic progenitors were delivered into the striatum of a parkinsonian mouse by a composite scaffold made of poly(l-lactic acid) (PLA) nanofiber incorporated in a xyloglucan hydrogel. Controlled release of glial-derived neurotrophic factor (GDNF) was also investigated by covalent binding with scaffold, non-covalent mixing, or combined approaches. The results showed enhanced proliferation and cell survival in scaffolds that GDNF was both mixed and covalently bound to the scaffold [118]. Although covalent binding of growth factors in the scaffold provides sustained release, the issue with this approach is preventing rapid degradation and potential loss of bioactivity of the immobilized protein. To solve this problem, a porous chitosan scaffold was first fabricated, and poly(methyl methacrylate-*co*-

methacrylic acid) (PMMA-co-MAA) nanoparticles were immobilized in the scaffold. Using this method, growth factors can be loaded in the nanoparticles and circumvent the chemical cross-linking of growth factors to the scaffold, reducing the adverse effects on growth factors bioactivity [119].

3.3. Impact of biomaterials on immune response

The immune system is typically considered a barrier to the successful transplantation of cells [120–124]. For years, the only approach to circumvent this barrier has been the use of an immunosuppressive regimen accompanied by transplantation. This type of reaction is known as T helper 1 (T_H1) immune response since T cells are involved in regulating immune system reactions [14,125–127]. Due to the impact of immune system response on cell survival, studies have focused on developing approaches to prevent immune cells attachment to the cell surface and fibrosis reduction. For instance, Le et al. developed hyaluronic acid (HA) microrods to alleviate fibrosis in a cardiac model [128].

Recent studies have shown that biomaterials are capable of modulating immune system responses. Deeper insight into the types of immune responses revealed that these responses are not limited to those associated with fibrosis and inflammation; rather, there is another immune response that can mediate tissue regeneration defined as T helper type 2 (T_H2) [129]. Therefore, studies were conducted on how this balance can be tilted toward the latter responses to promote successful transplantation by the regulatory role of the immune system.

Among developed biomaterials, ECM-derived platforms have shown promising results for modulating immune response in transplantation. Bone and cardiac-derived ECM have been proven to convert T cells into T_H2 cells [21]. Fig. 3 and Table 5 summarize issues in the transplantation phase and the proposed solutions.

4. Step 3: Long-term survival after transplantation

After cell transplantation, the main challenges are unwanted cell migration, cell detachment, limited cell secretome, and differentiation [2,141,142]. Limitations associated with poor or late differentiation of cells are related to the availability of biochemical cues, such as growth factors, signaling molecules, and nutrients present in the cell microenvironment to promote cell ingrowth and to maintain cell phenotypes once stem cells differentiate into specific cell types [143].

To promote long-term cell survival and cell function, innovative cell-based therapies rely on technologies and techniques to ensure cell adhesion and proliferation, maintaining cell phenotypes for long periods of time. These technologies include tissue engineering approaches to produce scaffolds and matrices with desired features for cell growth, 3D printing, micro and nanofabrication techniques.

Table 5
Common limitations in the transplantation phase and proposed approaches to address them.

Challenge	Solution	Considerations	Reference
Mechanical forces exerted on cells during transplantation	Microcarriers Shear-thinning hydrogels	Optimal size to strike a balance between sufficient transport and release of cells, stability, immunogenicity, and ease of transplantation. Cell density and the microbead composition affect the viability and differentiation of cells. Shear-thinning hydrogels can rapidly restore their original elastic modulus faster than other hydrogels upon removing shear stress.	[4,61–65,70–74,90]
Anchorage-dependent cell death	Use of biomaterials containing integrin ligands Materials composed of natural extracellular matrix (ECM) Bioinks and hydrogels from decellularized ECM for cell encapsulation Use of RGD sequences designed to mimic ECM proteins	ECM can provide a structure capable of mimicking the 3D microenvironment as well as containing proteins vital for maintaining cell proliferation. Importance of maintaining a balance between cell survival enhancement and side effects such as hyperplasia and tumorigenesis in case of growth factor delivery.	[115–117,130,131]
Nutrient transport	Tuning biomaterial size and porosity	Optimized size and porosity of biomaterials, like microcarriers and hydrogels affect cell survival and facilitate nutrient delivery to encapsulated cells. The use of porous hydrogels can reduce cellular oxygen stress, help prevent oxidative damage, and promote homeostasis in cells by upregulating pathways like the TNF signaling and the NF-κB signaling pathway. Porosity can also provide a high friction coefficient and low elastic modulus for bone tissue transplants. Pore size can influence the phenotype of infiltrating immune populations. Pore sizes within the range of 30–40 μm induce a shift in macrophage phenotype toward a pro-regenerative expression profile. Additionally, they contribute to a decrease in the formation of foreign body giant cells and an increase in angiogenesis.	[132–134]
Cell dispersal	Rapid gelation	Rapid gelation ensures consistent cell density and prevents cell dispersal after transplantation. Rapid gelation achieved by bioorthogonal cross-linking reactions enables rapid gel formation to facilitate efficient cell encapsulation without generating toxic by-products. Secondary cross-linking by using temperature and photocrosslinking can achieve faster gelation.	[135–138]
Immune responses	Immunomodulatory materials	Foreign body response and integration of biomaterials in tissues are the major inflammatory responses to biomaterials. Structure and surface modifications can alleviate the immune response. Use of immunomodulatory biomaterials capable of M1-to-M2 transition of macrophages. ECM-derived platforms can mediate tissue regeneration by tilting the balance of T cells toward T helper type 2 cells (T_H2).	[21,129,139,140]

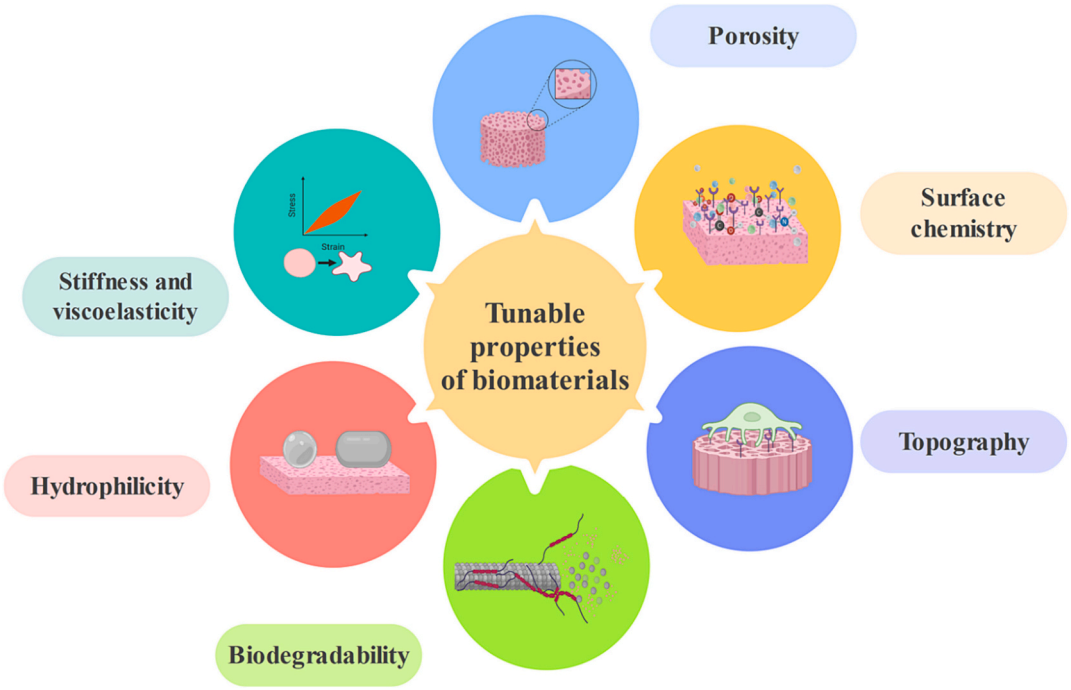

Fig. 4. Tunable properties of biomaterials to promote long-term survival after transplantation. Using biomaterials with dynamic mechanical properties can provide control over stiffness and viscoelasticity during cell differentiation to direct cell fate toward the preferred lineage. Engineering biomaterials to be hydrophilic can enhance their attachment after transplantation, preventing cell detachment as one of the issues for long-term survival after transplantation. The porosity of biomaterials should also be tuned to deliver biochemical cues necessary for long-term survival. The topographical features of the biomaterial should also mimic the native ECM to improve the proliferation and differentiation of cells over long periods of time after transplantation.

4.1. Cell adhesion and migration

Cell adhesion and migration can be induced by modifying the biomaterials' properties and by modulating cell responses with the introduction of biophysical and biochemical cues that direct and promote the desired tissue formation [144,145]. Biophysical factors that influence cell migration and adhesion after cell transplantation include porosity, pore size, stiffness, viscoelasticity, and topography, as illustrated in Figure 4. Biochemical cues such as growth factors, peptides as well as genetic regulators (RNA and DNA) can promote successful cell transplantation, long-term cell survival, and proper cell function [144].

Also, growth factors can be used to promote proliferation, maintain

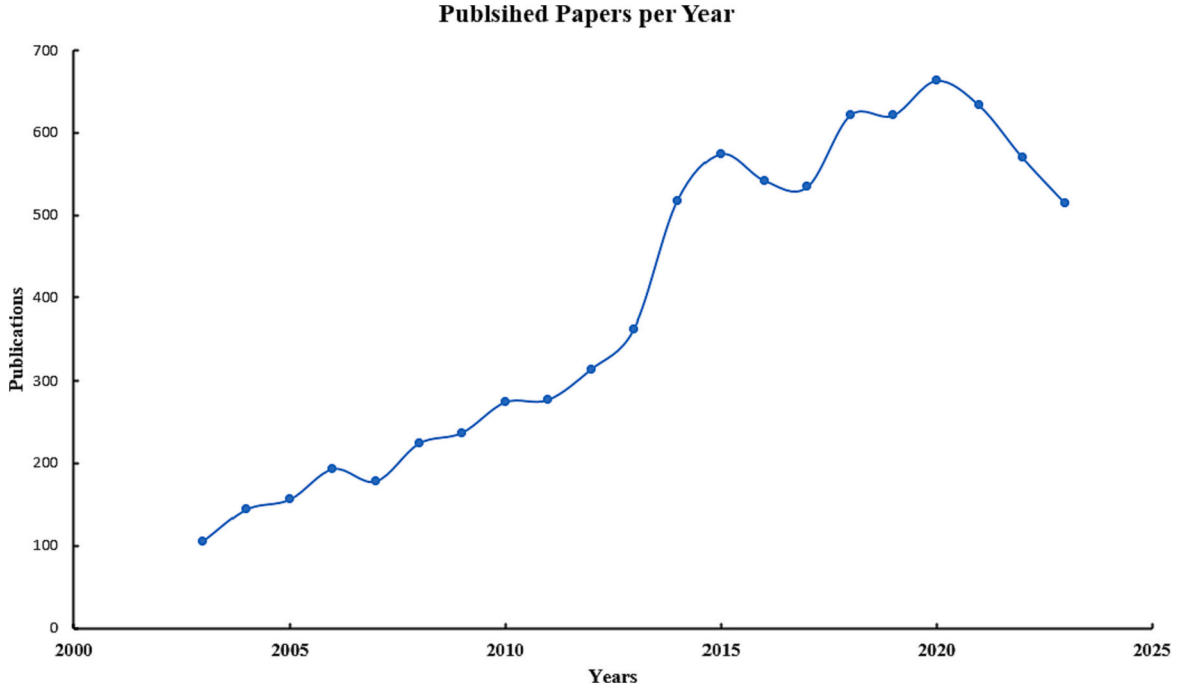

Fig. 5. The number of published works on "biomaterials for cell transplantation" indicates a steady increase over the past two decades. The growth in publications represents biomaterials' growing interest and importance, particularly for translational studies. Since the last six years, around 700 papers have been published each year in this field. For example, compared to 2013, the number of published articles in this area has increased two times and reached 621 in 2018.

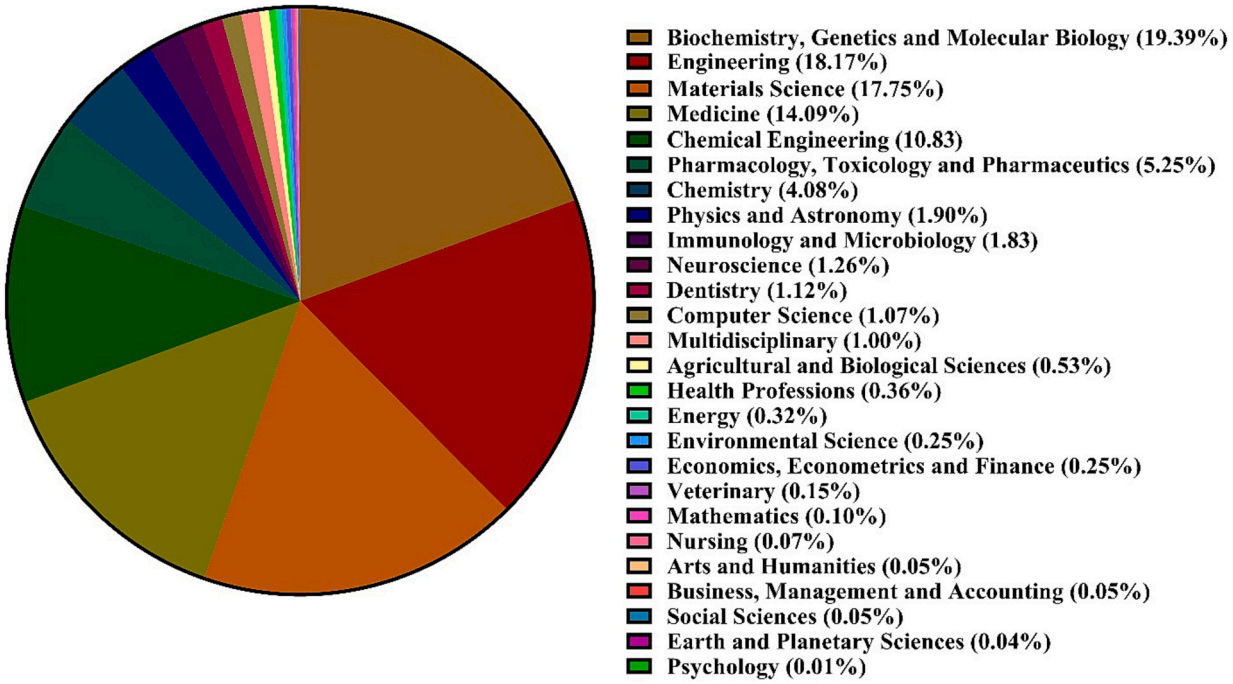

Fig. 6. Distribution of research papers in biomaterials based on their field. Biochemistry and molecular biology, material science and engineering, medicine, chemical engineering, pharmacology, and chemistry are among the areas with growing interest in conducting research on biomaterials.

cell phenotype, and enhance cell adhesion. However, one of the major drawbacks of using growth factors in cell-based therapies is their rapid degradation and high cost. For instance, VEGF has a short half-life time of ~30 min; therefore, other strategies need to be implemented to maintain cell phenotypes for the long term [146]. As mentioned before, tuning biomaterials properties can alleviate this issue through sustained release [147].

4.2. Cell secretome

Another important consideration for cell survival during this phase is the limited cell secretome, which is defined as the group of molecules that are secreted by a cell to the extracellular space under specific conditions and time. These molecules include soluble factors, lipids, and extracellular vesicles. Cell secretomes can be induced in different ways, for example, it has been shown that promoting hypoxia and inflammation results in a secretome-preconditioned cell environment with the release of chemo attractants such as interleukins (IL) and cytokines. It has been observed that the presence of those molecules in a secretome-preconditioned state has had more beneficial effects in angiogenesis and the central nervous system (CNS) related diseases compared with an un-preconditioned cell environment; however, monitoring and evaluating possible side effects of an induced inflammatory state is necessary [148].

4.3. Cell differentiation

Cell differentiation is a very complex process, and it is an important part of the regeneration of the organ's function after cell transplantation. It is regulated by vast signaling pathways and is strongly influenced by the cell's microenvironment. Since the dominant condition of the microenvironment continuously changes during development, it is vital to provide scaffolds with dynamic mechanical properties to promote differentiation after transplantation [149–153].

Controlling the mechanical properties of hydrogels over time to promote cell attachment and differentiation offers the possibility of optimal organ functionality after cell transplantation through the release of signaling molecules modulating cell survival [144,145,154,155]. Stiffness is a mechanical property of biomaterials that has a big influence on cell fate after transplantation. Scaffold stiffness can be tuned by a secondary cross-linking derived from an external stimulus, such as pH, light, magnetic field, and temperature [21,156–158]. For example, the incorporation of elastin-like proteins as a thermoresponsive cross-linking component into an injectable hydrogel regulates the final storage modulus between 1 kPa to 2.75 kPa *via* changing the amount of the incorporated protein [159]. In a study, hydrogels with stiffness above 50 kPa have promoted chondrogenesis and osteogenesis in mesenchymal stem cells (MSCs). On the other hand, for neural tissue regeneration, hydrogels with lower stiffness values are desirable [146]. Moreover, molecular weight, gelation, composition, and cross-linking are the other significant variables controlling the biophysical properties of the polymeric constructs. These processing factors manipulate the rigidity and stiffness [12,152]. For example, by incorporation of microbeads into an alginate with high molecular weight, the stiffness property can be tuned in the bulk alginate and enable further optimizations of the biomaterial's design [160,161].

Thus, current efforts are focused on the development of biomaterials that can match the stiffness and viscoelasticity of native tissues to promote cell differentiation after transplantation.

4.4. Other tunable properties

Viscoelasticity is another vital feature to factor in when preparing hydrogels with an application in cell therapy. Viscoelasticity of tissues directs and modulates cell behavior to maintain homeostasis in living tissues. For instance, viscoelastic alginate hydrogels with fast stress relaxation time promote MSC osteogenic differentiation with an increase in the production of mineralized collagen I [162].

The porosity and pore size have a big impact on the diffusion of molecules to maintain cell proliferation and promote angiogenesis and differentiation. Recent advances in tissue engineering and cell therapies are focused on the development of scaffolds and substrates with homogeneous pore sizes and pore density, one of these advances are techniques that have been implemented, such as electrospinning, 3D printing, and stereolithography [163–166].

With the advent of state-of-the-art techniques for nano and microfabrication as well as 3D printing, it is now easy to produce a variety of scaffolds and surfaces with different patterns and topographies [145,146]. It has been shown that neural development can be assisted and promoted by seeding neural stem cells onto surfaces with micropatterns and nanopores.

4.5. Impact of cell delivery platform degradation on cell viability

Degradation of cell matrices used in cell therapies such as hydrogels is a limiting factor for cell survival and for successful cell transplantation. By-products that are the result of the degradation of polymers can have a negative effect on cell viability. Altering the degradability of hydrogels is a promising solution to this problem, for example, the backbone of polymer can be modified to provide resistance to oxidation. Ultra-violet light or visible light irradiation can be used in photoresponsive gels to enhance or induce low degradation rates [167–171]. In some cases, the degradation of hydrogels is desirable to promote cell proliferation, so whether or not rapid degradation has a negative or positive impact on the cell's fate depends on the composition of the polymers and the specific application [172,173].

5. Conclusion and future directions

Cell transplantation presents potential therapeutics for regenerative medicine, but several challenges are yet to be overcome to develop a commercial product. On a high level, these challenges could be classified into 3 different stages of pre-, during, and post-transplantation. One challenge is the cell viability and functionality during the isolation, expansion, modulation, and storage of the product. The next challenge is functional integration of the cell graft with the host upon transplantation. And finally, host induced insults including immunological complications, mechanical forces, lack of sufficient oxygen and nutrients which are current road-blocks academic and industrial research are attempting to solve for cell transplantation technologies.

We reviewed the reported utilization of biomaterials to mitigate the above obstacles. Cell viability has been promoted through strategies such as deferring gelation to the transplantation stage and using biodegradable and biocompatible biomaterials. During transplantation, biomaterials such as microcarriers and shear-thinning hydrogels have been developed to protect cells from mechanical forces and enhance cell viability. These biomaterials provide structural support, protect cells from shear stress, and enable controlled co-delivery of cells and growth factors. Unwanted cell migration, cell detachment, limited cell secretome, and differentiation are known as the major challenges for the long-term survival after transplantation. Tuning biophysical factors, such as porosity, pore size, stiffness, viscoelasticity, and topography along with biochemical cues like growth factors, can promote cell adhesion. Using biomaterials with dynamic mechanical properties can facilitate the direct differentiation of cells to the preferred lineage. Overall, engineered biomaterials offer promising solutions to improve cell transplantation and support the clinical translation of cell therapy in the future. Further research and optimization of biomaterial properties *via* a fit-for-purpose strategy is necessary to enhance the effectiveness of cell transplantation and promote successful regenerative outcomes.

6. Bibliometric analysis

The bibliometric analysis holds paramount importance in research as it helps researchers identify emerging trends within a specific field. In the conducted bibliometric analysis, we aimed to examine the trends, key contributors, and research hotspots in the domain of biomaterial engineering for cell transplantation. A comprehensive search was conducted on major academic databases such as PubMed, Scopus, and Web of Science (WOS). The search was limited to articles published from 2018 to 2023, ensuring a focus on recent advancements with keywords included “biomaterials for cell transplantation, “biomaterials for cell therapy, “and “biomaterials for cell encapsulation.” The collected articles were further sifted according to the scope of this review and by considering the relevance of their purview to the challenges and solutions mapped out in this work. According to Fig. 5, the number of publications on “biomaterials engineering for cell transplantation” has shown a steady increase over the past two decades. The growth is indicative of the growing interest and importance of biomaterials in the field. In these recent six years, about 700 papers have been published each year in this field. For example, compared to 2013, the number of published papers in this area has increased two times and reached 621 in 2018.

Moreover, some specific keywords have also been searched on the academic databases to evaluate their bibliometric analysis. Firstly, the keywords “microcarriers in cell transplantation” and/or “microcarriers in cell encapsulation” were studied through the databases to evaluate the trend of these fields. The bibliometric analysis showed that about 253 papers have been published in the last six years. For example, in 2018, there were about 30 published papers, while this number reached about 106 in 2023. Secondly, the bibliometric analysis of research on shear-thinning hydrogels in cell transplantation and cell encapsulation has been studied. According to the results, more than 670 research works have been conducted in the last six years. Also, the bibliometric analysis of integrin ligands and bioink shows more than 450 papers have been published regarding the application of integrin ligands in cell transplantation or encapsulation. The number of published works on bioinks has also substantially increased during the last six years. For instance, the number of published works between 2013 and 2017 was about 30, while more than 256 works have been published since 2018. Also, the keywords “RGD in cell transplantation” and/or “RGD in cell encapsulation” have been analyzed. Similarly, the number of published works in this area has been increasing. More than 260 papers in this field have been published since 2018, which is more than the 190 works published between 2013 and 2017.

Notable journals publishing research in this area include Biomaterials, Biomaterials Science, ACS Biomaterials Science and Engineering, and Biomaterials Advances. These journals serve as key outlets for disseminating biomaterials and cell transplantation research findings. Moreover, according to Fig. 6, fields gaining attention include biochemistry and molecular biology, material science and engineering, medicine, chemical engineering, pharmacology, and chemistry. Biomaterial engineering for cell transplantation is a dynamic and evolving field, witnessing a consistent increase in research output. This analysis provides a snapshot of the field's current state, offering insights for researchers, particularly those involved in translational biomedicine.

CRediT authorship contribution statement

Amirmasoud Samadi: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Ali Moammeri:** Data curation, Writing – original draft, Writing – review & editing. **Shamim Azimi:** Writing – review & editing. **Bexi M. Bustillo-Perez:** Writing – review & editing. **M. Rezaa Mohammadi:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

Authors have no competing interests and no AI support was implemented in drafting the manuscript.

Data availability

No data was used for the research described in the article.

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