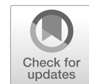

Influence of Biomimetic Materials on Cell Migration

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6.1 Biomimetic Materials in Tissue Engineering

Tissue engineering is a multi-disciplinary field that purposes tot the advance of biological replacements that recover, maintain, or promote the tissue function (Langer and Vacanti 1993; Ma 2004, 2005; Rice et al. 2005). To regulate the tissue formation in three dimensions (3D) situation, highly porous structure of scaffold is important in a typical tissue engineering strategy. In addition the scaffolds supply the synthetic extracellular matrix (ECMs) or microenvironments for attachment, proliferation, differentiation, regeneration or tissue genesis by the defining of 3D geometry for tissue engineering (Ma 2004, 2005; Liu and Ma 2004). As a result in tissue engineering, chemical and physical structures, or biologically functional moiety are significant to the biomaterials.

The diverse materials have been studied as scaffolds for tissue regeneration to satisfy the tremendous needs in tissue engineering. Because of the lack of degradation in biological situation (Liu and Ma 2004), some metals were not suitable for scaffold applications although they were used for medical implants due to their excellent mechanical properties (Catledge et al. 2004). The ceramic or inorganic materials; calcium phosphates or hydroxyapatite (HAP), has been studied for mineralized tissue engineering because of their excellent osteo-conductivity, however they were also limited due to their lowly porous structures or brittleness. On the contrary, polymers can be great candidate for scaffolds because they have good design flexibility so that the structure or composition can be modified to the particular demands. For these reasons, polymers have been widely studied in diverse tissue engineering applications, including bone, cartilage tissue engineering (Rice et al. 2005; Liu and Ma 2004; Meinel et al. 2005; Huang et al. 2007).

The emulating the advantageous features of the natural ECM may be valuable for the scaffold to serve as the impermanent ECM for regeneration of cells. However, it is unnecessary for the scaffold to completely copy the natural ECM, because the process of neo tissue genesis in tissue engineering is not correctly the same as the developmental or wound healing program. The tissue

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I. Noh (ed.), *Biomimetic Medical Materials*, Advances in Experimental Medicine and Biology 1064,
https://doi.org/10.1007/978-981-13-0445-3_6

engineering could accelerate the regeneration process compared to the natural development program, so the natural ECM is not suitable for scaffold in tissue engineering applications. Highly interconnected macro-or micro-pore structures helps cells to make quick and uniform population, this is essential for the tissue engineering and regenerative process however mature tissue matrix sometimes does not possess those structures. Therefore the optimal tissue engineering applications for accelerating of tissue regeneration require the appropriate designed scaffold features; pore size, porosity, inter pore connectivity. Lastly, the feasible pathogen transmission and immune rejection should be always concerned when using the natural ECM.

The biomaterials play a critical role in the most tissue engineering approaches (Hubbell 1995). The biomaterials can perform as a substrate to help the cells attach or migrate. It also helps cells to be implanted with a mixture of various cell types as a cell delivery vehicle, or be utilized as a drug carrier to initiate the specific cellular function in the localized area (Marler et al. 1998; Murphy and Mooney 1999). The advance of biomaterials for tissue engineering applications has focused on the devising of biomimetic materials that can interact with surrounding tissues by biomolecular identification (Hubbell 1999; Healy 1999; Sakiyama-Elbert and Hubbell 2001). The extracellular matrix (ECM) proteins are not particularly adsorbed on the surface of biomaterials after they are exposed to the biological conditions, then the cells interact with the surface of biomaterials through the adsorption of ECM proteins.

Biomolecular identification of materials by cells can be performed by two major devising approaches. One strategy is to incorporate the cell-binding peptides into biomaterials via physical or chemical adjustment. The cell-binding peptides contain both a long chain of ECM proteins and short peptide sequences derived from unscathed ECM proteins that can cause certain interactions with cell receptors. The biomimetic materials possibly imitate various roles of ECM in tissues. For example, the surface of biomaterials which is cell non-adhesive inherently can change to the cell adhesive surface by the immobilization of signaling peptides (Shin et al. 2002). The specific protease enzymes can also make the material degradable using the union of peptide sequences into materials (West and Hubbell 1999) or the union of peptide can cause the cellular responses (Suzuki et al. 2000). The other strategy is to endue biomaterials with bioactivity by union of soluble bioactive molecules; growth factors and plasmid DNA into biomaterial carriers. The materials released these bioactive molecules and start or modulate the new tissue formation (Whitaker et al. 2001; Richardson et al. 2001; Babensee et al. 2000).

6.2 Cell Migration

Cell migration plays important role in physiological phenomenon and cancer metastasis, immune response or embryonic development. The interaction between cell and the extracellular matrix (ECM) highly regulate the cell specific process characteristics. Cell polarization and protrusion at the leading edge also can influence on the cell migration and these phenomena are dependent on attachment of cells to the ECM or actin polymerization. The cell translocation or retraction of the rear which caused by the transmission of traction forced was followed by these events (Vicente-Manzanares et al. 2005; Lock et al. 2008).

Focal adhesions (FAs) are complexes of various proteins, and these mediate the signal transduction or adhesion to the ECM (Yamada and Geiger 1997). The actin cytoskeleton is connected to the ECM by FAs physically through the transmembrane heterodimer cell receptors; integrins, and also through the focal adhesion kinase (FAK) and vinculin which comprise the signaling pathways and mechano-transductive pathways (Huttenlocher and Horwitz 2011). The repeating cycles of FA assembly and disassembly during cell migration is caused by the rapid change in the protein composition over time in response to the external signals (Huttenlocher and Horwitz 2011; Zaidel-Bar et al. 2003). The characteristics of FA; size or morphology might determine the cell migrations (Kim and Wirtz

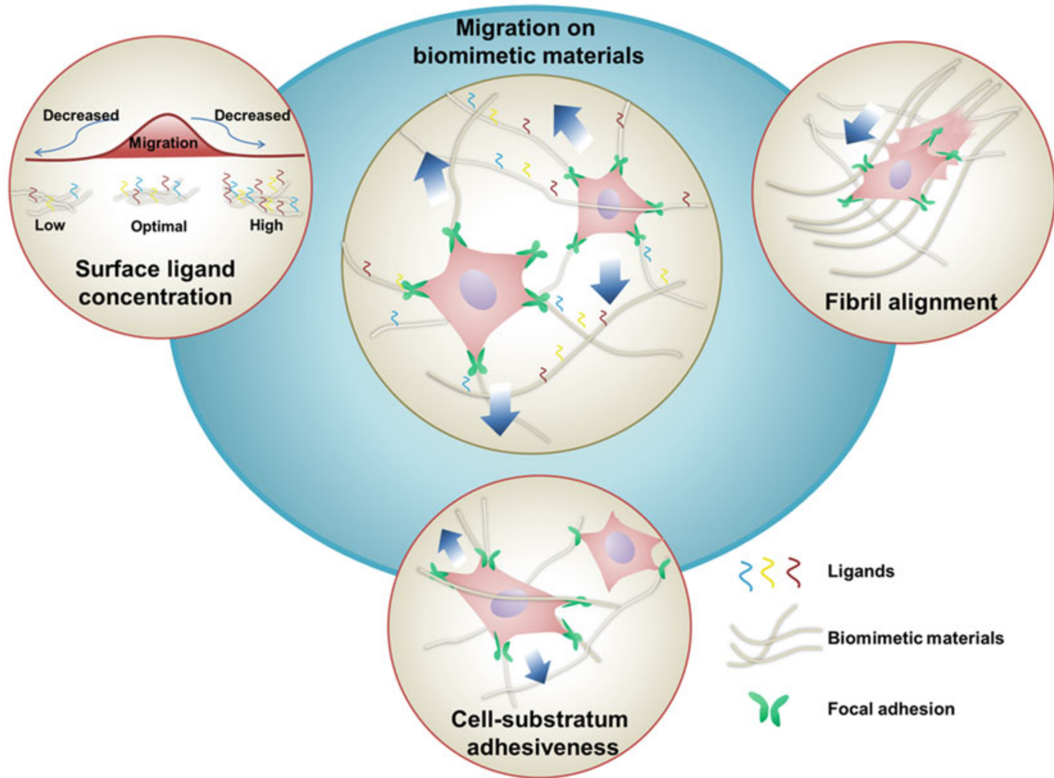

Fig. 6.1 Schematic diagram of cell migration on biomimetic materials

2013). The diverse size of FAs using the nanopatterned surface correlated with the particular cell migratory events (Slater et al. 2015). In addition, studies about the relationship between the cell migration and physical/chemical properties of the substrate have been performed. The ligand density by substrate, the expression levels of integrins and the ligand-inegrin affinity affected to the cell migration too (Palecek et al. 1997; Bergman and Zygourakis 1999). Also the adhesiveness level of cell substratum is related with the maximum speed of the cells (Palecek et al. 1997; Bergman and Zygourakis 1999; Kim et al. 2013).

The tremendous studies about the cell migration have been performed, however the molecular mechanism coordinating the cell motility is still not fully understood. It is well known that the external stimulation can regulate the cell response, such as mechano-transduction signals or stiffness, dimensionality of the ECM (Friedl and Wolf 2010; Petrie et al. 2009). Therefore, it is well accepted that the modulation of physical or chemical material parameters make the biomaterials alter the cell motility. Figure 6.1 showed the schematic diagram of cell migration on the biomimetic materials. In this review, cell migration on biomimetic materials has been introduced at mimicking the natural properties of the *in vitro* or *in-vivo* matrix.

6.2.1 Cell Migration with Collagen

The most plentiful protein in mammals, collagen type I has a triplehelical structure and this is made of three polypeptide chains which contain the gly-X-Y holding th 4-hydroxypoline and proline (Kadler et al. 2007). Collagens could be purified from human tissues (placenta) or animal tissues (skin, tendon). The increase of PH or temperature of precursor solution can reconstitute the ECM

protein into the fibrous matrix (Patterson et al. 2010). Collagen type I is widely used by treated with proteases for removing the small nonhelical telopeptides which presents at the end of the triple helical domain and is used for the cross species immunogenic character of the most proteins. However, the disease transmission and concerns of immunogenicity still remain for clinical application of this material (Lynn et al. 2004). Some recombinant human collagen type I and III are commercially sold, and methods for recombinant collagen expression have been studied for avoiding those risks (Ruggiero and Koch 2008).

The even macroscopic or permanent microscopic alignment of fibrous collagen matrix could be obtained by the dipole moment of fibrous collagen. The alignment of fibrous collagen under the strong magnetic field has been studied for inducing the directed cell migration; for example the neuritis grow along the direction of fibrous alignment (Ceballos et al. 1999).

6.2.2 Cell Migration with Fibrin

The fibrin is a special protein network which is formed in spontaneous tissue repair for clinically using from cryo-precipitated human blood plasma or autologous sources. The circulating glycoprotein homodimer of heterotrimer; which is called polymerization of fibrinogen combine the fibrin matrix spontaneously in the existence of thrombin protease. Fibrino-peptide on the fibrinogen is cleaved by the thrombin which prohibit the chemical or physical self –assembly or the molecule polymerization. The chemically cross linked network by the XIIIa which is blood transglutaminase factor and the fibrous structure of its compound (Patterson et al. 2010) depend on the formation of the cross-linked character (Lorand and Graham 2003; Standeven et al. 2007; Weisel 2004). Normally the fibrin is not the ECM because it is not generated by the cells around the local environment, however ECM is very important material that it is a critical member of regenerative matrices and plays role of a provisional matrix by remodeling and replacing with ECM molecules.

The proteolytic degradation may effect on the mechanism of cell migration in fibrous collagen matrix, however the migration of cells in fibrin is almost related with the cell associated proteolytic activity. The differences of cellular response in the fibril collagen may result from the small scaffold size of the fibrous matrices and the strong fibrous interactions, and the nature of network formation and covalent stabilization.

6.2.3 Cell Migration with Glycosaminoglycans

The long unbranched polysaccharides augmented the structure of ECM proteins in the biochemical or biomechanical functions. The components of ECM proteoglycans are not attaché to the core of protein covalently, and are entagled in the extracellular space except for the hyaluronic acid case. The glycosaminoglycans directly effect on the tissue regeneration through the interactions of cell-surface receptors, however the strong anionic polymers supply the compressive strength to the ECM by absorbing the water (Toole 2004).

Hyaluronic acid hydrogels have been studied for diverse uses; such as the dermal wound healing by keratinocyte transferring or cartilage repair by chondrocyte transplantation (Price et al. 2007; Tognana et al. 2007). Some cell surface receptors including CD44, RHAMM, and ICAM-1, interact with the hyaluronic acid and the incorporation of other functional biomolecules increase the biological activity of hyaluronic acid (Turley et al. 2002). The degradation of hyaluronic acid gel is due to the dyaluronidase (Kim et al. 2008), meanwhile the cell migration is driven by the diverse MMPs activities so using the MMP-sensitive cross-linkers could improve the migration of cells into the hydrogels. Also the wound healing or proliferation of fibroblasts can be improved by the functionalizing of hyaluronic acid gels with protein fragments or peptides from the fibronectin (Park et al. 2003; Ghosh et al. 2006). The migration of cells in-vivo is coupled to the degradation of ECM molecules via cell secreted or cell associated proteases expression, because the

matrix degradation is enzymatically rather than hydrolytically. Therefore the most of hydrogels for the biological applications including fibrin or hyaluronic acid hydrogels are degradable.

The degradation of synthetic hydrogels is mediated by cell and can be controlled by the incorporation of protease substrate sequences (Kim et al. 2008; Chau et al. 2008; Lévesque and Shoichet 2007; Lutolf et al. 2003). For rendering of covalent cross linking (Kim et al. 2008; Lévesque and Shoichet 2007; Lutolf et al. 2003) or self-assembling (Chau et al. 2008) to the degradation of hydrogels enzymatically. Furthermore, hydrogels which contains the incorporation of the enzyme units can control the degradation too. The organization or deposition of collagen type II by encapsulation of chondrocytes in vitro effected on the duration or timing of lipase exposure, and the presence of lipase can be caused the degradation of caprolactone units contained photo cross linked PEG gels (Rice and Anseth 2007). The erosion of the hydrogels for space of cell spreading or ECM production, can direct the cell migration or cell to cell connection, produce the channels and three-dimensional structures for example the interconnected channels made by two-photon methodology. The combination of photolabile tethered biologically active functionalities can effects on the locally modified chemical environments and also can enhance the chondrogenic differentiation of encapsulated human MSCs upon removal of RGD (Kloxin et al. 2009).

6.2.4 Migration in Tenascin-C Mimetic Peptide Amphiphile Nanofiber Gel

The glycoprotein tenascin-C is very important in spinal cord regeneration (Yu et al. 2011; Zhang et al. 1997). The expression of the axon ingrowth is shown highly in spinal cord injury and regions (Zhang et al. 1997). The spinal cord injury inhibit the tenascin-C expression, and the inhibition of tenascin-C reduce the supraspinal synapse formation and axon regrowth with the neurons of spinal motor and recovery of damaged locomotor (Yu et al. 2011). Tenascin-C also can guide the neural progenitors in development of brain (Thomas et al. 1996). The expression of protein that contribute to the stem cell niche by altering the response to the growth factors is increased in the subventicular zone (SVZ), and this protein also promote the FGF2 sensitivity and decrease the BMP4 sensitivity, which enchance the acquisition of EGF receptor (Garcion et al. 2004). The expression of tenascin-C is also increased in the rostral migration stream in the extracellular space (Thomas et al. 1996), which is a pathway that the migration of neuroblasts from SVZ to the olfactory bulb, where they changed into the new interneurouns.

The integrin-dependent pathways which helped cell adhesion can activate the tenascin-C. Many studies have discovered that the enascin-C with a linear peptides can promote the length of neurite (Meiners et al. 2001) via interaction with $\alpha_7\beta_1$-integrin (Mercado et al. 2004). The electrospun polyamide fibers were connected with the peptides covalently, and these were coated onto the coverslips (Ahmed et al. 2006). Some primary neurons; spinal motor, dorsal root ganglion and cerebellar granule neurons induce the increase of average lengths of neurite when they cultured in vitro in the tenascin-C peptide coated with the polyamide fibers (Ahmed et al. 2006). The materials with this peptide have effected on the non-neuronal systems too. Recently, one study showed that this peptide coated with self-assembled nanofibers could enhance the osteogenic differentiation of rat mesencymal stem cells (Sever et al. 2014).

The signaling of neurons to increase their length of neurite and the ratio of cells which positively on β-III-tubulin relative to backbone PA gels could be effected by the incorporation of the tenascin-C and PA gels. The length of neurite or the ratio of to β-III-tubulin-positive cells was not increased significantly by adding the scrTN-C PA gels. However, when the β_1-integrin blocking antibody treated to the gels, length of neurite and the ratio of positive cells to β-III-tubulin with neurites were dropped in TN-C PA gels, but not in scrTN-C PA gels because the

scrTN-C PA gels were not seriously different from the TN-C PA gels. According to these results, the length and number of cells with neurite is raised by the TN-C PA, and also β_1-integrin interaction affected too. However the mechanism on the peptide sequence is not fully understood because the TN-C PA is not seriously different from the scrTN-C PA.

The promotion of cell migration by the development of PA was the main purpose, and Eric et al. showed that the native channel for the migration like the rostral migration stream was existed by using the material with physical directional signals such as aligned fibers (Eric et al. 2016). The migration of native or transplanted cells could be directed by the neural stem cells or neural progenitor cells to the regions of neuronal loss. The expression of tenacin-C in the RMS is also detected when the neuroblasts moved on the surface of astrocytes (Thomas et al. 1996). The β1 integrin is very important in migration of neural cell (Jacques et al. 1998; Leone et al. 2005), therefore the incorporation of a tenascin-C derived from β1 integrin and nanofibers could enhance the migration of NPC derived cells. Compared to the backbone PA alone, the incorporation of PA mixtures which including the backbone PA and TN-C PA promote the migration of cells, meanwhile the backbone PA alone and incorporation of PA and scrTN-C did not influence on the cell migration.

6.2.5 Human Microvascular Endothelial Cell Migration on Biomimetic Surfactant Polymers

The migration of cell has been studied a lot in vitro because it is very important in physiological and pathological procedures (Kouvroukoglou et al. 2000; Hubbell et al. 1991; Garcia et al. 1998; Asthagiri et al. 1999; Byzova et al. 2000; Chon et al. 1997; Lauffenburger and Horwitz 1996; Nehls et al. 1998). Cell migration plays a role in various situations such as regeneration of damaged vascular wall, angiogenesis or colonization of cells in biomaterials. The EC migration is significantly important for succeeding of EC seeding on the surface to the implantation. At low density of cell seeding, the speedy migration and colonization is important, and some materials can induce these advantageous features. The migration of cells also important in the regions of cell loss because of the fluid shear stress, even confluent monolayer of ECs covered the implantation area.

The receptor cytoskeleton interactions, cytoskeletal formation or reorganization, and the detachment of tail ends, cell adhesion onto the surface are mediated with the migration of cells. The integrins or ligand interactions with factors could decide the direction or speed of cell migration (Kouvroukoglou et al. 2000; Domanico et al. 1997; Friedl et al. 1998; Maheshwari et al. 2000; Palecek et al. 1997; Simon et al. 1997). The integrin/ligand binding affinities, integrin expression levels, and ligand levels are the member of these factors (Maheshwari et al. 2000; Palecek et al. 1997; Simon et al. 1997). The average speed of cell migration has been shown that the cell to surface adhesive strength is dependent on the variety of cell types theoretically and experimentally (Maheshwari et al. 2000; Palecek et al. 1997; Wu et al. 1994). The $\alpha_4\beta_1$ and the $\alpha_5\beta_1$, the particular integrins could influence on the migration of cells to the fibronectin, as well as the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ which is vitronectin receptors involved in the migration of diverse types of cells, such as endothelial cells in angiogenesis (Maheshwari et al. 2000; Simon et al. 1997; Eliceiri et al. 1998).

The RGDS, YIGSRG (the adhesive sequence of laminin), the example of adhesive peptide sequences which are covalently immobilized, have influenced on the changes of cell persistence (the time between significant directional changes) and cell speed (Kouvroukoglou et al. 2000; Olbrich et al. 1996; Mann and West 2002). The migration of fibroblasts was decreased by adding the RGDs on the surfaces compared to the non-adhesive peptides (RDGS or RGES) (Olbrich et al. 1996), and RGDS and YIGSRG surfaces increased the random migration or persistence time of endothelial cells that non-adhesive peptides (Kouvroukoglou et al. 2000). However, the increase of surface peptide

density which composed of three different adhesive peptides inhibited the migration of smooth muscle cells seriously (Mann and West 2002). Therefore, the density of surface ligand and receptor affinity can influence on the adhesion strength to the surface, shear stability, signaling and EC migration (Garcia et al. 1998; Asthagiri et al. 1999; Palecek et al. 1997; Chan et al. 1999; Ruoslahti and Obrink 1996; Xiao and Truskey 1996).

One study showed that the series of biomimetic polymers which could be used to change the surface of existing biomaterials were designed for enhancing the appropriate adhesion and function of ECs on the biomaterial surfaces (Sagnella et al. 2004). The limiting the undesirable platelet activation and adhesions was caused by the maltose sugars which acts as a steric guard against the adsorption of non-particular proteins likely to the glycocalyx functions (Holland et al. 1998; Qiu et al. 1998). The surfactant polymer on the hydrophobic surface is self-assembled by the side chains of alkyl, so that the EC adhesion increased by the appropriate orientation of The RGD peptides.

The controlling the density of surface peptides could change the rate of EC migration or activity on these surfaces (Sagnella et al. 2004). The 100% of RGD polymers could induce the strong adhesion of ECs and wide spreading than other surfaces because it has the highest density of surface peptide. On 100% of RGD surfaces, HMVEC spread more even the cells were seeded at confluent density, because the increased integrin binding sites per area induced the cells to attach in more places and effectively spread out further. However the shorter distance migrating time and the lower cell density were observed in the smaller surface area covered by the migrating HMVEC population on the 100% RGD surface.

In increased ligand concentration, the decrease of cell migration is related with the increase of cell spreading for EC and other cell types (Palecek et al. 1997; Mann and West 2002; Burgess et al. 2000; Gobin and West 2002; DiMilla et al. 1993). The increase of the concentration of RGDS, VAPG, or KQAGDV inhibited the smooth muscle cell migration (Mann and West 2002). Previous study showed that the changing of surface ligands could control the adhesive strength via cell migration. Another study identified that 8 RGD per collagen monomer induce the highest coefficient of random migration of mouse melanoma cell via 3D collagen scaffold, however the density of peptide decreased above or below this number (Burgess et al. 2000). At concentration of 3.5 μmol/ml of RGDS, the migration of fibroblast and smooth muscle cells in ECM-like PEG hydrogels was highest, however the migration was decreased at above or below of this concentration (Gobin and West 2002). Similarly, full concentration of ECM proteins increased cell migration too (Palecek et al. 1997; DiMilla et al. 1993), so these results suggested that the highest migration is caused by appropriate ligand concentration which is optimal density.

The 100% of RGD surface showed slower migration that 75% RGD surface, and lower RGD promoted the migration of HMVEC even more. At the initial edge of 50% surface, HMVEC migrated further and showed higher density of cells with increase of radial distance than other surfaces. However, more decreased density of peptides induced drop of migration behavior. Unlike the described studies related in surfaces (Burgess et al. 2000; Gobin and West 2002; DiMilla et al. 1993), cell adhesion or growth were not influenced by biomimetic polymer system when the attached peptide did not exist. The adsorption of non-particular protein was inhibited by the glycocalyx-like properties of the oligosaccharide- rich surface (Holland et al. 1998; Ruegsegger and Marchant 2001). The EC adhesion and long term growth were not assisted by the 25% of RGD surface (Murugesan et al. 2002). Therefore, the density of peptide or, cell receptor density, ligand-receptor affinity could affect migration of cells (Palecek et al. 1997; Simon et al. 1997).

6.2.6 Biomimetic-Engineered Poly (Ethylene Glycol) Hydrogel for Smooth Muscle Cell Migration

Smooth muscle cell (SMC) migration plays a key role in a variety of physiological and pathological situations, ranging from vascular development to intimal hyperplasia after vascular injury (Willis et al. 2004; Gerthoffer 2007; Louis and Zahradka 2010). During vascular development, migration of pericytes and smooth muscle precursor cells occurs after the formation of an endothelial cell tube, assisting in the development of vessel wall construction and biomechanical functionality of the blood vessels (Gerthoffer 2007; Louis and Zahradka 2010). In response to vascular injury, SMCs up-regulate the secretion of matrix metallo-proteinases (MMPs) and increase their rate of cell migration, which is required for wound healing and vascular repair (Louis and Zahradka 2010). The development of materials that facilitate SMC migration has been a critical strategy in vascular tissue engineering because of the essential role of cell migration in vascular remodeling (Mann et al. 2001a, b; Almany Seliktar 2005; Liu Chan-Park 2010). However, excessive SMC migration, followed by SMC proliferation, if uncontrolled, will induce pathogenic vascular remodeling, which is a key step in the development of intimal hyperplasia (Willis et al. 2004; Louis and Zahradka 2010). Therefore, understanding the mechanisms involved in SMC migration and the development of strategies to regulate this process have become emerging areas of research.

Published studies of SMC migration on two-dimensional (2D) surfaces have suggested that cell migration is largely governed by the balance between attachment and detachment, presenting a biphasic dependence on cell-substratum adhesiveness (DiMilla et al. 1993). However, conditions for cell migration in vivo are more complex. Besides providing a variety of biochemical cues to guide cell function, the extracellular matrix (ECM) also imposes biophysical resistance to cell movement (Friedl and Brocker 2000; Friedl et al. 1998; Even-Ram and Yamada 2005).

Naturally derived materials, such as collagen gel and fibrin gel (Li et al. 2003; Shi et al. 2010; Ucuzian et al. 2010), have been utilized to investigate cell migration in three dimensions, because they possess many critical biological functions such as cell adhesion and biodegradability (Rosso et al. 2005; Chen and Hunt 2007). However, biological materials used in vitro have some deficiencies, including relatively poor mechanical properties, batch-to-batch variability, and limited design flexibility, which restrict their potential to become an ideal model (Rosso et al. 2005; Chen and Hunt 2007; Pampaloni et al. 2007).

The role of SMC migration as an essential process in physiological and pathological vessel wall remodeling makes the study of mechanisms involved in cell migration a major focus of research (Willis et al. 2004; Gerthoffer 2007; Louis and Zahradka 2010). In contrast to cell migration on 2D surfaces, 3D cell migration is more complex, because migration is mediated not only by biochemical factors (e.g., adhesive ligand concentration), but also by biophysical factors (e.g., network cross-linking density) (Friedl and Brocker 2000; Friedl et al. 1998; Even-Ram and Yamada 2005).

Cell-matrix adhesion is a governing parameter of cell migration on 2D surfaces (DiMilla et al. 1993), consequently, it is reasonable to anticipate that cell-matrix adhesion also will play a key role in 3D cell migration. To explore the effect of a single parameter (e.g., adhesive ligand concentration) on cell migration in a 3D model, the interdependence of variables (e.g., adhesive ligand concentration vs. hydrogel network property) should be considered. To investigate the effect of adhesive ligand concentration on the hydrogel network, studies of mass swelling ratio as a function of RGD-PEGMA concentration were performed. The results indicated that the hydrogel network was not affected by the inclusion of RGD-PEGMA, while adhesive ligand concentration was in the range of 0–2.5 mM. Therefore, this concentration range (0–2.5 mM) was chosen to study the effect of adhesive ligand concentration on SMC migration. Similar to previous studies of cell migration on 2D surfaces (DiMilla et al. 1993; Wu et al. 2012) and within 3D matrices

(Lutolf and Hubbell 2003; Gobin and West 2002; Raeber et al. 2007), a biphasic relationship between migration distances and cell-matrix adhesiveness was found (Lin et al. 2014). Since cell migration is a product of the net force between counteracting detachment and adhesion forces, it is hypothesized that at a low ligand concentration, weak cell-matrix adhesiveness results in a decrease in traction forces for forward movement, which subsequently slows cell migration. In contrast, in the presence of a high ligand concentration in the 3D network, strong cell-matrix adhesiveness inhibits cell detachment, which results in decreased migration (Lutolf and Hubbell 2003; Gobin and West 2002).

The effect of the hydrogel network on cell migration in 3D gels was evaluated by varying the concentration of GIA-PEGDA in the hydrogels. Mass swelling ratio studies showed that a variation in GIA-PEGDA concentrations results in a significant change in mass swelling ratios of the hydrogels (Lin et al. 2014), which is an important parameter that is closely related to the biophysical properties of the hydrogel network (e.g., mesh size, cross-linking density) (Beamish et al. 2009; Lutolf and Hubbell 2003; Munoz-Pinto et al. 2009; Beamish et al. 2010). At a constant concentration of RGD-PEGMA (0.441 mM, the concentration that shows maximum migration in 5% GIA-PEGDA gels) in the swollen hydrogel, increasing GIA-PEGDA concentrations significantly decreases migration distances (Lin et al. 2014). This observation is consistent with previous studies, in which the network properties of PEG hydrogels were tuned by PEG molecular weight. Therefore, along with cell-matrix adhesiveness and proteolysis, network cross-linking density plays a critical role in 3D cell migration.

6.2.7 3D Printing of Biomimetic Microstructures for Cancer Cell Migration

The cancer cells move to another site from the origin region via the circulatory or lymphatic system, this is a complex event of chain and called metastasis (Lauffenburger and Horwitz 1996; Steeg 2006). The patients who have the metastasizing stage of cancer will not survive less than a year (Decaestecker et al. 2007). Some tumors; glioblastomas, are dramatically increased by the migration, therefore the understanding about the migration of cancer cells could help to study the metastasis. The study about various factors to affect migration of cells is very important to advance the method for treating or targeting the cancer disease. Additionally the designing of accurate 3D model of cancer tissue is aided by the current drug test in 2D culture.

One study used the chick embryo's thin chorioallantoic membrane (CAM) mixed with fluorescently labeled cancer cells for observing the migration of cancer cells in vivo to develop more accurate model (Leong et al. 2012). Another study showed that the process of breast cancer metastasis was mimicked by using the transgenic mice (Jenkinson et al. 2004), however the effectiveness of the mice model needed more time to mature the metastasizing cancers and was very expensive (Zhou et al. 2011). For studying about metastasis, in vitro 2-D models have been designed (Jenkinson et al. 2004; Yamada and Cukierman 2007; Watson et al. 1995), for example; the micro-carrier bead assays or monolayer wound model (Decaestecker et al. 2007; Ghajar et al. 2007; Mathew et al. 1997; Chaffer et al. 2006). Additionally, the migration assay of single cell is very useful in migration analysis of separating cells from the cell growth (Decaestecker et al. 2007; Albrecht-Buehler 1977). Recently, in vitro 3-D models of migration system have been studied for more researching of cell migration (Rolli et al. 2010; Mak et al. 2011; Pathak and Kumar 2012), for example the linear polydimethylsiloxane (PDMS) channels was used to analyze the effectiveness of channel width and shape on the migration speed (Heuzé et al. 2011). Another study showed that the physical spatial gradients induce the response of cell migration (Mak et al. 2011), so that the feedback of mechanism about the metastasis of cancer cells into raised aggressiveness was identified. The increased width of channels also decreased the migration speed of cancer cells (Irimia and Toner 2009; Mathew et al. 1997).

One study showed that biomimetic 3D microstructure was created for study about migration of cancer cells by the technique of micro-fabrication (Lin et al. 2014). The scanning polymerization and projection polymerization were used for 3D bioprinting, and this maskless fabrication technique could make the delicate micro-pores and structures. Micromirror Device-based Projection Printing (DMD-PP) is a new technology to make three-dimensional structures in micro-scale biocompatible hydrogels (Lu and Chen 2008; Grogan et al. 2013; Suri et al. 2011; Soman et al. 2012a, b; Gauvin et al. 2012; Fozdar et al. 2011; Han et al. 2010; Zhang et al. 2012). Grogan et al. (2013) used the array of micro-mirrors to make scaffold of 3D structure by projecting the designed images onto the solution of photopolymerizable prepolymer (Grogan et al. 2013). The biomaterials are more pliable and have stiffness for micro-scale structures (Brown et al. 2005) than the PDMS platforms (Mak et al. 2011; Balaban et al. 2001; Vedula et al. 2012).

In addition, the versatility of the DMD-PP process allows rapid alterations of scaffold mechanical properties by altering the composition of the prepolymer solution. The DMD-PP method allows one to create 3D, biomimetic scaffolds in biomaterials with varying pattern design.

One study showed that the channel width did not influence on the migration speed of T1/2 cells, and these results similar with the in vivo study of cancer cell metastasis which identified that the morphology or physical interactions were changed via intravasation (Pathak and Kumar 2012; Gupta and Massagué 2006; Takeda et al. 2002). The procedure of cancer metastasis can describe the enhancing of migration speed by the thin channels (Pathak and Kumar 2012) and also explain the angiogenesis in advancement of tumors (Steeg 2006; Zetter 1998). The geometric signals could influence on the area of Hela cells or migration speed; dropping or promoting of cell area and migration speed. These results suggested that the size of vessel if important to the aggressiveness or metastasis of cancer cells (Gallego-Perez et al. 2012). So the different result in 10 T1/2 and Hela cells in geometric signals could suggest the appropriate plan to study about the metastasis of cancer.

6.3 What Is Coming Next in Cell Migration with Biomimetic Materials Research?

Until now, research on cell migration with biomimetic materials has been carried out using diverse ways; the molecular and structural levels of 2-D and 3-D situation. While all of these ways can make effective results, the methods for the homogeneous distribution and biocompatibility of scaffolds by cell migration needed to be focused with biomimetic materials. The studies about developing the plan for applying the effective methods should be progressed for cell migration with biomimetic materials.

Acknowledgement This research was supported by the Bio & Medical Technology Development Program of theNRF funded by the Korean government, MSIP (2017M3A9B3063638).

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