HHS Public Access

Author manuscript

Curr Stem Cell Rep. Author manuscript; available in PMC 2020 August 27.

Published in final edited form as:

Curr Stem Cell Rep. 2019 ; 5(3): 109–114. doi:10.1007/s40778-019-00161-2.

Engineered Biomimetic Neural Stem Cell Niche

Rita Matta[1], **Anjelica L. Gonzalez**[1]

[1]Department of Biomedical Engineering, Yale University, New Haven, CT, United States

Abstract

Purpose of review: Neural stem cells (NSCs) have the potential to proliferate and differentiate into functional neurons, heightening their potential use for therapeutic applications. This review explores bioengineered systems which recapitulate NSC niche cell-cell and cell-matrix interactions.

Recent findings: Delivery of NSCs to the cytotoxic injured brain is limited by low cell survival rates post-transplantation and poor maintenance of native niche bioactive components. The use of biomaterial platforms can mimic *in vivo* the environment of the two germinal areas of the adult brain in which NSCs thrive. An environmental mimic that includes extracellular proteins and moieties, along with appropriate biomechanical cues has recently demonstrated promising results in enhancing neurogenesis, aiding the production of a bioengineered niche.

Summary: Biocomposition, biomechanics, and biostructure can be manipulated through engineered platforms to re-create the biofunctionality of an NSC niche. Upon transplantation and delivery with biomimetic scaffolds, NSCs show potential to promote functional recovery and rebuild neural circuitry post neurological trauma.

Keywords

Neural stem cell; engineered niche; neurogenesis; biomimetic microenvironment; tissue engineering

Introduction

Stem cells play an important role in tissue maintenance and regeneration during homeostasis and disease. Stem cells can be maintained in a dormant, non-activated state, and upon activation by local or distant cues, they become activated, divide, and differentiate into a specified progeny [1, 2]. There are two germinal regions in the adult brain where neural stem cells (NSCs) reside: the subgranular zone (SGZ) within the dentate gyrus of hippocampus and the subventricular zone (SVZ) which lies lateral to the lateral ventricles [3, 4], as

Corresponding Author: Anjelica Gonzalez, 55 Prospect Street, New Haven CT 06511, Anjelica.gonzalez@yale.edu.

Conflict of Interest Rita Matta and Anjelica Gonzalez each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

depicted in Figure 1 Of these regions, the SVZ retains the largest pool of proliferating NSCs, which interact with blood vessels and ependymal cells. Blood vessels, consisting of endothelial cells (ECs) and pericytes (PCs), are in direct contact with basal processes extended by NSCs. These SVZ astrocytes give rise to transient amplifying cells, which will divide and become neuroblasts. In the adult rodent brain, neuroblasts migrate through a chain-like system to the olfactory bulb, where they proceed to differentiate to interneurons [4]. In the SGZ, radial glia-like NSCs, or SGZ astrocytes, give rise to precursor cells that proliferate before differentiating into neuroblasts. These SGZ astrocytes associate closely with the vasculature. Unlike the SVZ, SGZ neuroblasts will migrate radially into the granule cell layer to differentiate into neurons [4, 5].

In the SVZ and SGZ, interactions with the vasculature are critical, dictated by highly organized cell contacts and processes that NSCs extend toward the vascular cells. EC contribute toward creating an environment that directly impacts NSC fate and functionality through the release of several secreted factors including vascular endothelial growth factor (VEGF), neutrotophin-3 (NT-3) [6], and brain derived neurtotrophic factor (BDNF) [7]. PCs cover SVZ capillaries and have been suggested to play a role in regulation of capillary tone [9].). Although studies suggest PCs regulate blood flow in response to pathological state, experiments are limited by the poor ubiquiotus identification of PCs [8] •. Interestingly, SVZ astrocytes directly contact the PCs that surround SVZ capillaries, suggesting that NSCs and vascular cells may act in concert to maintain capillary tone and regulate blood flow [9]. However, the integrity of the blood brain barrier (BBB), the vascular barrier between blood components and the interstitial environment, is leaky where residing clusters of proliferating NSCs are located. Vascular leak in these areas provides these NSC access to factors within the blood, allowing the NSC niche to become remodeled by exposure to blood components. Blood components in the NSC niche can act as injury cues, indicative of a permeable BBB which has become compromised by injury, such as stroke [10] •. Through these vascular interactions, the environmental cues of the SVZ maintain NSCs in a quiescent state. Inhibited differentiation is, in part, regulated by EC-expressed ephrinB2 and Jagged1, respectively [11]. On the other hand, SGZ astrocytes express ephrinB2 where neuronal differentiation is promoted via EhB4 receptor expression on NSCs [12]. These results demonstrate that vascular responses to the same signal can induce different effects in the respective niches.

While resident cell types, including vascular cells are largely tasked with regulating the neural niche, the extracellular matrix (ECM) creates a structural framework for cell-protein interactions that drives biochemical and mechanotransductive signaling. Upon contact, the adhesion of cells to the protein network is primarily mediated by integrins, which trigger intracellular and extracellular responses. Both the SVZ and SGZ microenvironments consist of fractones, proteinaceous matrix structures consisting of mostly laminin [13]. Laminin, a basement membrane protein which promotes cell adhesion via α integrins, specifically α6β1 integrin [14]. Tenascin-C and chondroitin-sulfate glycosaminoglycan within the SVZ and SGZ also play important roles in neurogenesis [15, 16], regulating NSC proliferation and differentiation [17], respectively. Hyaluronan (hyaluronic acid, HA) within the NSC niche, plays a role in blocking differentiation and promoting RTK signaling pathways [14]. While primarily responsible for integrating the cell with its extracellular environment, NSC

presented integrins also interact with transmembrane proteins including cell adhesion molecules, such as e-cadherin (E-cadherin) and neural cadherin (N-Cadherin) [18], expressed by other NSCs. The expression of integrins that serve as cellular anchors to the extracellular environment, as well as cell-cell contacts, indicate that NSCs are adept at adhesion, migration and intercellular communication.

There is a growing body of evidence indicating the importance of extracellular cues on NSCs and how *in vitro* systems can be optimized for mimicry of the neural niche. By incorporating *in vivo* moieties into a base scaffold to mimic biocomposition, as well as modeling environmental biomechanics and topography, researchers can enhance the survival of NSC and control their differentiation state. Here, we discuss the use of biomimetic engineered polymers that support interactions between NSCs and resident cell types in the SVZ or SGZ while also re-creating a microenvironment that mimics the biochemical and/or biomechanical properties of the extracellular matrix. These biomaterials include biologic and/or synthetic protein that are designed to be biocompatible vectors for cell delivery. The ultimate goal of studies using tissue engineered scaffolds is to increase our knowledge and understanding of NSC fate and functionality *in vitro* while providing insight into systems that may be useful as NSC delivery vectors for use as reparative therapeutics following neurological injury or disease.

Biomimetic Engineered Systems

Requirements

The microenvironment to which cells are exposed, in particular NSCs, directly impacts cell proliferation, differentiation, and survival; therefore, careful consideration by tissue engineers of the complex composition is critical. This requires taking into account the structural elements present in the niche, including and not limited to resident cells and the ECM proteins and proteoglycans. In particular, the ECM mechanical and physiochemical properties directly dictate NSC fate. Two-dimensional scaffolds can recapitulate native ECM proteins, however, these systems are limited by their simplistic composition, ignoring NSC interaction with cells and ECM moieties through complex three-dimensional interactions. Therefore, three-dimensional architecture allows for probing of cell-cell and cell-ECM interaction in a more biologically replicative system. Achieving closer recapitulation of the niche microenvironment would allow us to maximize our knowledge of NSC biology and allow us to consider more fully the requirements for functional bioengineered systems to be used as research tools or therapeutic delivery agents for treatment of neuropathologies.

The physical properties of brain tissue can directly impact stem cell behavior. Of note, brain stiffness can be altered as a result of disease or injury, rendering a largely elastic tissue to become stiffened and lack pliability. Brain is an extremely soft tissue that has physical characteristics that vary according to age and area. However, the brain is typically characterized to have a tensile stiffness of ~1 kPa [19] ••. Mechanics of a substrate are known to impact differentiation and proliferation of NSCs/neural progenitor cells, dictated by changes in gene expression and morphology [20]. In fact, a temporal study demonstrated that NSCs are mechanosensitive between 12–36 hours of receiving chemical differentiation cues [20]. Through micro- and nanoscale topographic changes, NSC behavior can be

manipulated. For example, NSCs adjust their morphology and cytoskeletal arrangement in response to micropillars of varying stiffness and orientation. In addition, NSCs on 3-D graphene foams demonstrate enhanced NSC differentiation into astrocytes on stiff substrates as compared to a softer substrate, with stiffness of 64kPa and 30 kPa, respectively [21]. These studies highlight the ability of a biomaterial that re-creates not only the ECM biocomposition, but also the biomechanics and biostructure, to drive cellular health, quiescence and differentiation.

Biologic Biomaterials

Natural ECM components are the basis of biologic materials. These biomaterials are advantageous in maintaining NSC health and survival due to their engagement of laminins, glycoproteins and proteoglycans that are native to the neural niches. A study by Betancur et al. demonstrated the use of chondroitin sulfate proteoglycans containing lectin and HA binding domains, abundant in the SVZ and SGZ, were sufficient to maintain NSCs in an undifferentiated state. When this scaffold was enriched with fibroblast growth factor (FGF2) and implanted in to the brain of a the rat, it facilitated brain tissue repair following traumatic brain injury (TBI) [17]. Another study demonstrated that Stromal cell-derived factor-1 alpha (SDF1a) electrospun onto collagen mats was capable of inducing NSC polarized morphology [22]. Interestingly, a combination scaffold consisting of salmon derived fibrin, HA, and laminin demonstrated human neural stem cell/progenitor cell (hNSPC) proliferation and differentiation, where hNSPC interacted extensively with the scaffold due to fibrinogen and laminin binding integrins. To test the vascularization potential of this scaffold, ECs in co-culture with hNSPC led to enhanced vessel formation [23] •. These studies highlight the role of proteins, glycoproteins and proteoglycans occurring in the neuronal niche in supporting NSC maintenance and NSC interactions with additional niche resident cells.

Although NSCs can be exposed to specific ECM proteins, the entire ECM derived from specific tissues or organs, such as the central nervous system (CNS) or brain, can be utilized to create complex, mimetic matrices. Recent studies have demonstrated positive results for the facilitation of post injury healing through delivery of ECM matrices. In particular, Crapo et al. used porcine spinal cord and brain tissue-derived ECM, creating a scaffold which possessed microenvironmental cues that promoted NSCs to differentiate into neurons [24]. In addition, recent work by Modo et al. delivered a porcine bladder-derived ECM hydrogel into a rat subacute stroke cavity, leading to a reduction in lesion volume [25] ••. These studies highlight the potential use of these systems as a reservoir for local cell or drug delivery. Importantly, one study created a 3-D brain vasculature and ECM microenvironment utilizing a microfluidic device. Here, physiologically relevant cells, particularly ECs and NSCs, allowed for direct monitoring of NSC self-renewal and differentiation, where distinct effects on NSC behavior are seen as a result of cell proximity to the vasculature [26]. These studies demonstrate that ECM-derived scaffolds have a high potential for NSC maintenance could be delivery vehicles for therapeutic drugs or cells after injury due to neurological diseases.

The mechanical properties of biologic scaffolds have been correlated with NSC differentiation potential. Specifically, one study utilized human mesenchymal stem cells

(MSCs) seeded on a 3-D porous collagen I and HA scaffold, where a softer scaffold promoted neuronal lineage at 1 kPa and a stiffer scaffold promoted glial lineage at 10 kPa [27]. Multiple methods of altering a scaffolds mechanical properties have been used. An increased density of collagen can facilitate 3-D scaffold stiffening, as can an increase in the concentration of fibrinogen and laminin proteins. Perturbations of a substrate can also be used to manipulate a natural biomaterial mechanics. Recently, an HA hydrogel was rendered porous utilizing sacrificial crystals to produce a modulus which mimics that of the nervous system. The storage modulus of nontemplated gels was 100 Pa, compared to 0.1 Pa for urea templated gels and 0.6–8.5 Pa for potassium dihydrogen phosphate templated gels. Seeded neural progenitor cells subsequently were able to maintain their undifferentiated phenotype [28]. These findings stress the importance of the native brain mechanics for neural cell maintenance and differentiation.

Transitioning from 2-D substrates to 3-D complex systems are beneficial for optimizing *in vitro* assessment and throughput. Cell encapsulation within scaffolds have been used for delivery of NSC to rodent injury models. As one example, a 3-D gelatin methacrylate hydrogel with encapsulated induced pluripotent stem cells (iPSC)-derived NSCs facilitated delivery of cells into a rodent brain following spinal cord transection. The transplanted cells remained largely viable and became differentiated. As a result, the animal demonstrated a significant improvement in functional recovery post spinal cord transection[29]. A collagen composite scaffold with immobilized chondroitin sulfate and encapsulated human iPSC-derived NSCs also demonstrated sustained proliferation, differentiation and enhanced cell viability. Here, cells formed networks through interconnected parallel pore channels, presenting appropriate physiochemical cues to sustain these neural committed cells [30]. A study by Betancur et al. utilized chondroitin sulfate glycosaminoglycan matrices with encapsulated NSCs, though, these NSCs were maintained in an undifferentiated state. In contrast to the two studies detailed above, this matrix was enriched with FGF2, demonstrating that brain tissue repair, promotion of neuroprotection, and enhancement of NSC proliferation are possible with additional modifications to a 3-D biologically based scaffold [17]. These studies, among others, provide promising suggestion that NSC encapsulation within biological scaffolds may serve as a delivery unit for the repair and regeneration of brain tissue.

Synthetic Biomaterials

Synthetic biomaterials are attractive candidates for biomimetic scaffolds due to the fact their properties can be directly manipulated and controlled, whereas natural materials are limited in their modification potential. Mechanical stiffness, protein composition and concentrations, and degradation kinetics of synthetic polymers can easily be manipulated in order to generate a scaffold with the desired specifications. Most frequently, polymeric materials, including poly- (ethylene glycol) (PEG) and poly(Lactic-Co-Glycolic Acid) (PLGA), have been heavily used as the foundation for tissue engineering applications. PEG, an inert and biocompatible material, can be chemically modified through conjugation of peptide sequences or whole proteins. Additionally, the mechanical properties of PEG-based scaffolds are controlled by the molecular chain length of the polymer. PEG can, therefore, be manipulated chemically to incorporate ligands present in the neural niche and created to

mimic the soft nature of brain tissue. Beyond matrix proteins of the neural niche, growth factors can be conjugated to PEG constructs, inducing beneficial factors that can directly impact the local environment to which they are exposed. Though, arguably the most notable aspect of PEG-based delivery scaffolds may be the ability of PEG to induce water shielding of proteins through its super-hydrophilic nature. By preventing adsorption of soluble proteins to the PEG chain, PEGylated nanoparticles have evaded phagocytosing and damaging brain cell populations post implantation, prompting the use of PEG as a stealth coating to reduce immune clearance and enhance therapeutic capacity [31] •. With this in mind, Gonzalez and Matta et al. created PEG microbead constructs with encapsulated NSCs and ECs, demonstrating maintained NSC quiescence prior to and postdelivery due to the incorporation of ECs, as well as enhanced NSC viability. Interestingly, PEG encapsulation of delivered NSC resulted in reduced immune response as seen by a decrease in activated Iba+ microglia and CD45+ leukocyte infiltration post implantation, in contrast to NSC delivered alone (submitted).

Micropatterning technology has been an optimized in a way to allow for neuronal development. Neurites align along microchannels, favoring axon formation, and these cells have been assessed in injury models to observe cell integration, differentiation, and migration post trauma [32, 33]. Polydimethylsiloxane (PDMS) molds are fabricated with precise patterns, and these pre-seeded micropatterned scaffolds post implantation have demonstrated long term behavior versus cell engraftment. These NSCs also migrated to reconstructed tissues, suggesting that micropatterned implants can guide the maturation of grafted NSCs [33] •. PDMS molds can be utilized to manipulate NSC differentiation profiles and these platforms can be enhanced with conjugation or incorporation of ECM moieties to replicate niche microenvironments. Micropatterning can be accomplished through electrospinning of fibers or 3-D printing as well. As an example, Hsu et al. embedded NSCs into thermoresponsive water-based and biodegradable polyurethane, which were subsequently bioprinted and underwent gelation. The percentage of polyurethane dispersions impacted proliferation and differentiation of the NSCs, demonstrating a promising application for neural tissue engineering using 3D bioprinting technology [34]. In addition to 3D printing, electrospun polymeric fibers have been seeded with NSCs to observe neurite outgrowth and neuronal differentiation. Interestingly, using poly(DTE- co-10% DT-co-10%) PEG_{1k} substrates in 2D films or 3D microfibrous scaffolds with functionalized chimeras of N-cadherin and L1, two key neural cell adhesion molecules, enhanced neuronal differentiation profiles [35]. Neuron differentiation was increased in another study utilizing RGD conjugated to polyurea, suggesting this mimetic polymer composition is favorable for NSC survival and provides promising therapeutic potential for implantation [36]. Due to the tunable nature of polymeric materials, their role in mimicking neurogenic environments make them an exciting tool for continued exploration and development.

Composite of Biologic and Synthetic Biomaterials

The combination of biologic and synthetic materials allows for the advantages of both types of biomaterials to impart to surrounding and encapsulated cells, thus native protein incorporation and direct mechanical manipulation can occur simultaneously. For example, a multilayer film composed of HA and poly-L-lysine (PLL) was used by Lee et al. to alter

both the surface charge and material stiffness of a material onto which NSC were seeded. Here, the quantity of differentiated neurons was enhanced by the number of alternating layers, not by the surface charge of the terminal layer, and native HA and PLL pairing ultimately enhanced neurite length and regulated neuronal differentiation [37]. In addition, NSCs have been seeded on polyacrylamide gels with conjugated oligonucleotide-crosslinked ECM proteins. This manipulation created a mechanically tunable ECM system wherein the stiffness was be reversibly manipulated with oligonucleotide-based crosslinks. Through this study, it was concluded ECM stiffness plays a role in NSC lineage commitment through signaling via YAP and β-catenin interaction [20]. The extensive manipulation of the material's mechanics allows for a fine-tuned regulation of mechanosensitivity. Recently, Gonzalez and Modo et al. characterized and optimized the delivery of these fluorescent-tagged PEG microbeads to two rat stroke injury models, a photothrombotic and MCAO lesion, utilizing media, PBS, or a porcinederived ECM hydrogel as a delivery vehicle. Here, they saw enhanced retention of microbeads as well as cell infiltration, demonstrating a promising potential of transplanted cells to integrate into the host tissue **(unpublished)**. These studies together suggest that the use of bioengineered scaffolds can be enhanced by using a mixture of material subsets to replicate the native niche microenvironment.

Conclusion

Recent studies focusing on adult neurogenesis have suggested that mechanical and molecular cues from the neural microenvironment are capable of regulating NSCs during brain plasticity and recovery. Following brain trauma, the role of the NSC may be beyond that of merely serving as a source of neuronal progeny. This requires exploration of the relationship between lineage potential and functionality to discover the role of NSCs for therapeutic application. For such exploratory research, re-building the microenvironment of the neural niche *in vitro* can serve as a valuable research tool, allowing the recreation of cell-matrix and cell-cell interactions. Such studies will allow us to probe signaling hubs and molecular pathways that support NSC survival, quiescence and differentiation on the benchtop prior to attempts at cell transplantation *in vivo*. The continual optimization of engineered niches is multidisciplinary, requiring collaboration between neurologists, tissue engineers, and stem cell biologists. With an overarching goal of providing a metric to deliver viable cells to the injured brain, NSC maintenance in a biocompatible, biomimetic scaffold can revolutionize the state of current technologies.

Acknowledgments

Work from our laboratories was supported by NIH (R01EB016629–03).

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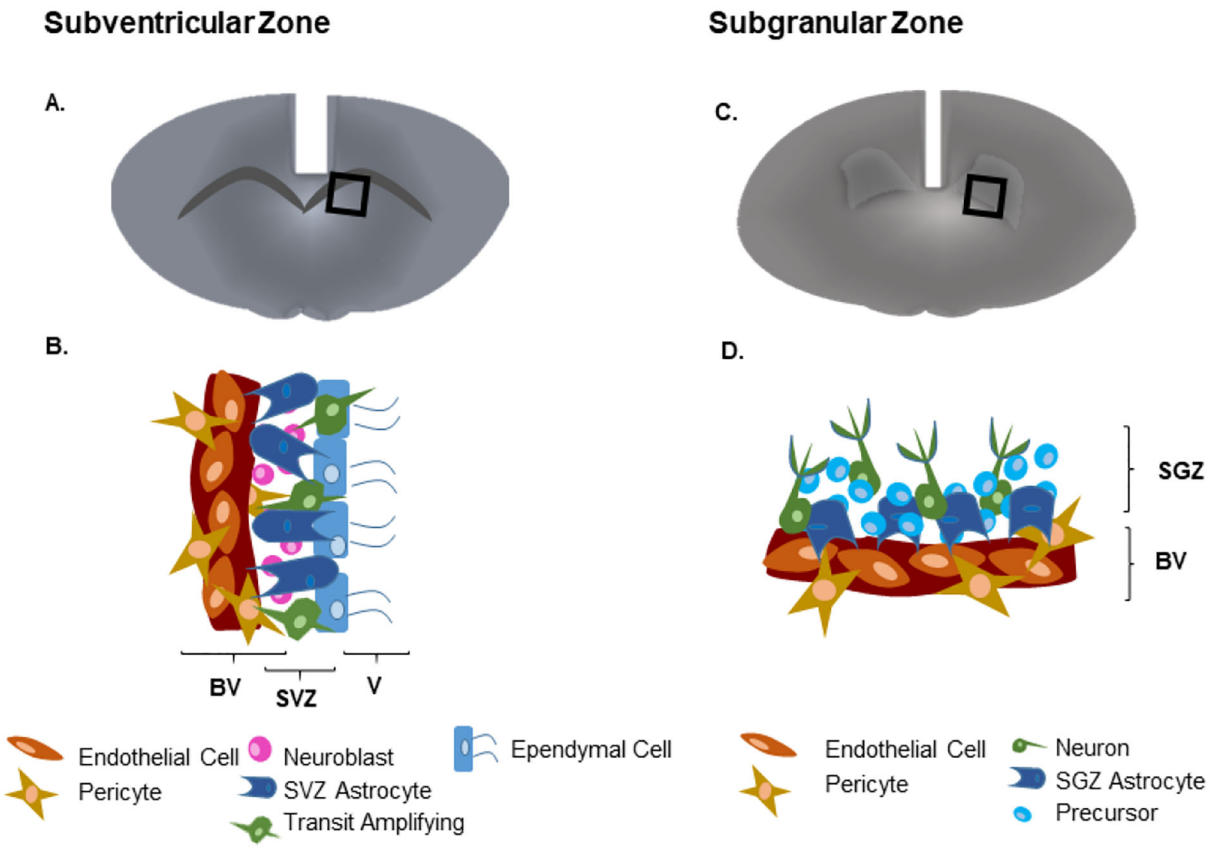

Figure 1.

a Subventricular zone (SVZ) location, lateral to the lateral ventricles, highlighting b cytoarchitecture of resident cell types lining the blood vessels (BV) in the SVZ, and lining the ventricle (V). c Subgranular zone (SGZ) within dentate gyrus, demonstrating d cytoarchitecture of SGZ and BV resident cells