9 Microenvironmental Regulation of Stem Cell Behavior Through Biochemical and Biophysical Stimulation

Bogyu Choi, Deogil Kim, Inbo Han, and Soo-Hong Lee

9.1 Stem Cells

Stem cells are classified into totipotent, pluripotent, multipotent, and unipotent stem cells based on their differentiation potential (Revel 2009). Stem cells can self-renew and differentiate into other cell types, suggesting their use in various applications such as cell therapy, tissue engineering, and regenerative medicine. Therefore, it is important to develop methods to expand stem cells and induce their differentiation by using biochemical and/or biophysical stimulation to realize this potential.

9.1.1 Pluripotent Stem Cells

Pluripotent stem cells (PSCs) can proliferate perpetually and can differentiate into cells that form the three germ layers, namely, the endoderm, mesoderm, and ectoderm. PSCs are a valuable tool for stem cell therapy, in vitro drug screening, and disease modeling. PSCs include embryonic stem cells (ESCs), ESCs produced by somatic cell nuclear transfer (SCNT-ESCs), and induced PSCs (iPSCs). ESCs are derived from embryos at the developmental stage, SCNT-ESCs are produced by transferring nuclei of somatic cells into enucleated eggs, and iPSCs are artificially generated by reprogramming adult cells. In 2006, Takahashi and Yamanaka achieved a seminal breakthrough in stem cell production (Takahashi and Yamanaka 2006). They found that mouse embryonic fibroblasts (MEFs) can be reprogrammed into iPSCs by exogenous transcription of four factors, Oct4, Sox2, c-Myc, and Klf4. iPSCs are very similar to ESCs but are associated with less ethical concerns and show enhanced patient specificity. For iPSCs, increasing the reprogramming efficiency without the risk from genetic manipulation should be overcome.

9.1.2 Multipotent Stem Cells

Multipotent stem cells such as mesenchymal stem cells (MSCs) derived from the bone marrow, adipose tissue, umbilical cord blood, nerve tissue, dental pulp, hair follicle, or brain can also self-renew and differentiate into different cell types after biochemical and/or biophysical stimulation. MSCs derived from mesodermal tissues differentiate into mesodermal cells such as osteoblasts, chondrocytes, or adipocytes. However, some studies indicate that MSCs can also trans-

B. Choi · D. Kim
Department of Biomedical Science, CHA University, Seongnam-si, South Korea

I. Han
Department of Neurosurgery, CHA University, CHA Bundang Medical Center, Seongnam-si, South Korea
e-mail: hanib@cha.ac.kr

S.-H. Lee (✉)
Department of Medical Biotechnology, Dongguk University, Goyang-si, Gyeonggi-do, South Korea
e-mail: soohong@dongguk.edu

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differentiate into ectodermal or endodermal lineage cells in vitro when cultured in an induction medium containing some soluble factors (Brzoska et al. 2005; Damien and Allan 2015; Gao et al. 2014; Li et al. 2013). Some MSCs express growth factors and chemokines that induce cell proliferation and angiogenesis (Chen et al. 2008; Doorn et al. 2011; Haynesworth et al. 1996) and exert anti-inflammatory and immunomodulatory effects (Aggarwal and Pittenger 2005; Iyer and Rojas 2008). MSCs have been used for treating various disorders such as spinal cord injury, bone fracture, autoimmune disorder, rheumatoid arthritis, and hematopoietic defects.

9.2 Biochemical Stimulation

Biochemical components such as growth factors, cytokines, enzymes, peptides, chemical reagents, and small molecules are commonly added to cell culture medium to regulate stem cell differentiation. Moreover, biochemical components can be immobilized or precoated on cell culture substrates or scaffolds to induce the differentiation of stem cells into different cell lineages. Biochemical factors bind to receptors present on stem cells or enter stem cells to activate different cellular signaling pathways, thus modulating their behavior. Here, we will explore some existing methods for inducing stem cell differentiation with biochemical factors, as listed in Table 9.1.

9.2.1 Biochemical Differentiation of Multipotent Stem Cells

Osteogenic differentiation can be induced using soluble factors such as ascorbic acid, β-glycerophosphate, bone morphogenetic proteins (BMPs), dexamethasone, NEL-like molecule-1 (NELL-1), phenamil, or tauroursodeoxycholic acid (TUDCA). BMP-2 stimulates the expression of major osteogenic genes such as those encoding osteopontin, osteocalcin, and Runt-related transcription factor 2 (Sun et al. 2015). Although BMPs are suggested to be the most potent osteoinductive proteins, they also induce pro-adipogenesis (Hata et al. 2003; Jin et al. 2006). NELL-1 induces highly specific osteogenic differentiation of MSCs both in vitro and in vivo (Zhang et al. 2010). TUDCA, an endogenous hydrophilic bile acid, suppresses adipogenesis and promotes angiogenesis and osteogenesis by reducing ER stress, preventing unfolded protein response dysfunction, and stabilizing mitochondria (Cha et al. 2014; Cho et al. 2015; Kim et al. 2017; Vang et al. 2014; Yoon et al. 2016). Wnt protein, specifically Wnt3a and Wnt4, is another factor that induces osteogenic differentiation by activating YAP/TAZ accumulation in MSCs (Byun et al. 2014; Park et al. 2015).

Transforming growth factor-β1 (TGF-β1), TGF-β3, kartogenin (KGN), and matrilin-3 are used to enhance chondrogenic differentiation. TGF-β1-tethered photocrosslinkable hydrogel system enhances sulfated glycosaminoglycan accumulation in vitro and cartilage regeneration in vivo (Choi et al. 2015). TGF-β3 is more effective for inducing the chondrogenesis of MSCs than TGF-β1 and TGF-β2 (Barry et al. 2001; Estes et al. 2006). KGN, a new low-molecular-mass heterocyclic molecule, induced selective differentiation of MSCs into chondrocytes and promoted cartilage repair after its intra-articular injection into an animal model of osteoarthritis (Johnson et al. 2012). KGN-conjugated chitosan nanoparticles and microparticles also show potential as efficient intra-articular drug delivery systems for treating osteoarthritis (Kang et al. 2014). Matrilin-3, a non-collagenous extracellular matrix (ECM) protein, enhances the chondrogenic differentiation of adipose tissue-derived MSCs both in vitro and in vivo (Muttigi et al. 2017).

Poly-L-lysine (PLL) is coated on cell culture dishes to enhance cell adhesion through interaction between positive charges on PLL and negative charges on cell membrane (De Kruijff and Cullis 1980; Pachmann and Leibold 1976). Immobilization of PLL on cell culture plates increases the expansion and erythroid differentiation of human hematopoietic stem cells (HSCs) (Fig. 9.1) (Park et al. 2014). Moreover, PLL induces neural differentiation of MSCs (Cai et al. 2012).

Table 9.1 Biochemical factors that regulate cell behavior

Cell	Cell behavior	Biochemical factor	Reference
Human MSC	Chondrogenesis	TGF-β3	Barry et al. (2001)
		BMP-6	Estes et al. (2006)
		KGN	Johnson et al. (2012) and Kang et al. (2014)
		Matrilin-3	Muttigi et al. (2017)
	Osteogenesis	NELL-1	Zhang et al. (2010)
		TUDCA	Cha et al. (2014) and Kim et al. (2017)
Human/murine MSC	Osteogenesis	Wnt3a, Wnt4	Byun et al. (2014) and Park et al. (2015)
Human HSC	Erythropoiesis	PLL	Park et al. (2014)
	Neovascularization	TUDCA	Cho et al. (2015) and Yoon et al. (2016)
Murine MSC	Adipogenesis	BMP-2	Hata et al. (2003) and Jin et al. (2006)
	Chondrogenesis	TGF-β1	Choi et al. (2015)
	Osteogenesis	BMP-2	Sun et al. (2015)
Mouse neural progenitor cell	Neurogenesis	PLL	Cai et al. (2012)
Human PSC	Cardiomyogenesis	CHIR99021, DMH1	Aguilar et al. (2015) and Fonoudi et al. (2015)
	Neurogenesis	CHCHD2,	Zhu et al. (2016)
		Noggin, SB431542	Chambers et al. (2016)
		LDN, CHIR99021	Chambers et al. (2009)
	Astrogenesis	Retionic acid, FGF8, FGF2, EGF	Krencik et al. (2011)
	Pancreatic differentiation	Activin, Wnt, FGF-10, CYC, retinoic acid, DAPT, Ex4, IGF-1, HGF	D'Amour et al. (2006)
		Act A, CHIR, KGF, retinoic acid, SANT1, LDN, PdbU, SANT1, Heparin, Betacellullin, ALK5i, CMRL	Pagliuca et al. (2014)
		GDF8, FGF7, retinoic acid, GSK3βi, VitC, SANT, TPB, LDN, ALK5i II, T3, GSi XX, N-Cys, AXLi	Rezania et al. (2014)
MEF	Reprogramming into iPSC	Oct4, Sox2, c-Myc, Klf4 (OSMK)	Takahashi and Yamanaka (2006)
		OSMK + E-cadherin	Chen et al. (2010) and Redmer et al. (2011)
		ALK5 inhibitors in replace of Sox2	Huangfu et al. (2008a, b), Ichida et al. (2009), Lee et al. (2012), Lin et al. (2009), Mikkelsen et al. (2008), Staerk et al. (2011)

9.2.2 Biochemical Differentiation of Pluripotent Stem Cells

Biochemical differentiation of PSCs in vitro is traditionally achieved by inducing uncontrolled spontaneous differentiation or directed differentiation of these cells into specific cell lineages (Ding et al. 2017). Spontaneous differentiation produces a mixed population of cell lineages from all three germ layers, and the differentiation is uncontrollable. Directed differentiation of PSCs by using soluble factors can be successfully used to generate various cell types such as cardiomyocytes, neural cells, pancreatic beta

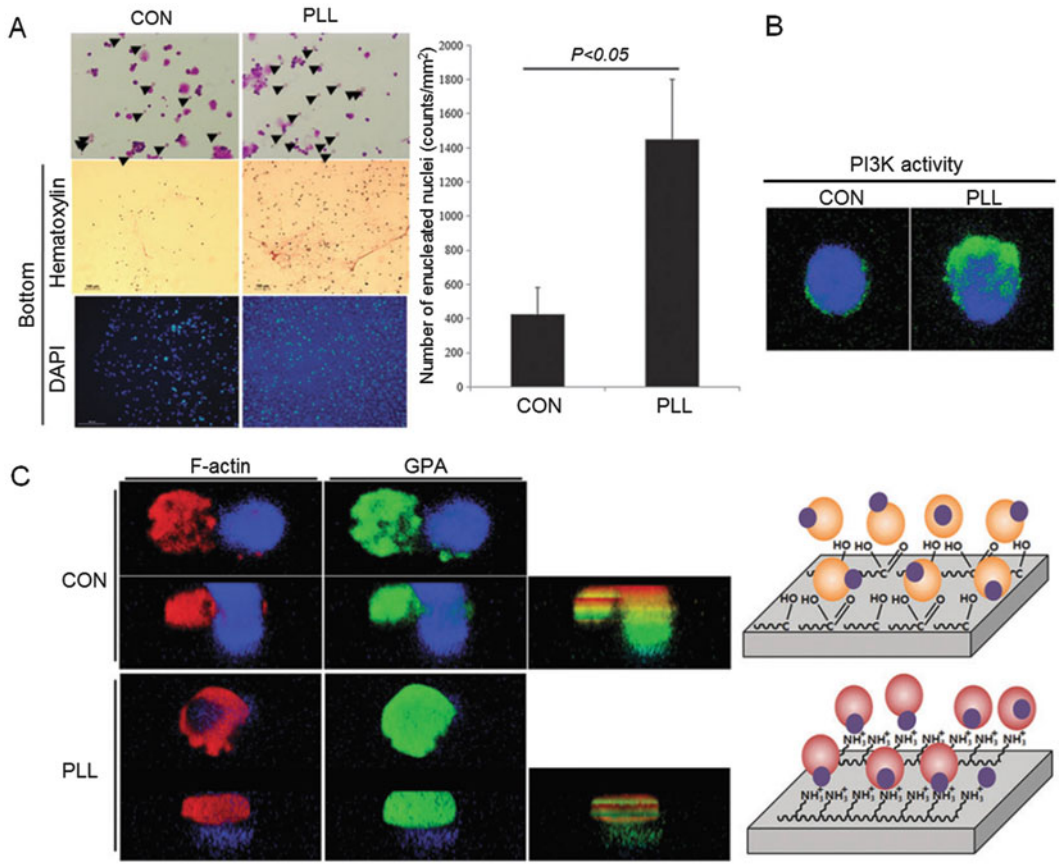

Fig. 9.1 Interaction between HSCs and PLL-coated substrate stimulates downward enucleation. PLL substrate enhances enucleation of HSC (**a**) through stimulation of PI3K activity (**b**). Furthermore, PLL substrate localizes the extruded nuclei downward (**c**), possibly due to the positive charge of PLL substrate

cells, and hepatocytes. However, the efficiency of and purity of cell types obtained through directed differentiation are low.

Functional cardiomyocytes can be produced by culturing EBs in a differentiation medium containing non-essential amino acids such as L-glutamine, β-mercaptoethanol, and 20% fetal bovine serum (FBS), followed by microdissection of beating areas (Zhang et al. 2009). Addition of small-molecule Wnt signaling inhibitors or activators, BMP inhibitors, or shRNA also induces the differentiation of PSCs into cardiomyocytes (Aguilar et al. 2015; Fonoudi et al. 2015; Zhang et al. 2013).

Various protocols have been developed for the neurogenic differentiation of PSCs. Differentiation of PSCs to neuroectoderms can be mediated with CHCHD2, a mitochondrial protein, that suppresses the TGF-β signaling pathway (Zhu et al. 2016). Highly pure astrocyte-like cells have been generated by adding retinoic acid, sonic hedgehog, epidermal growth factor, basic fibroblast growth factor (bFGF), ciliary neurotrophic factor, and 10% FBS to cell culture medium (Krencik et al. 2011). Neural cells can also be generated from PSCs by adding small-molecules to inhibit dual SMAD signaling and activate Wnt signaling (Chambers et al. 2009, 2016). Numerous clinical trials have assessed the potential of human iPSCs and ESCs to undergo neurogenesis for treating spinal cord injury and retinal diseases. However, generation

of mature neural cells from PSCs remains a challenge.

Pancreatic hormone-expressing endocrine cells can be successfully produced from human ESCs by adding and/or removing growth factors such as activin, Wnt, FGF-10, KAAD-cyclopamine (CYC), all-*trans* retinoic acid, γ-secretase inhibitor DAPT, exendin-4, insulin-like growth factor 1, and hepatocyte growth factor to and/or from cell culture medium over five-stages protocol (D'Amour et al. 2006). ViaCyte Inc. (San Diego, CA) is performing clinical trials to assess the efficacy of hESC-derived pancreatic endodermal cells for treating type I diabetes (Agulnick et al. 2015; Kimbrel and Lanza 2015). Addition of activin A, FGF, retinoic acid, BMP inhibitor (LDN), and some gene inhibitors also induces the pancreatic differentiation of PSCs (Pagliuca et al. 2014; Rezania et al. 2014). However, the complexity of these multistep protocols, cost of production, and scaling up should be overcome before using these strategies in clinical practice.

9.2.3 Biochemical Reprogramming Into iPSCs

Takahashi and Yamanaka showed that MEFs could be reprogrammed into iPSCs by inducing forced expression of four transcription factors, namely, OCT4, SOX2, c-MYC, and KLF4 (Yamanaka 4 factors), that are important for ESC function (Takahashi and Yamanaka 2006). This seminal development gave Yamanaka the 2012 Nobel Prize in Physiology or Medicine. Since this pioneering discovery, many researchers have developed various methods to enhance reprogramming efficiency by using biochemical factors. Overexpressed epithelial-cadherin can replace OCT4 during cellular reprogramming, thus enhancing reprogramming efficiency (Chen et al. 2010; Redmer et al. 2011). Addition of high concentration of FBS (>20%), ascorbic acid (vitamin C), histone deacetylase inhibitors, DNA methyltransferase inhibitor (5-azacytidine), or SB431542 (a TGF-β signaling inhibitor) to cell culture medium also enhances reprogramming efficiency (Esteban et al. 2010; Kwon et al. 2016). ALK5 inhibitor, LY364947 or E-616452, can be used to replace Sox2 to reprogram MEFs into iPSCs (Huangfu et al. 2008a, b; Ichida et al. 2009; Lee et al. 2012; Lin et al. 2009; Mikkelsen et al. 2008; Staerk et al. 2011), and CCAAT/enhancer-binding protein alpha (C/EBPα) can boost up the iPSC reprogramming efficiency by upregulating Klf4 and increase several chromatin-modifying complex proteins that activates pluripotency program (Di Stefano et al. 2016).

9.3 Biophysical Stimulation

Many researchers have extensively investigated the effects of various biophysical factors, including matrix stiffness, nanotopography, three-dimensionality, external stress and strain, electrical stimulation, hydrostatic pressure, electromagnetic field, ultrasound, and photostimulation, on cell behavior, as listed in Table 9.2.

9.3.1 Stiffness

In 2006, Engler showed that substrate stiffness regulated stem cell fates and was correlated with in vivo ECM elasticity (Fig. 9.2) (Engler et al. 2006). Human MSCs preferred neurogenesis, myogenesis, and osteogenesis on a soft gel (0.1−1 kPa) mimicking the mechanical stiffness of brain, on an intermediate gel (8−17 kPa) mimicking the mechanical stiffness of muscle, and on very stiff gel (25−40 kPa) mimicking the mechanical stiffness of bone, respectively. Human adipose tissue-derived MSCs undergo adipogenesis on a soft substrate (2 kPa) in the absence of inductive soluble biochemical factors (Young et al. 2013). Neural stem cells (NSCs) expressed high levels of neurogenic biomarker β-tubulin III on substrates having stiffness similar to the brain tissue (Saha et al. 2008). Increase in substrate stiffness increases the expression of type A lamin, a mechanosensitive cellular molecule (Swift et al. 2013). Skeletal muscle stem cells rapidly lose their regenerative potential when

Table 9.2 Biophysical factors that regulate cell behavior

Cell	Cell Behavior	Biophysical Factor	Reference
Human MSC	Differentiation (soft: neurogenesis, intermediate: myogenesis, stiff: osteogenesis)	Stiffness (soft: 0.1–1 kPa, intermediate: 8–17 kPa, stiff: 25–40 kPa)	Engler et al. (2006)
Human MSC	Adipogenesis	Stiffness (soft: 2 kPa)	Young et al. (2013)
Rat NSC	Neurogenesis	Stiffness (~500 Pa)	Saha et al. (2008)
Mouse cell/human MSC	Soft: adipogenesis Stiff: osteogenesis	Stiffness (soft: 0.3 kPa, stiff: 40 kPa)	Swift et al. (2013)
Mouse muscle stem cell	Self-renewal	Stiffness (soft: 12 kPa)	Gilbert et al. (2010)
Human PSC	Neurogenesis	Stiffness (0.1–0.7 kPa)	Keung et al. (2012)
MEF	Reprogramming into iPSC	Stiffness (soft: 0.1 kPa)	Choi et al. (2016)
Human MSC	Osteogenesis	Nanotopography	Dalby et al. (2007)
Mouse ESC	Differentiation	Nanotopography	Lapinte et al. (2013)
Human MSC	Multipotency	Nanotopography	McMurray et al. (2011)
Human iPSC	Pluripotency	Nanotopography	Reimer et al. (2016)
Human MSC	NPo: adipogenesis, NPi: osteogenesis	Nanotopography	Park et al. (2012)
Human PSC	Osteogenesis	Nanotopography	Kingham et al. (2013)
Human iPSC	Cardiogenesis	Topography (microgrooved surface)	Rao et al. (2013)
Human MSC	Neurogenesis	Topography (nanogratings surface)	Yim et al. (2007)
MEF	Reprogamming into iPSC	Topography (microgrooved surface)	Downing et al. (2013)
Human MSC	Myogenesis	Cyclic strain	Gong and Niklason (2008)
Human MSC	Osteogenesis	Cyclic uniaxial tension	Haudenschild et al. (2009)
Human MSC	Chondrogenesis	Dynamic compression	Haudenschild et al. (2009)
Mouse skin fibroblast	Reprogramming into iPSC	Orbital shaking	Sia et al. (2016)
Human PSC	Vascular smooth muscle cell	Tensile stress	Wanjare et al. (2015)
Human MSC	High tension: osteogenesis Low tension: adipogenesis	Intracellular tension	McMurray et al. (2011)
Human MSC	Endothelial differentiation	Shear stress	Dan et al. (2015)
Human iPSC	Cardiomyogenesis	Electrical field	Hirt et al. (2014)
Human NSC	Cell migration	Electrical field	Feng et al. (2012)
Human NSC	Neurogenesis	Electrical field	Pires et al. (2015) and Thrivikraman et al. (2014)
Mouse fibroblast or human dermal fibroblast	Reprogramming into iPSC	Extremely low-frequency electromagnetic field	Baek et al. (2014)
Human MSC	Osteogenesis	LIPUS	Kang et al. (2013)
Human iPS	Neurogenesis	LIPUS	Lv et al. (2013)
Human epidermal stem cell	Proliferation, cell migration	He-Ne laser (632.8 nm)	Liao et al. (2014)
Mouse MSC	Osteogenesis	Visible blue light (405 nm)	Kushibiki and Awazu (2009)

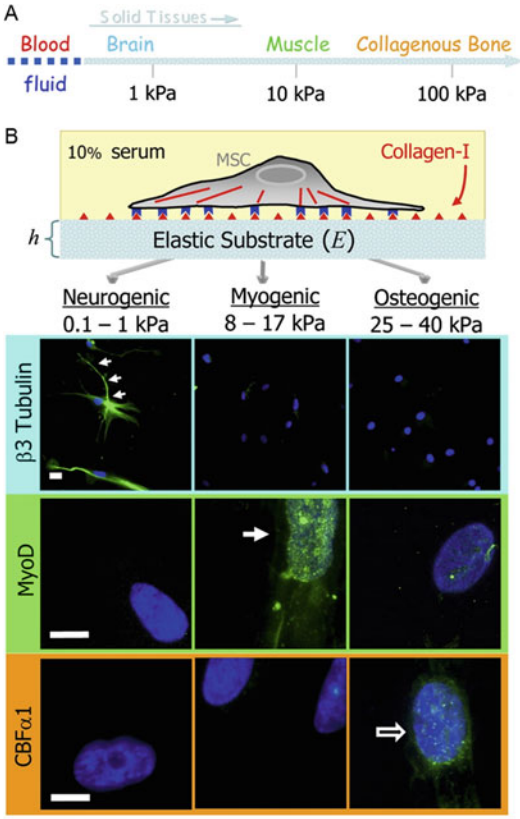

Fig. 9.2 MSC differentiation is regulated by substrate stiffness. Different solid tissues are made up of specific range of elastic modulus (**a**). Through substrate modifications to various matrices that mimic each solid tissue, MSC differentiates to each lineages (**b**)

grown on stiff culture dishes but retain their self-renewal and regenerative capacities when grown on soft hydrogels (Gilbert et al. 2010). Substrates with different stiffness induce the differentiation of different stem cells in a similar manner. Optimal substrate stiffness for the differentiation of stem cells into specific lineages differs based on stem cell source, substrate used, and differentiation protocol used. PSCs also sense and respond with the stiffness of microenvironments. Soft microenvironments (0.1−0.7 kPa) promote early neurogenic differentiation of human PSCs without affecting their proliferation (Keung et al. 2012).

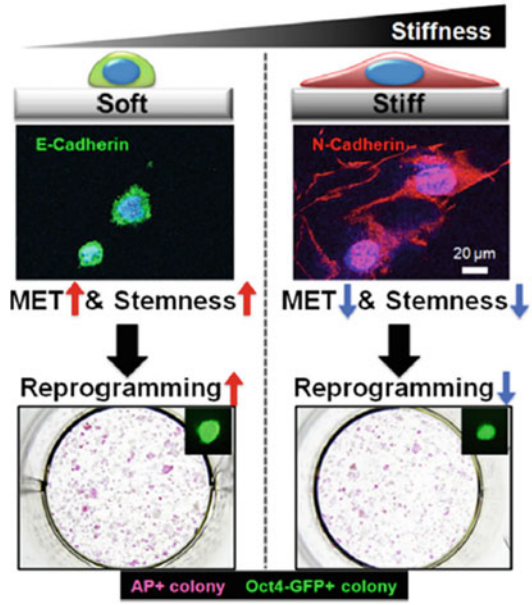

Fig. 9.3 Generation of iPSCs is affected by matrix stiffness. As the substrate softens, MET change and stemness increase, resulting enhanced reprogramming efficiency into iPSCs

Generation of iPSCs is also affected by substrate stiffness. Soft substrates enhance reprogramming efficiency by increasing the expression of MET and pluripotent markers (Fig. 9.3) (Choi et al. 2016).

9.3.2 Topography

Stem cell adhesion, phenotype, and differentiation are highly sensitive to substrate topography (Dalby et al. 2014; Ding et al. 2017; Griffin et al. 2015; Park and Im 2015). The effect of surface topography on stem cell phenotype depends on the shape (pillars, pits, and gratings), dimension (feature size, spacing, and height), arrangement, and composition of a substrate (Dalby et al. 2007; Lapointe et al. 2013; Murphy et al. 2014; Wang et al. 2015). Presence of highly ordered nanoscale pitted patterns in a substrate inhibits the adhesion of cells to the substrate (Dalby et al. 2007).

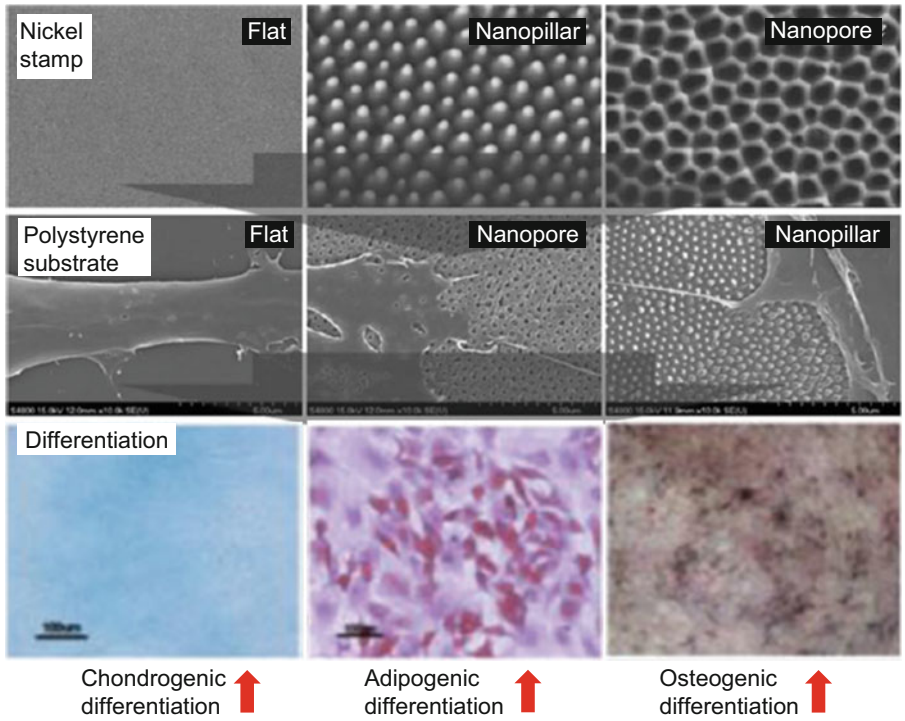

Fig. 9.4 Behavior of ASCs cultured on NPo- and NPi-containing substrates. Fabrication of each nano-featured polystyrene substrates were established using fabricated nickel stamp, and ASC differentiation trends show each flat, NPo, and NPi surface enhances chondrogenic, adipogenic, and osteogenic differentiation, respectively

Expression of human bone marrow-derived MSC (BMSC) and adipose-derived MSC (ASC) markers depends on the size of pits (McMurray et al. 2011). High-density arrangement of smaller topographical features promotes the proliferation and pluripotency of human iPSCs (Reimer et al. 2016).

Substrates with 120-nm diameter pits and an average 300-nm spacing (randomly offset by 50 nm) induce the osteogenesis of human BMSCs (Dalby et al. 2007). Human ASCs cultured on a polystyrene surface containing nanopores (NPo; 200-nm diameter/400-nm depth) undergo enhanced adipogenic differentiation, while those cultured on a polystyrene surface containing nanopillars (NPi; 200-nm diameter/650-nm height) undergo osteogenic differentiation (Fig. 9.4) (Park et al. 2012). Disordered nanotopographies enhance the osteogenesis of human ESCs (Kingham et al. 2013). Fibronectin-coated microgrooves (4-μm width/10-μm depth/10-μm spacing) improve the maturation and function of human iPSC-derived cardiomyocytes (Rao et al. 2013). Human MSCs cultured on 350-nm PDMS nanogratings show significantly upregulated expression of neuronal markers β-tubulin III and microtubule-associated protein 2 compared with human MSCs cultured on microgratings and flat surface (Yim et al. 2007).

Substrate topography also affects the reprogramming of MEFs into iPSCs (Downing et al. 2013). Elongation of MEFs on parallel microgrooved surfaces modulates epigenetic states and improves reprogramming efficiency.

9.3.3 External Stress and Strain

In addition to the intrinsic physical properties of the stem cell microenvironment, such as substrate stiffness, extrinsic mechanical stimuli such as stress or strain are important for regulating the differentiation of stem cells (Keung et al. 2010).

Cyclic strain inhibits the differentiation of hESCs by upregulating the phosphorylation of TGF-β1, activin A, Nodal, and SMAD2/3 and promotes the myogenesis of BMSCs (Gong and Niklason 2008). Cyclic uniaxial tension induces the osteogenesis and dynamic compression induces the chondrogenesis of human BMSCs (Haudenschild et al. 2009). Dynamic culturing with orbital shaking at 100 rpm significantly improves the reprogramming efficiency of iPSCs (Sia et al. 2016). In the presence of uniaxial tensile strain, vascular smooth muscle cells derived from human iPSCs and human ESCs align perpendicular to the strain axis and show increased ECM gene expression (Wanjare et al. 2015). Compressive and tensile forces induced by fluid flow, cell–cell interaction, and cell–matrix interaction regulate MSC behavior in vivo (Hao et al. 2015; Liu and Lee 2014). Human BMSCs with high intracellular tension differentiate into osteoblasts, whereas those with low intracellular tension or low actin–myosin interaction differentiate into adipocytes (McMurray et al. 2011). Shear stress stimulates the differentiation of human MSCs obtained from different tissues into endothelial-like cells (Dan et al. 2015).

9.3.4 Non-contact-Dependent Factors: Electric Field, Ultrasound, and Photostimulation

In addition to cell–matrix interaction-dependent factors such as substrate stiffness and topography, non-contact-dependent factors such as electromagnetic field, low-intensity pulsed ultrasound (LIPUS), and light of varying wavelengths affect stem cell behavior.

Electrical stimulation is of interest for both cardiac and neural differentiation because of its importance in embryonic development. Pulsed biphasic electrical field of 2 V/cm every 4 ms promotes human iPSC-derived cardiomyocytes to develop a phenotype similar to native cardiomyocytes (Hirt et al. 2014). Human ESC-derived NSCs migrate toward positive charged regions in the presence of a small direct-current electrical field (Feng et al. 2012). Application of an electrical field to NSCs or BMSCs grown on an electroconductive matrix enhances their neurogenesis (Pires et al. 2015; Thrivikraman et al. 2014). Extremely low-frequency electromagnetic fields replace SOX2, KLF4, and c-MYC during somatic cell reprogramming of iPSCs (Baek et al. 2014).

Ultrasound frequencies also regulate stem cell behavior. LIPUS enhances the osteogenic differentiation of human ASCs and is used for bone fracture healing and callus distraction (Claes and Willie 2007; Kang et al. 2013). LIPUS stimulation enhances the proliferation and neural differentiation of human iPSC-derived neural crest stem cells (Lv et al. 2013).

Photostimulation also modulates stem cell behavior. Irradiation with helium–neon lasers (632.8 nm), which are used clinically to promote wound healing, induces the proliferation and migration of human epidermal stem cells (Liao et al. 2014). Irradiation with visible blue light (405 nm) enhances the osteogenesis of and bone formation by mouse MSCs (Kushibiki and Awazu 2009).

9.4 Conclusion

Stem cells are a very promising cell source for the cell therapy of various diseases because of their self-renewal and differentiation capacities. For successful application of stem cells and biomaterials in tissue engineering and regenerative medicine, stem cell behavior such as adhesion, proliferation, survival, and differentiation in response to biochemical and biophysical cues

must be precisely regulated. Furthermore, results of biochemical and biophysical stimulation studies involving three-dimensional microenvironments will play an important role in more accurately predicting the in vivo behavior of stem cells.

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