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Review

Stem cell niche: Dynamic neighbor of stem cells

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ABSTRACT

Stem cell niche is a specialized and dynamic microenvironment around the stem cells which plays a critical role in maintaining the stemness properties of stem cells. Over the years, advancement in the research activity has revealed the various important aspects of stem cell niche including cell-cell interaction, cell-extracellular matrix interaction, a large number of soluble signaling factors and various biochemical and biophysical cues (such as oxygen tension, flow, and shear and pore size). Stem cells have the potential to be a powerful tool in regenerative medicine due to their self-renewal property and immense differentiation potential. Recent progresses in in vitro culture conditions of embryonic stem cells, adult stem cells and induced pluripotent stem cells have enabled the researchers to investigate and understand the role of the microenvironment in stem cell properties. The engineered artificial stem cell niche has led to a better execution of stem cells in regenerative medicine. Here we elucidate the key components of stem cell niche and their role in niche engineering and stem cell therapeutics.

1. Introduction

Stem cells are being widely utilized in biomedical science in various therapeutic approaches because of their unique properties of self-renewal and immense potential to differentiate into almost all cell type that makes up the body. Based on the range of differentiation potential, stem cells are also classified as pluripotent, multipotent and unipotent. Expression of key pluripotent specific genes such as Oct3/4, Sox2, Klf4, Nanog and some other molecular factors, is responsible for conferring stemness in stem cells. Apart from these molecular milieus, microenvironment, where the stem cell resides and receives stimuli, plays a pivotal role in differentiation potential and maintenance of stem cells in a quiescent state and thus plays an important role in the therapeutic potential of stem cells. Primarily, stem cell niche is a dynamic and specialized microenvironment that regulates stem cell survival and functioning by producing factors that act directly on stem cells (Gattazzo et al., 2014). The key component of various stem cell niches includes diffusible and cell surface-associated signaling molecules, inflammatory, specific neuronal, glial, vascular and mesenchymal cell types and physical factors such as oxygen tension, temperature, matrix rigidity, shear stress, etc. (Wong et al., 2012). These niche factors lead to activation of certain intracellular signaling pathways that eventually determine the fate of a cell whether it is to divide, differentiate or to undergo apoptosis. However, the identities of most cells that populate the niche, including stem cells, remain elusive (Ceafalan et al., 2018).

A cautious examination of the interfaces amid stem cells and their cellular cohorts within and outside the niche are imperative for the advancement of impending therapies. Stem cell niche from embryonic stem cells (ESCs) and adult stem cells including epithelial stem cells (epithelial SCs), intestine stem cells (ISCs), hematopoietic stem cells (HSCs), muscle stem cells (MuSCs) or satellite cells, adipose-derived stem cells (ASCs) and neural stem cells (NSCs) has been studied extensively in order to decipher the therapeutic application of stem cell niche.

Although, all the studied stem cell niches are having the same basic constituent but depending upon the respective organs, stem cell niches exert different sets of signaling pathways for regulating the stem cell properties and also harbour varying degree of biophysical conditions. Among all the known stem cell niches, HSCs niche in the bone marrow is the most extensively studied niche that was first proposed by Schofield in 1978 (Schofield, 1978). HSCs niche secretes various growth factors such as stem cell factor (SCF), CXC-chemokine ligand 12 (CXCL 12), thrombopoietin (TPO) etc., that promote the HSCs maintenance and haematopoiesis. The signaling mediated by these factors, such as CXCL12/CXCR4 signaling, regulates the HSC engraftment after transplantation (Crane et al., 2017). In addition, NSC niche is of particular importance as it contributes to balance between NSCs quiescence and NSCs proliferation to direct the NSCs either towards neurogenesis or gliogenesis (Conover and Notti, 2008). Moreover, the interaction between MuSCs or satellite cells and surrounding niche helps in the regulation of satellite cell quiescence, self-renewal, proliferation and differentiation. Wnt/β-catenin signaling from

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surrounding niche cells promotes myogenic commitment and differentiation of satellite cells, while Notch signaling is involved in muscle regeneration and maintenance of quiescence state of satellite cells (Luo et al., 2005; Yin et al., 2013). In addition, the surrounding niche cells of ASCs contribute to angiogenesis, self-renewal and differentiation into preadipocytes via various signaling pathways; for example, bone morphogenetic protein (BMP) and Wnt signalling pathways are crucial for adipocytes production from ASCs whereas various autocrine and paracrine regulators affect self-renewal and angiogenesis respectively (Kaewsuwan et al., 2012).

In order to completely implement the unique potentials of stem cells in therapeutic application, in vitro technique, that is niche engineering is being developed to form an artificial niche using the major components of stem cell niche (Metallo et al., 2007). Furthermore, well-studied niche of different stem cells helps in accurate engineering of stem cell niche microenvironment in vitro that provides precise control over stem cell expansion as it is very crucial for successful stem cell-based translational, clinical and therapeutic applications. So, the aim of this review is to shed light on the biological and therapeutic aspects of the neighborhood relationship of stem cells with their niche including the various components of stem cell niche and advancement of in vitro stem cell niche engineering that will help to execute the stem cell-based therapies.

2. Components of stem cell niche

Prior to stem cell niche engineering, it is inevitable to have a thorough knowledge of the common elements of stem cell niche which include cell-cell and cell-extracellular matrix (ECM) interactions, major diffusible signaling factor and key signaling pathways as depicted in Fig. 1. Apparently, the interaction of stem cells with niche factors is crucial for maintenance of stemness property and spatiotemporal differentiation of stem cells. These interactions influence the various functions of stem cells such as aging, wound healing and biological responses of stem cells (Choi et al., 2015).

2.1. Cell-Cell interaction

Cellular contact of stem cells with surrounding cells and adjacent stem cells is responsible for self-renewal and differentiation of stem cells. In the microenvironment of niche, stem cells communicate with the surrounding heterologous cells via gap or adherence junction, direct cell-cell contact and through secretion of soluble factors (Madl and Heilshorn, 2018). Stem cell-cell interaction via gap or adherence junction is mediated by cadherin protein, a protein family of homophilic adhesion receptor. Various types of cadherin proteins have been reported so far that play a role in an adhesive attribute of the stem cell niche especially N-cadherin mediates association between HSCs and osteoblast while M-cadherin facilitates adherence between MuSCs and muscle fibre (Hosokawa et al., 2010; Ferraro et al., 2010). In addition, other ECM proteins such as ephrin and Notch receptor and its ligand actively participate in direct cellular association of stem cells with surrounding cells (Vazin and Schaffer, 2010). In NSCs niche, cellular contact between NSCs and neighbouring cells through adhesion protein ephrin modulates the signaling pathways that lead to neurogenesis and NSC self-renewal (Ricard et al., 2006). In HSCs niche, the interaction between HSCs and oesteoblastic cells is facilitated by Notch signaling that supports the HSCs self-renewal and function. Furthermore, in ISCs niche, ISCs are in direct contact with Paneth cells and these cells secrete various signaling factors such as epidermal growth factor(EGF), transforming growth factor(TGF)-α, Delta-like ligand(Dll)1, DLL4 and Wnt3a which in turn modulate the ISCs self-renewal, proliferation and homeostasis (Sasaki et al., 2016). In conclusion, cellular interaction between stem cells and surrounding cells plays a pivotal role in dynamism of stem cells and regulates the mobility of stem cells.

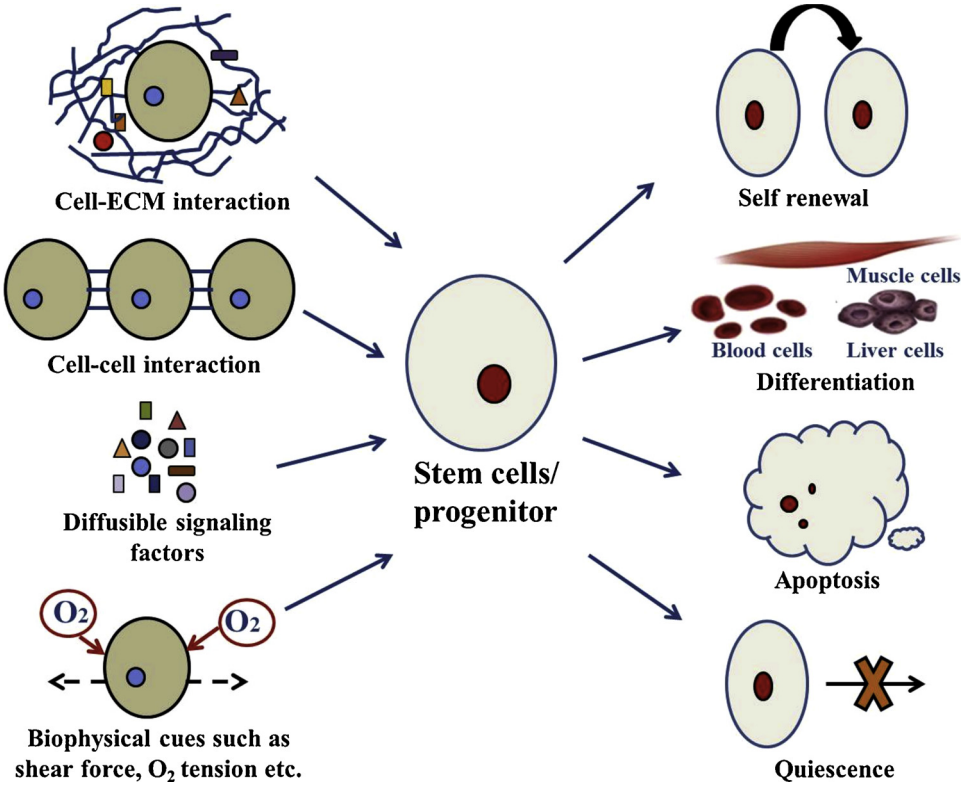

Fig. 1. Representation of key components of stem cell niche: cell-cell and cell-ECM interaction, various diffusible molecules and mechanical and biophysical factors regulates the stem cell properties.

2.2. Cell-ECM interaction

ECM is tissue-specific, dynamic and complex biophysical, mechanical and biochemical environment that regulates the cell behavior and also vital for development, function and repairing of particular organ by modulating the production, degradation and remodelling of its component (Gattazzo et al., 2014). As far as interaction between stem cell and ECM is concerned, direct interaction is mediated by a range of ECM proteins, including integrins, laminin, fibronectin, tenascin-C, collagen VI, etc. (Tierney et al., 2016). Among all the ECM proteins, integrin and laminin are the most prominent regulators of stem cell function. Integrins are a large family of 24 distinct heterodimeric (α- and β-subunit) receptor proteins having a different combination of 18 α-subunits and 8 β-subunits, and these different integrins possess cell-specific expression and ligand specificity (Brizzi et al., 2012), while laminins are a large family consisting of 15 distinct heterotrimeric extracellular glycoproteins made up of α, β and γ subunits (Mak and Mei, 2017).

In context to stem cell niche, integrins play a role in stem cell migration, proliferation, survival and differentiation by connecting the extracellular surrounding to intracellular cytoskeleton. Different integrins have been reported so far that are involved in stem cell and ECM interaction. The α6β1 integrin binds to the laminin protein in ECM and play pivotal role in the homing of spermatogonial stem cells, and also essential for attachment of NSCs to the vascular niche (Kanatsu-Shinohara et al., 2008; Shen et al., 2008). Another integrin chain α9 binds to the ECM protein tenascin-C and plays a crucial role in proliferation of HSCs, and it is also a vital component of NSCs niche (Kazanis et al., 2007; Nakamura-Ishizu et al., 2012). Furthermore, it has been established that α4, α6, α9 and β1 integrin chain helps in HSCs homing in the bone marrow (Gattazzo et al., 2014). In the hair follicle, α8β1 integrin on arrector pili muscle interacts with the ECM protein nephronectin and maintains the proper position of hair follicle stem cells (HFSCs) (Fujiwara et al., 2011). In addition, satellite cells (or MuSCs) interact with their niche, that is, basal lamina, through α7β1 integrin (Kuang et al., 2008). However, laminin-111 via integrin α6β1 signaling mediates satellite cells proliferation and self-renewal and thus results in long-term regenerative capability of muscle cells (Rayagiri et al., 2018). Furthermore, loss of function study of ECM proteins, tenascin-C, fibronectin and collagen VI, in satellite cell niche revealed that these ECM proteins actively regulate the stage-specific function of satellite cells (Tierney et al., 2016).

Furthermore, β1 integrin maintains a stable stem cell pool and also controls the stem cell renewal and differentiation. β1 integrin maintains the stem cell population by influencing the symmetric versus asymmetric division. β1 integrin in partnership with various signaling molecules, such as paxillin, HEF1, zyxin and integrin-linked kinase, modulates the mitotic spindle function and orientation and thus controls the stem cell division (Fielding et al., 2008). In continuation, it has been reported that β1 integrin in coordination with Notch pathway controls self-renewal and differentiation of mammary stem cells and NSCs (Campos et al., 2006; Brisken and Duss, 2007). In addition, loss of function of ECM proteins such as fibronection, collagen and laminin in ESCs niche leads to embryonic lethality (Ahmed and Constant, 2016). Apart from the integrins and laminin, other major proteins that play a role in cell-ECM interaction include CD44, Robo4, etc. CD44 is important for the homing of HSCs during transplantation, while Robo4 cooperates with CXCR4 receptor in HSCs and plays a role in adhesion of HSCs to the surrounding niche (Ferraro et al., 2010; Mendelson and Frenette, 2014).

2.3. Key signaling factors in stem cell niche

Determination of stem cells fate either to maintain the quiescent state or self-renewal or differentiation greatly relies on various diffusible milieus of a large number of signaling factors present in the ECM (Redondo et al., 2017). Major signaling factors including cytokines, such as SCF, FMS-like tyrosine kinase-3, TPO etc., several growth factors such as basic fibroblast growth factor (bFGF), TGF-β family, hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), EGF and vascular endothelial growth factor (VEGF) and various small biomolecules such as retinoic acid (RA), activin-A, leukemia inhibitory factor (LIF), nitric oxide, etc. are found in the stem cell niche (Brizzi et al., 2012; Redondo et al., 2017). All these molecules immobilize in niche and form a concentration gradient that is crucial for arbitrating their effect on the stem cell function.

2.4. Signaling pathways in stem cells niche

The diffusible molecules in ECM influence the fate of stem cells by activating certain signaling pathways through the paracrine effect. Major signaling pathway that plays the key role in stem cell niche function includes Wnt/β-catenin, BMP and Notch signaling. Among these, Wnt and BMP pathways are crucial and effectively control the self-renewal and differentiation of stem cells into particular cell lineage, and they are also highly conserved in the invertebrate and mammalian stem cell niches (Ferraro et al., 2010). Moreover, other signaling pathways including hedgehog (Hh) and stromal cell derived factor-1 (SDF-1) signaling also contribute substantially in functional ontology of cell lineage-specific stem cell niche.

Wnt signaling initiates upon binding of Wnt receptor ligand to cell surface receptors frizzled (Fzd) which upon activation induces the phosphorylation of intracellular protein disheveled (Dvl) which in turn prevents the GSK3β from phosphorylating the β-catenin and this non-phosphorylated active β-catenin moves to the nucleus and expresses the target gene (Singh et al., 2017). Wnt/β-catenin pathway exerts different effects on stem cell in tissue-specific manner. In bone marrow niche, Wnt signaling pathway mediates self-renewal and proliferation of HSCs and controls skeletogenesis by inhibiting the differentiation of mesenchymal stem cells (MSCs) into chondrocytes and adipocytes and by promoting the osteoblast differentiation (Stoddart et al., 2017). In the skin, Wnt signaling stimulates the differentiation of multipotent epithelial SCs and hair follicle morphogenesis (Huelsken et al., 2001). Additionally, a cross talk of Wnt and Notch signaling determines the fate of hair follicle stem cells (HFSCs) in skin (Veltri et al., 2018). Of late, it has been revealed that gradient of Wnt protein in ISCs niche controls self-renewal, proliferation and differentiation of ISCs (Farin et al., 2016). In the brain, active β-catenin resultant of Wnt pathway helps in the expansion of NSCs population (Chenn and Walsh, 2002).

BMP signaling, one of the members of the large TGF-β family, regulates different properties of stem cells in different tissues same as Wnt/β-catenin signaling does. In the bone marrow, BMP signaling regulates the HSCs proliferation and thus controls the number of HSCs (Zhang et al., 2003). In skin, BMP signaling plays a crucial role in self-renewal of hair follicle stem cells by inhibiting the differentiation of these stem cells and also regulates the melanocyte stem cell niche and thus governs the skin pigmentation (Kulessa et al., 2000; Clavel et al., 2017). A cross talk between BMP and sonic hedgehog (Shh) signaling pathway in dental epithelial stem cell niche determines the epithelial stem cell fate during tooth development (Li et al., 2015). Moreover, in the nervous system, BMP signaling promotes the differentiation of NSCs into astrocytes cells while inhibition of BMP signaling leads to differentiation of NSCs towards neurons (Temple, 2001).

The Notch pathway usually takes place at cell-cell interaction thus it plays an important role in stem cell niche. Notch signaling pathway initiates when Notch ligands belong to the Delta-Serrate-Lag2 family, binds to Notch receptor and subsequent cleavage by enzyme γ-secretase releases the Notch intracellular domain (NICD) in the cytosol which translocates into the nucleus and interacts with CBF1/SuH/Lag1 (CSL) transcription factor and switches on the expression of target genes viz. involved in self-renewal of stem cells (Verma et al., 2013). In the skin, Notch signaling promotes the differentiation of epidermal progenitor

cells. Recently, Notch signaling has been established as a prominent pathway in gastric stem cells (GSCs) proliferation and differentiation into gastric epithelial cell (Demitrack and Samuelson, 2017). Notch signaling has been found to regulate the HSCs self-renewal and promotes the proliferation of long-term repopulating HSCs (Mendelson and Frenette, 2014). In addition, Notch signaling maintains the undifferentiated state of NSCs and consequently promotes the self-renewal of NSCs (Varnum-Finney et al., 2000; Hitoshi et al., 2002). Besides, interplay of Notch and EGFR signaling pathway helps in the maintenance of NSCs and neural progenitor cells (NPCs) pool in adult subventricular zone (SVZ) of brain (Aguirre et al., 2010). Moreover, dental pulp stem cell niche mediated Notch signaling regulates the proliferation and migration of dental pulp stem cells and thus helps in healing of injured dental pulp (Mitsiadis et al., 2017).

Hh signaling involves the binding of ligand protein, Hh to its receptor patched (ptc), and leads to accumulation of plasma membrane protein smoothened (smo) which allows the release of full length cubitus interruptus (ci) that acts as transcriptional activator (Ingham et al., 2011). Hh signaling establishes the germline stem cells (GSCs) niche precursor by ci- activated traffic jam (Tj) protein which causes suppression of cadherin (Lai et al., 2017). Moreover, SDF-1/CXCR-4 signaling plays an important role in HSCs maintenance and also controls the HSCs attachment within the HSC niche (Chotinantakul and Leeanansaksiri, 2012).

3. Niche engineering: the next big thing in stem cell therapeutics

The goal of niche bioengineering is to develop strategies, devices and novel techniques that can imitate the local microenvironment for the controlled culture of stem cells (Tan and Barker, 2013). In order to reconstruct the artificial niche, key attributes of the stem cell niche including soluble signaling factors, cell-cell and cell-ECM interactions, mechanical and biophysical factors are imitated in dynamic, controlled manner. These artificial niches include 3D platforms incorporating elements such as ECM proteins and growth factors, biochemical and biophysical factors (flow and shear), mechanical factor (flexibility and tensile strength), pore size, the gradient of oxygen tension, etc. (Tan and Barker, 2013). This section of the review will highlight the different molecular and cellular scale of stem cell niche that is being used widely for developing the various niche engineering strategies and will also provide an insight into various niche engineering strategies developed so far.

3.1. Different level of niche engineering

Niche engineering strategies developed so far either by engineering the stem cell-ECM and cell-cell interaction, or by engineering the mechanical forces and biophysical cues or by engineering the surface-bound and soluble cytokines as stated in Fig. 2. Among all these approaches, cell-ECM interaction is the most commonly used approach for niche engineering because the cell-ECM interaction is a prominent regulator of stem cell niche function. Various cell-ECM interaction-based approaches including synthesis of unique biomaterial for effective stem cell culture, fabricated micro or nanoscale 3D scaffold, 2D micropatterning ECM and high-throughput ECM microarray have been applied in niche engineering (Peerani and Zandstra, 2010). The synthetic biomaterial that imitates the ECM that has been used for maintenance and differentiation of stem cells, for example, hydrogels made up of hyaluronic acid (HA) and semi-interpenetrating polymer network (sIPN) controls the self-renewal and differentiation of human embryonic stem cells (hESCs) and promotes the self-renewal of hESCs, respectively (Li et al., 2006; Gerecht et al., 2007). In addition, fabricated nanofiber scaffolds having the amino group conjugated through different spacers such as ethylene, butylene, etc. have been used to expand the HSCs (Chua et al., 2007). ECM microarrays are suitable for designing a novel surface coating that helps to grow stem cells and to investigate the role of ECM protein in stem cell fate determination (Anderson et al., 2004).

Cell-cell interaction is an important component of stem cell niche, and it has been exploited in the generation of various niche engineering approaches. Major cell-cell interaction-based niche engineering approach includes culturing of stem cells with Notch ligand DLL4- conjugated magnetic beads, tethering of cell surface protein to biomaterials, cell pair array in microwell fabricated with biomaterial such as polyethylene glycol (PEG) and microengineering of co-culture of two or more cell-type approach. DLL4-conjugated magnetic bead induces differentiation of HSCs into T-cells (Taqvi et al., 2006). Moreover, ESCs at the different stage of differentiation cultured in PEG-fabricated microwell and the resulting homotypic ESCs interaction directed the differentiation toward neuroectoderm (Parekkadan et al., 2008).

It has been reported that mechanical strain application to stem cells regulates the self-renewal and differentiation of stem cells (Peerani and Zandstra, 2010). Strain can be employed by mechanical strain-loading device or by modulating the cell culture geometry and substrate availability (Takeda et al., 2006; Guilak et al., 2009).

3.2. Techniques of stem cell niche engineering

This section of the article highlights the extensively used stem cell niche engineering techniques those rely on cell-ECM interaction including biomimetic or hydrogel approach and ECM microarray and soluble ligands-based niche engineering technique comprising droplet-based microfluidic approach.

3.3. Biomimetic approach

The biomimetic approach involves the artificial stem cells niche formation using the biomaterial that mimics the natural niche. These biomaterials are either natural or synthetic polymers that form a hydrated gel-like network which resembles the ECM and provides a suitable condition for culturing the stem cells. Depending on the biopolymer, two kinds of hydrogels are used for stem cell niche engineering, that is, natural hydrogels and synthetic hydrogels (Lee-Thedieck and Spatz, 2012).

Natural hydrogels are formed from natural biopolymers such as alginate, collagen, HA, glycosaminoglycan and various protein polymers. Hydrogels made up of alginate, HA and collagen have been used for differentiation and culture of ESCs and adult stem cells (Dawson et al., 2008). Studies have shown that HA hydrogels increase the proliferation of NSCs into neurons, glial cells and NPCs (Huang and Wang, 2017). In addition, HA hydrogels have been reported as a potent scaffold that helps in maintenance and expansion of haematopoietic progenitor cells (HPCs) without requiring any additional cytokines (Demange et al., 2013). Natural biopolymer carries the baggage of limitations such as immunogenicity, pathogen contamination and poor control over mechanical properties which insisted the researchers to develop synthetic biomaterial. Various synthetic biomaterial used for hydrogel formation includes polyacrylamide, acrylic acid, PEG, in addition, a number of ECM biomaterial elements such as integrin binding arginine-glycine-aspartic acid (RGD) motif, laminin epitope IKVAV, etc. have been reported for bioengineering of stem cell niche.

These synthetic biomaterials acts as cellular substrates either alone or as a copolymer. Polyacrylamide and acrylic acid copolymers have been reported to regulate the stem cell behavior (Kim and Healy, 2003). Furthermore, RGD motif-integrated polyacrylamide/PEG hydrogels enhance the osteogenic differentiation of MSCs and also provide supports in short-term self-renewal of hESCs (Li et al., 2006; Yang et al., 2005). In continuation, RGD- integrated PEG hydrogels promote the differentiation of NSCs into neurons growth and extension of neurites (Naghdi et al., 2016). In addition, the copolymer of PEG and poly (lactic-co-glycolic acid)/poly(L-lactic acid) is among the widely used cellular substrate for stem cell culture and it is hydrolytically

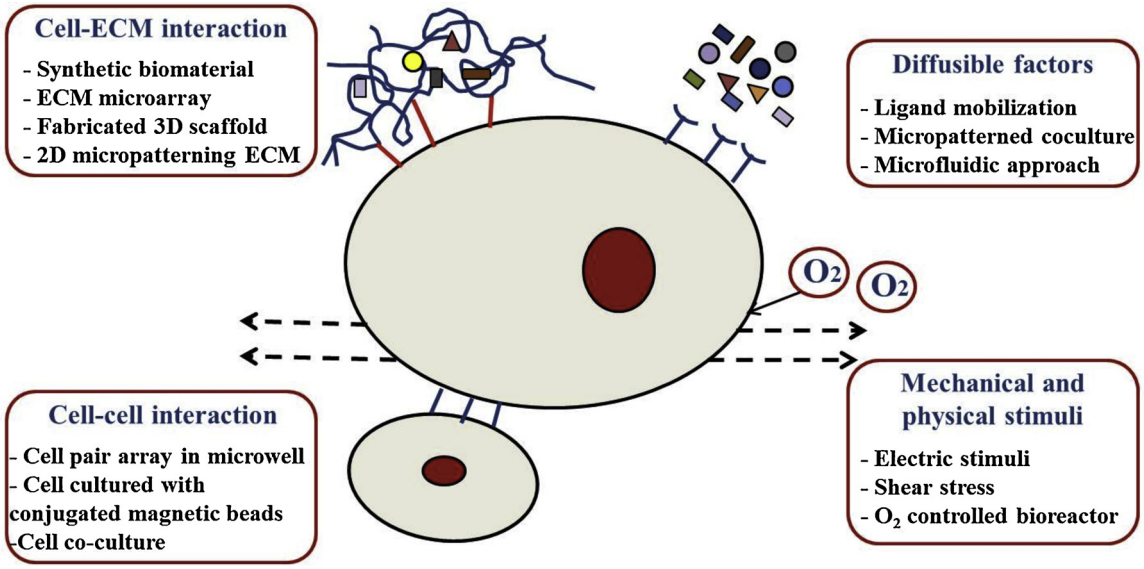

Fig. 2. Diagrammatic representation of niche engineering strategies developed so far at different level of stem cell niche.

degradable (Levenberg et al., 2003). In order to resemble the ECM, hydrogel scaffolds are supplemented with key growth factors and bioactive molecules such as PDGF,TGF-β, BMP, DLL4 etc. (Belair et al., 2014).

There have been various approaches for delivery of bioactive molecules developed so far which majorly include affinity-based and immobilized biomolecules-based delivery systems. Affinity-based delivery system relies on the introduction of heparan sulphate proteoglycan (HSPGs) such as heparin into scaffolds which act as the bioactive reservoir for signaling molecules (Vazin and Schaffer, 2010). In light of the fact that NSCs niche contains HSPGs, research group of Willerth et al. used the heparin-incorporated fibrin scaffold for the delivery of neurotrophic factors that resulted in increased neural differentiation of ESCs (Willerth et al., 2008). Moreover, heparin-incorporated cellular scaffold has been reported for the delivery of a number of signaling factors such as PDGF, Shh, BMP2, etc. In addition, an affinity-based delivery system having the benzylaminated dextran-modified hydrogel was developed as a long-term carrier of bioactive TGF-β (Degat et al., 2009). The immobilized biomolecule-based delivery system depends on the tethering of signaling factors and biomolecules to the surface of the scaffold. These biomolecules are tethered to the surface in an unequal manner that leads to the higher local concentration at one place while lower at other place and thus allows the spatial gathering of signaling biomolecules which further regulates the respective signaling pathways. The biomolecules are immobilized either by chemical conjugation or by using magnetic bead complex system. Surface-immobilized Shh in conjugation with interpenetrating polymer network (IPN) functionalized with bsp-RGD peptide, enhanced the osteogenic differentiation of MSCs (Ho et al., 2007). In addition, signaling factors including TGF3β and DLL4 immobilized on the surface using the magnetic bead complex system, have been shown to promote the chondrogenic differentiation of MSCs and T-cell differentiation from bone marrow HSCs (Taqvi et al., 2006; Motoyama et al., 2010).

However, research group of Gobbo et al. expanded the horizons of hydrogel-based niche engineering technique when they reported a microengineered platform containing the hydrogel microwell array and used this platform for successful differentiation of adipose cells from human mesenchymal stem cells (hMSCs) (Gobaa et al., 2011). Furthermore, a biofunctionalized macroporous PEG hydrogel 3D scaffold was developed and successfully tested for proliferation of human HSCs (Raic et al., 2014).

3.4. ECM microarray

ECM microarray technique involves the engineering of stem cell-ECM interaction as this interaction is vital in stem cell homing, mobilization and maintenance of stemness properties as well. ECM microarray not only provides a novel scaffold to grow stem cell but also is useful for high-throughput investigation to the role of various ECM proteins in various cellular functions. This approach comprises automatic pipetting of nanoliter volume of stem cells, various ECM and niche components including ECM proteins, ligands, growth factors, signaling factors, etc. that allows mixing of these components and dispenses onto a substrate and thus generates a spot of artificial niche with defined properties as depicted in Fig. 3 (Flaim et al., 2005). Due to its components, high-throughput ECM microarray offers greater efficiency in stem cell growth and differentiation in comparison to the traditional approach of biomaterial-coated microplate.

In addition, ECM microarray helps in screening out the most congenial combination of components for generating the artificial niche. In initial studies, ECM microarray has been used to differentiate the mouse embryonic stem cells (mESCs) into hepatocytes on artificial niche generated by depositing the print buffer suspension of laminin, fibronectin, collagen I, collagen II and collagen IV on 9.5% of acrylamide gel pad (Flaim et al., 2005). However, Malta et al. assessed the modulatory effect of ESCs-ECM interaction on definitive endoderm (DE) differentiation into liver and pancreas through the implementation of ECM microarray approach (Malta et al., 2016).

3.5. Droplet microfluidics approach

Droplet-based microfluidics is an expeditiously growing interdisciplinary research field that combines soft matter physics, biochemistry and microsystems engineering (Seemann et al., 2011). Essentially, microfluidics is a technology of system characterized by the engineered manipulation of a submilimiter amount of fluid (10^{-9}–10^{-18} L). Many microfluidic studies have revealed certain key properties of microfluidic technology such as rapid sample processing and precise control of fluid in an assay that made them a potential candidate to replace the conventional experimental approaches (Sackmann et al., 2014). In context to stem cell niche bioengineering, application of microfluidics relies on the precise controlling of fluidic properties such as diffusion, conviction and reaction. Microfluidics technology has various advantages in niche engineering as it not only mimics the microenvironment around stem cells but also can tune the composition of

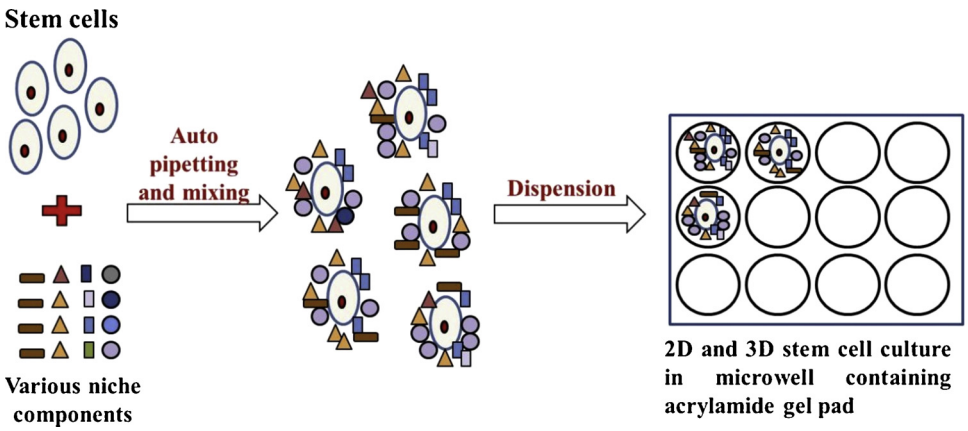

Fig. 3. Schematic presentation of ECM microarray: thousands of dots of artificial niche can be generated at a time by mixing the stem cells with different combinations of niche factors.

the local cell population and cell-cell interaction. Microfluidics can mimic the microenvironment of stem cells by combining the different fluidic properties, for instance, a gradient of signaling factor and biomolecules is established in the microfluidic device by combining conviction and diffusion. Microfluidics manipulates local cell population composition by combining with different structures on the substrate.

Droplet microfluidic technology is gaining popularity in stem cell niche engineering as this technology was developed by combining the principle of droplet microfluidics with synthetic hydrogel technology. In particular, hydrogel precursor solution and biomolecules, termed as discontinuous or dispersed phase were emulsified at correct ratio into an immiscible nonpolar solution like oil, called continuous phase to form the synthetic microgel or microniches in the microfluidic device. Like synthetic hydrogel approach, key hydrogel precursor molecules used in droplet microfluidic technology include synthetic polymers such as PEG, polyglycerol, self-assembling peptide, etc. or natural biopolymers such as collagen, agarose, alginate, HA, etc. The artificial niche formation using droplet-based microfluidic approach is illustrated in Fig. 4. Particularly, microgels with natural or synthetic hydrogel adopted for specific functions depending on their properties, for instance, microgels made up of synthetic polymers, have been used to encapsulate cells into microcapsules with standardized biophysical and biochemical properties, while microgels made up of natural biopolymer are widely used for generating 3D microniches as they provide better cell binding and biodegradability (Rossow et al., 2012; Ma et al., 2013). Although, microfluidic droplet formation is regulated by equilibration between shear forces and surface tension of the two immiscible phases. In the process, when two immiscible phases, hydrogel precursor biomolecule and nonpolar solvent, are mixed in the microfluidic device then a liquid-liquid interface is generated, and after that microdroplet starts growing by surface-induced instability using different device geometries as per the requirement of droplet frequency and droplet monodispersity (Allazetta, 2015). Further, a suitable reaction scheme is used to generate the microgel from the microfluidic droplet, and there are four types of reaction schemes have been categorized on the virtue of technique applied to dispense the liquid and to initiate the reaction. These chemical reactions are usually initiated by the time delay, temperature or photo-polymerization, inter-diffusion of molecules and by coalescing the droplets (Seemann et al., 2011). First three are commonly used reaction schemes as these are flexible in terms of required microfluidic schemes while the fourth reaction scheme is specialized considering it requires a complex microfluidic process and coalescence droplet. Photo-polymerization is widely used to generate spherical gel particle, and this reaction scheme is optimized for uniform distribution of particle (Lewis et al., 2005). The chemical scheme based on inter-diffusion of molecules is applied for fabrication of complex material

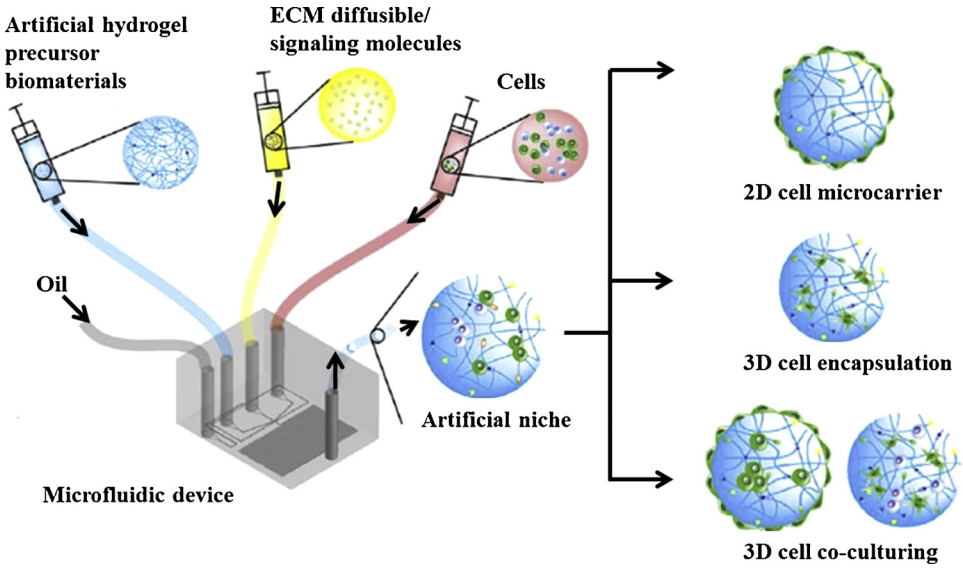

Fig. 4. Artificial niche formation using droplet-based microfluidic approach. Modified from Allazetta (2015).

such as core shell particles while chemical reaction initiated by coalescing the droplet involves the mixing of droplet content inside the droplet and effectively controls the volume of each liquid and to use an ambient phase where any of the dispensed chemicals is not soluble which avoids cross- contamination and clogging (Seemann et al., 2011).

In the context of stem cell, microgel based-technology serves for various applications including large-scale stem cell culture system, high-throughput screening and as 3D artificial microniche. Microgels are used as microcarriers, and in combination with bioreactor technology, they have been established as an alternative approach for large-scale production of stem cells in suspension. Microcarriers of varying size have been generated from various materials such as polystyrene, glass, cellulose, alginate, dextran etc. on which stem cells are spread and proliferated. Over the years, microcarriers have been successfully executed for the expansion and differentiation of mESCs, hESCs, MSCs and pancreatic progenitor cells (Fernandes et al., 2007; Serra et al., 2009; Eibes et al., 2010; Chen et al., 2011). In addition, microfluidics opened a new avenue in the area of high-throughput screening of different culture condition for stem cell growth and differentiation as it offers various advantages such as requirement of very lower amount of starting cells, precise control of cell number, dynamic alteration in stem cell culture condition, less time consumption, etc. (Zhang and Austin, 2012). Another application of microgel-based technology includes the formation of artificial 3D microniche in which cells are compartmentalized into monodispersed and physiochemical-defined matrices (droplet microfluidics) with a volume between 0.5 pL and 4 nL that provides an accurate insight into cell behaviour in response to microenvironment.

4. Therapeutic application of stem cell niche

The therapeutic potential of stem cells is attracting maximal attention in regenerative medicine. In continuation, the key strategy in regenerative medicine relies on the transplantation of cells in damaged and functionally deteriorated tissue or organ. Due to their immense potential to differentiate to form almost all cell type of body, stem cells have many applications in regenerative medicine. In general terms, the niche is not only the surrounding microenvironment of cells, which is a vital component of functional ontology of cells but also niche adapts precisely according to physiological and diseased condition of tissues (Bardelli and Moccetti, 2017). Because stem cell niche influences the function and behavior of stem cells by exerting various signals, this makes the stem cell niche a significant and potential entry point for therapeutic modulation of stem cell behaviour (Wagers, 2012). In the light of this fact, recent advances in in vitro remodelling of stem cells niche represent a potential therapeutic approach for regenerative medicine. In vitro targeting of stem cell niche helps in increasing the number of differentiated cells from stem cells and thus makes the way of transplantation easy. Proof of concept study of stem cell niche manipulation in cardiovascular diseases has been performed by various research groups. Behfar et al. reported the guided cardiopoiesis from hMSCs by modulating the culture environment using cardiogenic specific ECM signaling molecules including TGF-β1, BMP-4, activin-A, RA, insulin growth factor-1 (IGF-1), FGF2, α-thrombin and interlukin-6 (Behfar et al., 2010). In addition, engineered 3D ECM scaffold, either derived from decellularized heart or made up of synthetic hydrogels, provides a suitable microenvironment for structural organization and function of cardiac stem cells (Hasan et al., 2015). Moreover, combination of different niche signals including Notch, Wnt and BMP2 regulates the in vitro neural specification and differentiation of neural stem cells in microfabricated array system (Soen et al., 2006). Thus, NSC niche engineering may prove a potential therapy for various neurodegenerative diseases. Moreover, studies with skeletal muscle cells revealed that even modulation in in vitro substrate elasticity regulates the expansion and self-renewal of skeletal muscle cells (Gilbert et al., 2010).

Furthermore, diabetic and obese patients exhibit impaired regenerative potential of skeletal muscle cells and thus leads to ineffective wound healing. In this context, MuSC niche-based therapeutic approach could restore the regeneration of muscle cells and this may be of broad benefit to diabetic patients (Bardelli and Moccetti, 2017). In addition, stem cell niche modulation assists the chemotherapeutic ablation of tumors. Of late, alteration in inflammatory milieu of HSCs by modulating the INsF-α and G-CSF enhanced the efficiency of chemotherapeutic ablation of leukaemia cells (Essers and Trumpp, 2010). In one of the recent studies, research group of Swietlicki et al. showed that deletion of epimorphin, which affects the gut stem cell proliferation via effects on gut stem cell niche, caused increased the gut stem cell proliferation and regulated the epithelial crypt fission, and this result is of great importance to cure the disorders characterized by loss of intestine injury such as short bowl syndrome (Swietlicki et al., 2018). Thus, it is apparent that stem cell niche engineering could be a potential therapeutic approach for various degenerative and chronic diseases such as diabetes, neurodegenerative diseases, multiple sclerosis, muscular dystrophy, etc.

5. Conclusion and future perspective

Over the years, progression in the area of stem cell has revealed the various aspects of stem cell niche such as the interaction of stem cells to the other cells and to the ECM component, various diffusible signaling molecule, major signaling pathways, biophysical and biochemical components of stem cell niche. Interaction of stem cells with neighboring stem cell and another type of cells regulates the self-renewal and differentiation of stem cells, while the interaction between stem cells and surrounding ECM microenvironment controls the stem cell migration, proliferation and differentiation. Besides these interactions, various diffusible molecules in niche act via a number of signaling pathways including Wnt, Notch, BMP, etc. and plays a crucial role in a functional attribute of stem cells. A greater understanding of stem cell and their niche has promoted the researchers to develop various niche engineering technologies including biomaterials, microfabricated systems, etc. that provide in vivo niche- like environment to stem cells and offer remarkable control over key niche factors. Moreover, niche engineering technology provides liberty to researchers in terms of generating an artificial niche with known suitable material that in combination with in vivo studies will enable us to increase our understanding about which particular component and factor of niche plays a role in fate determination and behaviour of stem cells. In conclusion, these studies will set a new benchmark in stem cell research as the more accurate similarity of in vitro niches with in vivo niches will provide a well-defined stem cell microenvironment as a scaffold that can be used in various stem cell-based therapies of degenerating diseases in human.

Disclosure of potential conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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