HHS Public Access

Author manuscript

Curr Opin Chem Eng. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Curr Opin Chem Eng. 2017 February ; 15: 15–23. doi:10.1016/j.coche.2016.11.003.

The Diverse Roles of Hydrogel Mechanics in Injectable Stem Cell Transplantation

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Abstract

Stem cell delivery by local injection has tremendous potential as a regenerative therapy but has seen limited clinical success. Several mechanical challenges hinder therapeutic efficacy throughout all stages of cell transplantation, including mechanical forces during injection and loss of mechanical support post-injection. Recent studies have begun exploring the use of biomaterials, in particular hydrogels, to enhance stem cell transplantation by addressing the often-conflicting mechanical requirements associated with each stage of the transplantation process. This review explores recent biomaterial approaches to improve the therapeutic efficacy of stem cells delivered through local injection, with a focus on strategies that specifically address the mechanical challenges that result in cell death and/or limit therapeutic function throughout the stages of transplantation.

Introduction

Stem cell transplantation through systemic or local injection is a promising regenerative approach for injury and disease treatment. Despite the relative clinical success of systemic stem cell delivery, this strategy often relies on cell homing to the injury or disease site for increased efficacy. While local injection strategies do not require cell homing, the clinical application of this therapy is limited by low cell viability and poor cell function. Locally transplanted cells face several challenges at each stage of the transplantation process. This review explores the design of hydrogel systems for improving the therapeutic potential of locally injected stem cells with a focus on the role of mechanics throughout the transplantation process.

In their native environment, mammalian cells are surrounded by an extracellular matrix (ECM), which acts as a structural support and provides biochemical and biomechanical signals to regulate cell function. Cells are known to respond to mechanical cues in their

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microenvironment by altering their proliferation rate [1,2], migration speed [3,4], differentiation potential [5], and secretory function [6]. Similarly, the behavior of locally injected stem cells is influenced by interactions with their microenvironment. This microenvironment can include the native, host ECM as well as an engineered biomaterial. In injured or diseased tissues, the host ECM often becomes dysfunctional and may not be sufficient to support healing and therapeutic efficacy of transplanted stem cells. Engineered biomaterials have the potential to modify the local environment to improve the transplantation process. In addition, engineered biomaterials have the potential to improve cell viability and function during the local injection process.

Cell transplantation through local injection can be divided into three stages: injection, acute post-injection, and long-term survival and function. At each stage of transplantation, cells experience mechanical and structural challenges that can result in cell death and compromise cell function. For example, during the injection process, cells may experience mechanical forces that can damage the cell membrane, while post-injection, cells may experience a loss of structural support and hence an absence of mechanical cues. The relative importance of these different challenges can vary dramatically depending on the specific clinical application [7]. Consequently, engineered biomaterial strategies have been developed to address the specific mechanical challenges at each delivery stage. While all cell therapies (whether transplantation of stem, progenitor, immature or terminally differentiated cells) experience these same mechanical challenges, stem and progenitor cell therapies have the additional consideration that mechanical cues can influence their differentiation and maturation. Hydrogels have received significant interest as ECM mimics due to their high water content and water-swollen networks that allow for facile transport of water-soluble biomolecules [8,9] Additionally, these materials have tunable mechanical properties that span the range of physiological tissues [10]. While several injectable hydrogels have shown significant benefits in stem cell transplantation, there is no current material that is able to address all of the mechanical challenges of each transplantation stage in succession.

In the first section of this review, we discuss the challenges for each stage of the transplantation process with a focus on the mechanical requirements that can be addressed by biomaterials. Several studies have demonstrated that hydrogel mechanics play a critical role in successful cell transplantation, and careful consideration of the distinct mechanical features of the selected biomaterial can significantly improve therapeutic efficacy. In the second section we discuss biomaterial design strategies for stem cell transplantation focusing on several new materials designed to address distinct mechanical challenges at different stages of the transplantation process. We end with future directions for the design of injectable hydrogels focusing on materials that change their properties during the stages of stem cell transplantation.

Mechanical Challenges to Successful Stem Cell Transplantation

Stem cells face several distinct mechanical challenges during transplantation that have the potential to drastically reduce their viability and therapeutic efficacy. Current protocols for local injection generally result in poor cell viability, often with as few as 1–20% of cells surviving the transplantation process [11-14]. In this section, the transplantation process is

divided into three distinct stages: injection, acute post-injection and long-term survival and function to better elucidate the specific mechanical and structural challenges stem cells face throughout transplantation (Figure 1a).

Injection

During syringe injection, transplanted cells are exposed to mechanical stresses that can result in membrane damage and significant loss of acute viability. Current clinical protocols using low viscosity fluids such as saline for local injection through a syringe needle have been shown to result in substantial cell death, with up to 40% of cells not surviving the injection process [15]. It has been hypothesized that this cell death is primarily caused by membrane rupture that occurs as cells are exposed to extensional flow within the syringe needle, although shear stress and high pressure are also known causes of cell death [15].

Acute Post-Injection

The therapeutic efficacy of transplanted stem cells is influenced in part by cell survival and retention during the acute post-injection stage. The local environment and structure of the transplantation site will determine the mechanical signals provided to cells following injection. Injury models including spinal cord injury, cranial defects, and stroke cavity models, which require injection into a void space, lack a three-dimensional (3D) support matrix to promote the survival of adherent cells [16] and prevent cell dispersal. In contrast, during injection into dense tissue, such as intramuscular injections, the host tissue may provide mechanical support and promote cell survival. However, injection into dense tissue requires higher injection pressures and can still result in cell leakage at the transplantation site [17]. Additionally, cells may be confronted with several other survival challenges during the acute post-injection stage that are not inherently mechanical in nature, including hypoxia, low nutrient transport, and the immune and inflammatory response [18-20]. However, these challenges may be exacerbated or diminished by the mechanical microenvironment. For example, cells can alter their growth factor secretion in response to mechanical cues [21], which may assist in surviving hypoxia or inflammation.

Long-Term Survival and Function

Long-term stem cell therapeutic efficacy can be attained by two means: (1) support of endogenous tissue regeneration through paracrine effects [22,23] or integration of transplanted cells with host tissue [24]. Much of this success is dependent on long-term stem cell retention, proliferation, migration, and/or differentiation. All of these process are known to be influenced by the mechanical microenvironment *in vitro* [21,25] suggesting that modification of the mechanical microenvironment *in vivo* may be a strategy to promote long-term transplanted cell survival and function. In therapies that rely on paracrine secretion for therapeutic efficacy, multiple cell doses over time may be necessary to maintain a sufficient level of cell-secreted therapeutic factors, thereby complicating clinical translation [26-29]. In therapies that require transplanted cell integration into the host tissue, poor differentiation into specialized cell types may limit new tissue formation and function [30] and can lead to the formation of teratomas [24,31,32]. Overcoming these challenges may require the use of structural biomaterial supports that provide instructive mechanical cues to the transplanted cells.

Material Approaches to Address Mechanical Requirements of Cell Transplantation

The different stages of the transplantation process each have unique mechanical requirements that can be addressed using biomaterial design strategies to improve stem cell transplantation efficacy. In this section, we will outline methods currently employed to provide the mechanical support and cues needed throughout the stages of transplantation (Figure 1b).

Injection

Microcarriers—Several new biomaterial approaches have been utilized to limit cell death that results from membrane damage during the injection stage of transplantation. One current approach is the use of hydrogel microcarriers, in which cells are encapsulated within small particles, typically spheres, that can be injected through a syringe needle. Cells encapsulated in microcarriers are protected from damaging mechanical forces exerted during injection, which can improve their acute survival by as much as 2-fold, and thus increase their therapeutic potential [33]. Furthermore, delivering stem cells within microcarriers enables high local cell densities, which can promote paracrine signaling and enhance differentiation that may be important for later stages of the transplantation process. Thus, the majority of studies with microcarriers load a high concentration of either single cell suspensions or cell aggregates [34,35]. The microcarrier droplets can be produced using a number of techniques including ionic crosslinking [36-38], microfluidic droplet production [39,40], water-in-oil emulsion [33,41,42], photocrosslinking [39,41], and thermal crosslinking [34]. In addition, many of these techniques can be combined to produce more complex microcarriers. For example, injectable gelatin-methacrylate (GelMA) microcarriers have been designed using microfluidic platforms to generate droplets of controllable sizes, which are then crosslinked with ultraviolet light [39,43]. Furthermore, due to their small size, microparticles have the ability to act as porous space fillers upon injection into defects, which can aid in host tissue integration [40].

Shear-thinning Hydrogels—An alternative approach to microcarrier encapsulation is the use of shear-thinning hydrogels, which allow for encapsulation of stem cells through weak dynamic interactions (e.g., hydrogen bonding, hydrophobic interactions, electrostatic attractions, and host-guest interactions) between the polymer chains prior to cell delivery [44-47]. When exposed to shear stress, as experienced during injection, these associations disassemble, resulting in a significant decrease in viscosity. Often this crosslink disassembly only occurs at the interface of the hydrogel and the syringe, resulting in “shear banding” at the interface [46,47]. This allows the rest of the hydrogel to remain intact and undergo “plug flow”, thereby protecting encapsulated cells from membrane damaging forces [15]. Several shear-thinning hydrogels have demonstrated improved cell survival post-injection including alginate hydrogels [15], protein-assembled hydrogels [45,48], supramolecular beta-hairpin hydrogels [49], and hyaluronic acid-based hydrogels [50-52]. Using protein-assembled hydrogels, acute survival of iPSC-derived endothelial cells increased 2-fold compared to saline-delivered cells [48], while encapsulation in hyaluronic acid-based hydrogels lead to an ~1.2-fold increase in survival of injected iPSC-derived neural progenitors [52]. These

methods aim to improve survival of transplanted cells during the initial stage of transplantation, potentially improving overall cell engraftment.

Acute Post-injection

Several new biomaterial strategies have focused on improving cell survival and minimizing cell dispersion at the injection site and providing a cell-adhesive scaffold to promote acute cell retention within the host tissue. Three-dimensional mechanical support of transplanted cells helps prevent cell death due to anoikis, (i.e. anchorage-dependent apoptosis) and can prevent cell dispersal from the site of local injection. One approach to providing acute mechanical support after injection involves the control of hydrogel gelation kinetics. This can be accomplished through strategies including triggered gelation, or the use of shear-thinning hydrogels that are also rapidly self-healing.

Triggered Gelation—Ideally, gelation should be fast enough to promote homogenous cell distribution and acute cell retention at the transplant site, yet slow enough to prevent gelation within the syringe or catheter. Several systems have been designed to deliver cells in a viscous pre-polymer solution that will be triggered to gel *in situ* using biological stimuli, such as temperature [53], pH [54], ion concentration [55], or applied stimuli, such as light [56,57]. Temperature-triggered gelation has been used for a number of stem cell transplantation strategies through the incorporation of thermoresponsive polymers with a characteristic lower critical solution temperature (LCST) behavior. For example, thermoresponsive poly(N-isopropylacrylamide) (PNIPAM) has been routinely used to trigger *in situ* gelation in a number of hydrogel systems due to its LCST phase transition at approximately 32 °C. This results in rapid gelation at physiological temperature (37 °C), providing an effective approach to enhance cell retention [58,59]. Another material that can undergo temperature-triggered gelation is decellularized matrix hydrogels derived from native tissue [14,60,61]. In addition, the use of ECM-derived hydrogels capitalizes on the presence of tissue-specific biochemical cues and ligands to anchor adherent cells and improve cell survival. These materials have been used in several preclinical studies for stem cell transplantation based on their rapid *in situ* gelation. For example, the delivery of MSCs encapsulated in hydrogels derived from porcine lung tissue demonstrated increased cell retention at 24 hours following intratracheal delivery in a rat model [62].

Photopolymerization (and other mechanisms of triggered gelation using an applied stimulus) can lead to spatially controlled formation of crosslinked hydrogels at physiological pH and temperature. The incorporation of diacrylate or methacrylate functional groups has been shown to facilitate crosslinking and photo-triggered gelation in response to UV or visible light [56,57]. UV light has been used to crosslink diacrylate-modified polyethylene oxide solutions *in situ* resulting in increased stem cell retention following transdermal photopolymerization [63]. Similarly, other polymers including chitosan [64,65], alginate [55,66], gelatin [67,68], and hyaluronic acid (HA) [57] have all been modified with methacrylate functional groups to trigger gelation. For example, transdermal photopolymerization of methacrylated-gelatin has been shown to deliver and improve the integration of MSCs and endothelial-colony forming cells with host tissue for vascular therapies compared to non-photocrosslinked hydrogels [68].

Self-Healing Hydrogels—Shear-thinning, self-healing hydrogels have been used in a number of preclinical studies to provide protection during the injection stage and also promote acute cell retention post-transplantation. These materials undergo viscous flow when subjected to an applied shear stress and time-dependent recovery and reassembly of the hydrogel network upon relaxation [44]. When designed appropriately, these materials can demonstrate fast self-healing kinetics at the site of injection, thereby resulting in high levels of cell retention [31,50]. For example, an injectable hyaluronan/methylcellulose hydrogel demonstrated improved transplanted cell retention of iPSCs for spinal cord and retinal therapies [30,31]. In another design, hyaluronan modified to undergo rapid host-guest self-assembly was shown to improve endothelial progenitor cell retention after myocardial infarct [50]. Engineered protein-based self-assembly systems have also been shown to promote acute survival post-injection, resulting in a more than 2-fold increase in stem cell retention compared to saline-mediated delivery [48,69].

Long-Term Survival and Function

Influencing Stem Cell Differentiation—A large body of mechanotransduction research has studied the role of 2D and 3D hydrogel mechanics on stem cell differentiation and function, with substantial emphasis placed on MSC differentiation. Numerous studies have shown that substrate stiffness heavily influences stem cell fate, with compliant materials generally promoting soft tissue lineages (e.g. neural and fat cells) and stiffer materials leading to hard tissue lineages (e.g. bone cells) [25,70-73]. Substrate stiffness has been shown to play a role in stem/progenitor cell differentiation [51,74] and progenitor cell function [75]. For example, when cultured over a specific stiffness range, cardiac progenitors have enhanced electrical and contractile function [70,76,77]. Little of this work has been translated *in vivo* as these materials have been designed specifically for *in vitro* mechanotransduction studies. Complicating their direct application into clinical therapies, the mechanical cues experienced by transplanted cells may include both the mechanical properties of any engineered matrix, as well as that of the endogenous tissue. Furthermore, the mechanical cues of endogenous tissue may include aberrant signaling due to matrix stiffening (e.g. fibrosis) or matrix weakening (e.g. unchecked proteolysis) [78,79]. One recent study using injectable alginate hydrogels suggests that bulk matrix stiffness differentially promotes osteodifferentiation of transplanted MSCs and new bone formation in a cranial defect model [80], similar to results predicted by *in vitro* models [81]. In complementary work, improved differentiation and integration of transplanted muscle stem cells was observed when cells were transplanted on hydrogel constructs with an ideal stiffness range [74].

In addition to material stiffness, hydrogel degradation and matrix remodeling can play a significant role in stem cell behavior and differentiation [1]. MSC spreading and survival have been shown to depend on the degree of hydrogel degradation [82], which can influence stem cell fate [83]. For example, MSC-mediated degradation of a 3D matrix influences differentiation by altering the ability of cells to generate traction within the microenvironment [84]. Tuning of hydrogel degradation has been used to promote MSC differentiation towards chondrogenic lineages, resulting in improved deposition of

neocartilage ECM, which may prove beneficial towards long-term integration of transplanted cells [85].

Beyond the intrinsic mechanical properties of the matrix, the dynamic mechanical microenvironment is also known to impact cell differentiation and maturation processes [86,87]. For example, several *in vitro* studies have demonstrated that mechanical loading of stem cells through compression, tension, or shear can lead to differentiation into osteogenic [88-90], myogenic [91-93], or vasculogenic [94-96] phenotypes. These studies suggest that dynamic *in vivo* mechanical cues must be considered for specific clinical applications.

Influencing Stem Cell Secretome—For many potential regenerative medicine therapies, the transplanted cells may not directly participate in regenerating the damaged tissue, but instead function through the secretion of paracrine signals that promote host tissue regeneration [22,97]. Therefore, several studies have shifted focus to the therapeutic potential of stem cells based on their secretion of pro-survival and pro-regenerative factors [22,23,26,97]. Recent work has demonstrated the use of hydrogel design strategies to enhance the secretory profile of growth factors, chemokines, and cytokines from stem cells, also known as their secretome [21,98-101].

Hydrogel mechanical properties, such as stiffness and degradation, have been suggested to influence stem cell secretion. For example, substrate stiffness has been shown to regulate MSC secretion of paracrine signals, with intermediate and stiffer substrates (10-40 kPa) leading to increased levels of pro-angiogenic factors interleukin 8, vascular endothelial growth factor, and angiogenin compared to more compliant substrates (E ~ 0.5-2 kPa) [21,99]. Similarly, hydrogels with intermediate elasticity were found to significantly increase the secretion of pro-angiogenic factors from adipose-derived stem cells [102]. Unfortunately, increasing hydrogel stiffness and crosslinking density often results in slower hydrogel degradation kinetics [85,103]. With a decrease in hydrogel degradation, there may be an associated decrease in the diffusion of secreted soluble factors, thus limiting the therapeutic benefit of transplanted stem cells [104].

Future Directions

Currently no universal material fulfills all of the mechanical needs to improve stem cell survival and functionality during all three stages of transplantation. While some material mechanical properties may be needed for enhanced long-term retention and differentiation, these same mechanical properties may limit success in the earlier transplantation stages. Therefore, a promising future research direction is the development of biomaterials that can alter their mechanical properties over time to achieve diverse mechanical requirements throughout the multiple stages of transplantation.

One approach to modify biomaterial properties over time is the use of dual-stage or multi-stage crosslinking strategies. For example, several shear-thinning and self-healing hydrogels have been designed to undergo a second stage of crosslinking, and hence mechanical stiffening, in response to various stimuli. Temperature is a common stimulus to induce secondary crosslinking *in situ*, since many self-assembling hydrogels can be modified to

include a thermoresponsive element [30,58,105]. In this approach, cell viability is improved during the injection stage due to the shear thinning mechanical properties, acute cell retention is improved during the acute post-injection stage due to the rapid self-healing kinetics, and the temperature-triggered secondary crosslinking increases long-term cell survival due to the decreased degradation rate [58]. Alternatively, covalent crosslinking can be used as a secondary crosslinking mechanism to reinforce and strengthen injectable hydrogels [67,106,107]. For example, HA can be modified to undergo a first-stage of guest-host self-assembly followed by a second-stage of covalent crosslinking to prolong material retention and to improve integration with host tissue [67,107].

A second approach to modulating biomaterial mechanics and structure over time is to engineer complex degradation patterns into the hydrogel. For example, composite alginate hydrogels were created with regions that were fast degrading surrounded by a slower degrading material for use in MSC transplantation [80]. *In situ*, the fast-degrading regions created voids that enhanced cell survival through increased nutrient transport and cell migration across the host-transplant interface [80]. Meanwhile, the slow-degrading regions provided long-term mechanical support to promote osteogenic differentiation.

In the future, it is expected that creative biomaterials chemistry will be combined with novel microfabrication techniques to design a broad array of biomaterials that can stiffen and/or weaken over time at the length-scales and time-scales required to support all stages of stem cell transplantation. For example, a rich array of photoactive chemistry has already been employed in the design of *in vitro* biomaterials that exhibit this so-called “4D” control of mechanical properties [108,109].

Conclusion

In conclusion, a wide range of hydrogels with tunable mechanical properties are being developed to overcome the different mechanical challenges facing stem cells during each stage of transplantation: injection, acute post-injection, and long-term survival and function. While no universal material is currently capable of addressing all of the mechanical requirements, a promising future direction is the development of biomaterials that can adjust their mechanical properties for multiple transplantation stages. Thus, while current injectable biomaterials are already demonstrating that they can significantly improve transplanted stem cell viability and function, future innovation in biomaterials design is expected to even further enhance the therapeutic efficacy of transplanted stem cells.

Acknowledgments

This work was supported by the National Institutes of Health (R21-EB020235 to S.C.H. and T32-HL098049-06 to A.F.), Stanford Bio-X (IIP-7-75), CIRM (RT3-07948), Coulter Foundation (CP-2014-4), and Stanford Geballe Laboratory for Advanced Materials Postdoctoral Fellowship (to L.M.).

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Highlights

- Stem cell transplantation by local injection has seen limited clinical success
- Different transplantation stages present different mechanical challenges
- Hydrogels with tunable mechanics can overcome mechanical challenges at each stage

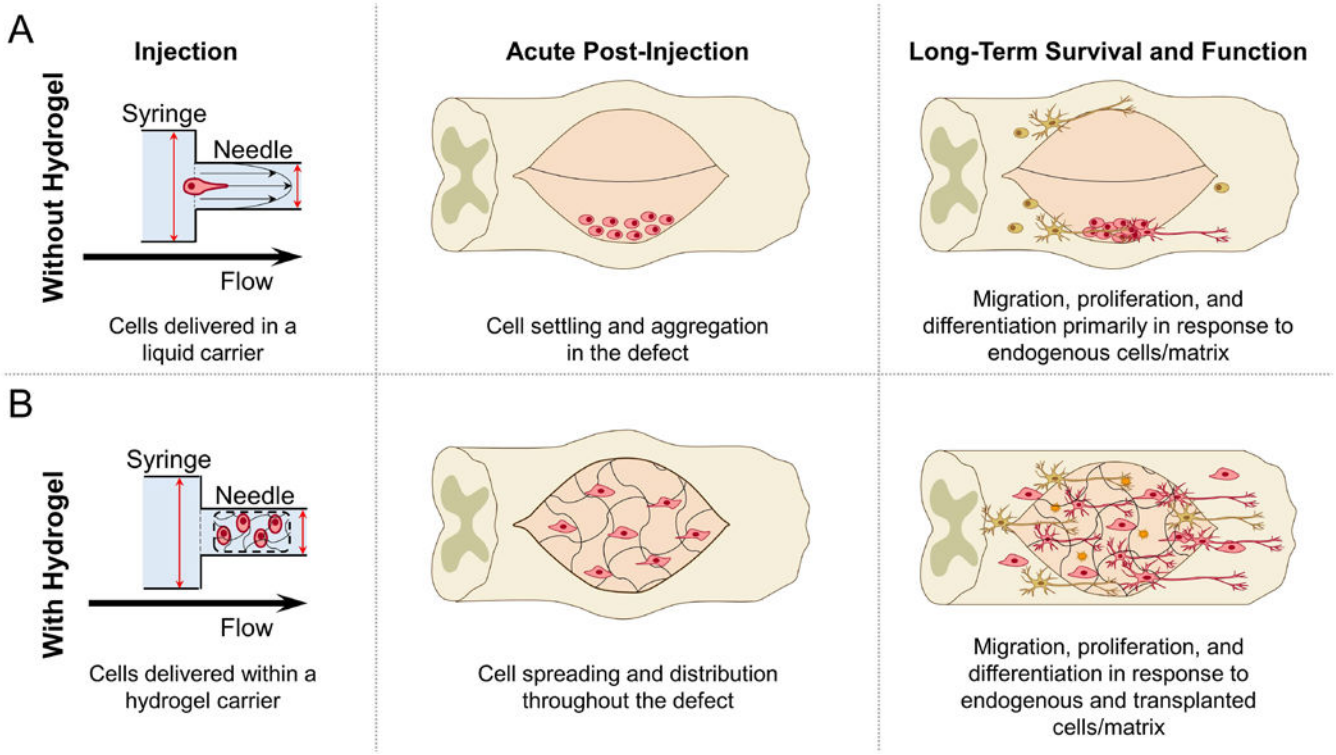

Figure 1. Comparison of stem cell delivery using a liquid or hydrogel carrier at each stage of transplantation

A) During injection, cells in a liquid carrier are exposed to mechanical forces that can damage the cell membrane and result in decreased cell survival. Post-injection, cells can settle and aggregate in the defect site without the structural support to promote cell adhesion. Long-term survival and function can be diminished without mechanical cues to promote transplanted cell proliferation, migration, differentiation, and secretion. B) Cells encapsulated in a hydrogel carrier can be protected from mechanical forces exerted during the injection stage. Post-injection, cells can adhere and spread within a hydrogel support matrix throughout the defect site. Finally, long-term mechanical cues from hydrogels can support transplanted and endogenous cell migration into and out of the defect, as well as promote stem cell proliferation, differentiation, and secretion for tissue regeneration.