Cell-Surface Interaction and Biological Behavior of Cells: An Overview

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Generally, cell interactions with the surface of biomaterials are mediated by chemical groups and biological intermediates. Cell behavior includes adhesion, proliferation, migration, differentiation, and function can be under the impression of cell-surface interaction. Therefore, Knowledge of cell-surface interaction is useful in the engineering and production of ideal cell-tissue based products. According to this important, this study was designed to review the interaction between cells and the surface of polymeric structures in cell culture conditions. This study gave an overview of the effects of key parameters on cell attachment, proliferation, migration, differentiation, and cell fate in culture. The cell-material surface interactions focus on the communication between surface properties of the substrate, protein/water adsorption, cell adhesion, and its function. Surface modification as compared to non-modified surface improves the intrinsic properties of a surface which yields a convenience of the biocompatible construct. However, the quality of notable parameters between cell and surface express the main role in tissue engineering, and subsequent can be led to high- quality cell-tissue based products.

Keywords: Cell Interaction; Biomaterials; Tissue Engineering; Attachment; Differentiation; Migration

Introduction

Tissue engineering is an interdisciplinary field that defined as the combination of cells and engineered material (scaffolds) alone/or alongside bioreactor technologies. The dynamic structure and the composition of the novel bio-materials provide the cell fate through cell-matrix interactions (1). In an ideal description of tissue engineering, the bio-compatible material is a necessary component to prevent an unacceptable influence (1, 2). The most basic objective of bio-compatibility is essential to promote specific cell fates from attachment to a stable differentiated phenotype (3). The proteins like collagen and elastin with diameter ranging between 10- 300 nm generate the fibrillar framework of extra cellular matrix (ECM). In addition, ECM proteins alongside glycosaminoglycan's provide the cell binding sites (4). Therefore, in a successful clinical trial along with commercial issues, the improvement of scaffold should be engaged the size, shape, mechanical properties and intricate relationships with cells and host tissues (3). On the other hand, the dynamic balance between cells and a three-dimensional environment is a considerable tremendous phenomenon during cell growth and terminal differentiation (5). Tissue engineering must be promoted as a self-healing therapy for body tissues and the serial biological events are triggered in response to the surrounding matrix by cellular attachment (1). These interactions mediate cell signaling networks and are influenced by the various structural parameters and surface chemistry. Additionally, the bio-mimetic surfaces with nano-patterns and defined functional groups enhance the cellular spreading more growth, differentiation and motility (5, 6). Therefore, the knowledge of the cell niches and scaffold environments is required for exploring biophysical and immobilized signaling processes to further control over cell fate on the engineered construct. In this study, the biological behavior of cells alongside to attachment properties of different bio-materials has been reviewed.

The present study, in light of the above introduction, describes the cell-surface interaction and the biological behavior of cells in particular. This aspect of tissue engineering is examined furthermore and the cell-surface interaction which are important for the cell-tissue production are discussed in detail. Google Scholar, Scopus, and MEDLINE databases were searched for relevant articles. The main keywords used in the search were "cell" OR "cellular" AND "surface" OR "polymer" AND "interaction". Then, the merits and limitations of recently published papers on the topic of our study were discussed.

Cell Attachment and Agents

Commonly, synthetic scaffolds require further protein or peptides to ameliorate cell attachment and matrix degradation. Fibronectin (FN) promotes the cellular attachment by mediating of integrins and via different concentrations of the various types of adsorbed proteins, which will alter the cellular attachment subsequently (7). Keselowsky *et al.* showed the adsorption of fibronectin and integrin determine surface chemistry and the level of hydrophilicity which affect the cellular recognition and cell activity (8). On the other hand, the attached cell numbers and DNA synthesis rate are increased by induction to more adhesion. If the adherent sites on the cell or substrate surface are suppressed, less attachment and DNA synthesis will happen immediately. In a study, for determination of DNA synthesis during the cellular attachment, [3H]thymidine was added to the culture medium and was compared to the cell numbers (8). The results of DNA synthesis correspond to the percentage of attached cells that are created by ongoing proliferation (8). However, in the absence of cell attaching agents like FN along with FGF, endothelial cells lost their growth potency gradually (9, 10) due to using a high concentration of RGD-containing peptides, cell growth promoted successfully. Thus, fibronectin just works by binding of its RGD segments with integrins on the cell surface (9, 10) and the cells enter to synthetic cycle from G0 to S phase by over expression of regarding genes (9). In another study for determination of the essential role of RGD sequence, soluble GRGDSP (Gly-Arg-Gly-Asp-Ser-Pro) or GRGESP (Gly-Arg-Gly-Glu-Ser-Pro) hexa-peptides were applied on the plate surface. These proteins with the concentration greater than ≈10 ng/ml, inhibited the cellular attachment by occupying membrane receptors via their adhering segments of FN (9). Poly HEMA (poly hydroxyethylmethacrylate) was other reactive agent with RGD sequence which has been used to suppress the cell attachment by the intervention of cell-surface interactions (9, 11, 12).

On the other hand, 9- 12 nm RGD motif acts are known as the adhering molecule to ECM and cells. The surface coverage with a sufficient density of RGD is crucial for cell differentiation as well as spreading and the inter-spacing of RGD of 58 nm perfectly able to make the cell adhesion (13). The main role of RGD was determined by Kafi *et al.* (14). They focused on RGD array establishment on silicon-based Au surfaces to fabricate the 2D/3D-nanostructures. The mat was ordered as nano-dots with the islands of 35 nm and a diameter of 70-75 nm. The 3D-RGD array was made into nano-rod (45 nm distance and 62 nm diameter) and nanopillar (35-40 nm diameter and 65-70 nm distance) (14). This assessment confirmed that a substrate with a controlled and special architecture surface determines the array of deposited proteins. However, the cell attachment and spreading were significantly higher on 3D-nanopillar array due to more binding sites for integrin. Thereupon, cells tended to enhance the adherent strength on 3D-RGD nanopillar modified Au substrates compared to other modified and non-modified substrates (14).

The other important adhering molecule which referred as one of the major bio-molecules within ECM is Collagen. The different density of collagen produces a special force and morphology and the successful cell linkages with substrate is happen with a transition level of collagen density at ≤ 160 μm^{-2} (15). So a suppressive effect will be happened on the surface adhesion when the collagen density is more or less than 160 μm^{-2}. With the different density of collagen, the applied force on the surface would change and at the high collagen density, the surface force becomes 1.0 pN which is lower than the needed force for trapping of an integrin segment (15).

Cell Attachment and Cell Cycle

The regulation of cell morphology and growth by adhering proteins like FN with RGD sequence involves the cytoskeleton network. Thus the attachment of cells with FN alters the function of transmembrane proteins or ion channels and starts the regulation of growth regulation (11, 12). The induction of intracellular signaling pathways depends on the transmembrane and cytoskeleton components (16). For example, the cell spreading on FN is capable to activate Na+/H' antiporter. Consequently, the cellular growth is suppressed by inhibition of this channels (9). Extra-cellular matrix (ECM) is one of the sequential conversions within the metastasis of tumor. Adhesive molecules of ECM are elucidated to shift and fluctuation of the cell attachment to ECM and endothelial cells makes the metastasis in tumor (17). Recently, human hepatoma SMMC-7721 cells were investigated and the contribution of adhesive molecule including integrin β1 showed the notability of cell adhesion to the endothelial cells. The higher expression of integrin β1 makes SMMC-7721 cells able to have a stronger adhesive force compare to the endothelial cell and promote cell cycle to S phase (18).

As mentioned, the interactions with ECM lunch signaling which is terminated to nucleus and proliferation. Gigges *et al.* demonstrated that the primary human osteoblasts (HOB) showed fewer S-phase cells on a nano-scale pit with near disordered arrays. That was because of the more cell spread, stronger

contractile stress and larger adhesion complexes on near disordered surfaces in comparison with other ordered substrates (18). Furthermore, Saos-2 osteosarcoma cells were studied using force spectroscopy for quantification of the adhesion force during cell cycle (19, 20) Weder *et al.* demonstrated that the less cell attachment had been happened during mitosis by changes both surface and cytoplasmic proteins. After S-phase, the work of detachment has been started to reduce to G2/M under the reorganization of cytoskeleton proteins rather than cell surface proteins (21). Yang *et al.* reported that a cell cycle inhibitor like p27 is able to eliminate the beneficial impression of the adequate adhesion for conduction of the cell proliferation. The addition of Lovastatin and Farnesol (for inhibiting of S-phase), ECM tensile forces was dissipated to enter the cell cycle. In this way, after autophosphorylation of focal adhesion kinase (FAK) on Tyr-397, some signaling proteins such as Src family kinases, p85, the regulatory subunit of PI3K, phospholipase C-γ and Grb7 are activated. In the following, the proceeding of signaling rout ends up MAP kinase cascade to regulate cell cycle progression (22). In a same way, The capillary development and more extended of endothelial cells on ECM molecules under the angiogenic mitogens represented the urgent motivating potential of FGF (9).

The three-dimensional (3D) fate of cells in vivo is related to the balance of cellular force and involved substrates resistance. So the alteration of surface molecular architecture subsequently will change the outcome of this balance and makes the different biochemical events. The reason could be related to the thermodynamic and kinetic properties of cellular attachment that are changed during the cell growth cycle (23, 24). Thus, in the following bio-mimicry, 3D of collagen gels should mimic the connective tissue for cultured cells efficiently. On the other way, collagen gels are studied for considering the tumor and cellular interactions with the environment (15). The 3D structure of collagen is considered as mechanically stressed gels and cells receive the isometric tension. Thus by detaching cell loaded gels from the plate's surface, cells would be relaxed and unloaded (25).

Cell Attachment and Mechanism

The direction and magnitude of applied force alter FACs positions the same as the intracellular components by transfer of tensions from integrins .In a study by Chicurel *et al.* the response of neurotransmitter to mechanical tension is applied across integrins by the release of calcium (25). By studying of the site of applied force, the FAC adhesions are the enough rapid components of membrane for transduction of signals. Thereupon, the changes in ECM mechanics affect on FAC position inside the cellular membrane and these alterations lead to cytoskeleton structure of the cell. For instance, by impressing of integrins with microbeads released intracellular calcium in the response of magnetic forces in spite of other membrane receptors additionally, the tissue development is guided by modulation of gene expression under the signal transduction. Thus cell cycle events as proliferation, maturation, migration, and apoptosis are selected on the basis of transitions that come from ECM and are able to influence inside cellular components. By restriction of cells on the smaller adhesive areas, the cell cycle is led to apoptosis and DNA synthesis is reduced gradually. In contrast, the separation of these regions in 3-5 nm diameter as the size of FAC, the cells are flattened and started to proliferate in the response to the better extension (26). Even about cultured smooth muscle cells, contraction by cytoskeleton distortion could be modulated (26). Yeung *et al.* introduced the surfaces with the various level of elastic moduli were derived from Acrylamide (27). Their results approved that the cell extended morphology and attachment caused the higher expression of α5-integrin on stiff surfaces which were made by the function of more cross-linkers. Thus the strong adhesion is generated by the higher contractile force of cytoskeleton which binds to integrins (27). The total generated force by separated focal adherent regions is assumed as a sufficient force compare to the force which is generated by a larger area. By studying of cardiac myocytes, it is clarified that the force direction of focal adhesions is determined by the direction of pattered elastic dots on the surface. Since the forces of myocytes (~70 nN) unlike fibroblasts (~20 nN) were higher, so the area with vinculin adhesions was larger, too. For studying the dynamic behavior of focal adhesions, 2, 3-butanedione monoxime (BDM) is used for the inhibition of actomyosin contractions. When the generated force of fibroblast attachment was coordinated with the durability of focal adhesions, the relaxation time of focal adhesions forces was increased. On the other hand, the focal attachments number is reduced in result of the correlation. In principle, the resulted force ends up to force per molecule as a magnitude of 1 pN that is lower than the measured force of an individual focal adhesion (28). Therefore, as mentioned, the cellular dynamic behavior is considered that the applied force on focal adhesions alters the conformation of multi molecular compartments and finally their new folding would lead to a new binding activity. This phenomenon is seen apparently when the embryo receives the applied forces from the surrounding environment. The fate of the different embryo layers is determined as special morphogenesis and differentiation on the basis of applied force from other cell types.

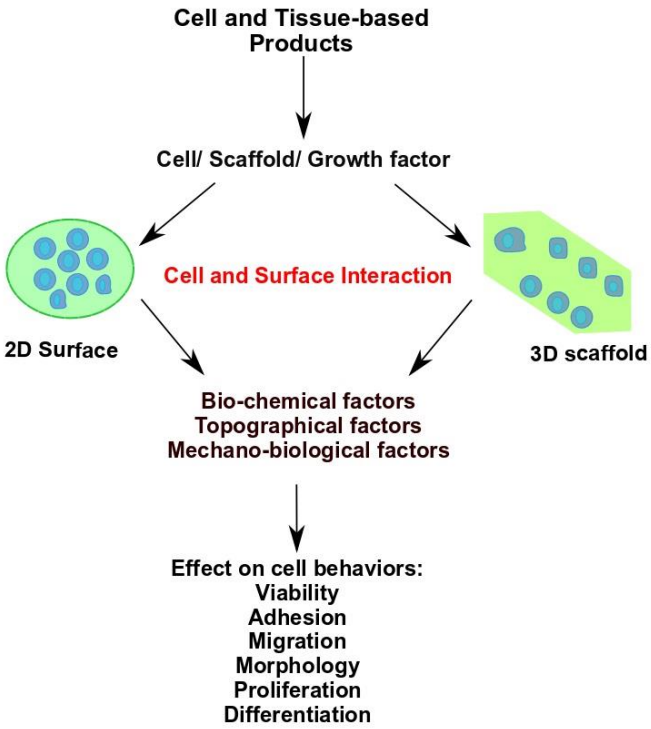

Figure 1: Scheme of the cell-surface interaction and effects on cellular behavior

The Cell Attachment and Migration

Recently, it was approved that shear stress affects the size of dental tissue and the expression of alkaline phosphates. The size of new tissue and gene expression arising from shear stress, confirms that the cell differentiation is influenced by mechanical tensions strongly. Thus, the up-regulation of ALP activity of cell-polymer construct under shear stress exposed the modulation of differentiation (29).

In addition, by applying shear stress, cells induce to reorient in the direction of flow, but cell behavior tends to be perpendicular to the direction of stretching by higher rate of ECM protein generation (30). So the cell behavior changes when cells are cultured on the stiff or soft region (Figure 1). In a study, the rate of cell migration was investigated on the substrate rigidity by a gradient of collagen. The less displacement of the receptor-ligand complex made larger tension on rough portions. Thus, cells receive higher power for activation of tyrosine phosphorylation which leads to a stronger migration. Furthermore, the cells were cultured on soft substrate, started to move over a long distance to land on a substrate with the stronger receptor-ligand complex in stiff portion (31). Summary, the attachment on the stiff surface provides more force that applies to an embedded environment. Thus, more calcium influx makes stronger interactions and migration to stiff regions.

Besides, the adsorption or capture of proteins rapidly happens in presence of the hydrophobic surface. The interaction between proteins and a hydrophobic substrate is performed by specific linkages against a hydrophilic surface (30). Generally, there is a significant inverse relationship between the roughness and hydrophobicity magnitude. The major difference between 2D and 3D substrates is considered the amount of stiffness that determines the force of cell contraction (23, 32). During the interaction of the cell and the surface, generation of forces by myosin and actin within the structure of cytoskeleton makes a movement as 5 nm with an average force of 3-4 pN. On the other hand, the more ligand density result in higher traction forces between the cells and the surface. Accordingly, the higher degree of substrate stiffness implies larger focal adhesions. Effectively, the cell migration strength should be confined by increasing traction force (30). Generally, the surface stiffness is postulated to guide the cellular movements because of enhancement of the myosin activation (31). Based on the above mentioned, if cells were restricted on the small islands (30 μm^2), the cell extension would be more appropriate and be able to lunch the proliferation cycle by entry into S phase. After auto-phosphorylation of focal adhesion kinase (FAK) on Tyr-397, some signaling proteins such as Src family kinases, p85, regulatory subunit of PI3K, phospholipase C-γ and Grb7 are activated in following of the proceeding of signaling rout ends up MAP kinase cascade to regulate cell cycle progression (23). The cell extension ability is noticeably more than the most ECM binding under the limitation of applied force in small areas for focal adhesions (33). Besides, the compressive force is able to induce tendency into the differentiating phase by overexpression of special genes. For instance, an optimal compressive force on the human osteoblastic cell line Saos-2 motivated the production of bone morphogenetic proteins (BMPs) to make a stronger differentiation (34, 35).

The Nanoscale and Cell Attachment

A scaffolds could be reinforced with a culture surface and some bioactive molecules (36, 37). For example; reduction in fiber diameter leads to the higher ratio of the surface for cell attachment expose (36, 38). The most difference between a nano-textured surface and a flat substrate is discussed about the surface energy. At first, the decreased air content on a nano-topographical surface makes the lower contact angle which is stated by Cassie–Baxter equation (39). A nano-topographical structure with 13 nm islands significantly is able to induce more cell extension (30). Electro-

spining constructs scaffolds by various parameters such as diameter and direction of fibers. In a study by Kumbar *et al.* PLGA was electrospuned into matrices by the range of fiber diameter as 150– 225, 200–300, 250–467 and 500–900 nm (40). After cell seeding, the separated effect of these scaffolds was investigated via the fluctuated expression of collagen types I and III as well as elastin (40). Thus the varying fiber diameters influence on the expression level of ECM structural proteins (40).

In tissue engineering field, the wound healing process strongly depends on the composition of ECM (38, 41, 42)). Thus, for the successful establishment of a new tissue, not only the appropriate cell extension is very important, but also having a suitable mechanical property of ECM is known as a serious requirement (42). Alternatively, scaffolds like PLGA provide the extended qualities by the alteration of surface area (40). The Micrographing of a surface with typical mean heights of 13 nm, diameters of 263 nm and center to center spacing of 527 nm by AFM, presents the cell extension possesses a proper morphological property (43). The influence of surface nano-topography on the bone healing was described by Sabattini *et al.* They analyzed the response of bone mesenchymal stem cells and osteoblasts on Oseean surface which was made by Ca and P impregnation. Alkaline phosphatase (ALP) as a specific marker of bone differentiation showed significantly higher expression due to induction of its nano-topographycal surface properties. The surface chemistry of Ca and P on this nano-textured substrate could be another factor for stronger differentiation (44). The electrospun nano-fibers provide high surface area and porosity for seeded cells which need the appropriate interactions (45). The nano patterned surface enable to afford the cell requirement for perfect adhesion and differentiation. Electrospin technologies could be provided a nano-fibrous scaffold through nano diameter, regular and parallel fibers (46). As mentioned, cell behaviors including adhesion, proliferation, migration and differentiation rely on the favorable interactions and as well as biocompatibility of scaffolds. On the other hand, electrospinning process can prepare scaffolds with aligned directed fibers. For myo-tubes differentiation, it is needed the orientation of the cells in along the same longitudinal axis for the more powerful contraction. Skeletal muscle cells are matured by formation of multinuclear cells in the result of cell fusion and the gene expression of cultured cells on aligned and random scaffold which confirm this outcome (45). The same as culture plate, the impact of substrate stiffness on scaffold was evaluated using of the calcium or barium cross-linker gradient by Genes (47). Based on their results, cross-linkers made a surface with more stiffness by modulus measurement for chondrocyts. The more stiffness is not applicably the reason of absolute attachments, but decreases linearly time needed for adhesion (47). In the similar way, TiOx substrate which had been made by supersonic cluster beam deposition (SCBD) had a surface roughness ranging from 15 to 30 nm. So the nano-scale morphology reflects more available area as the nucleation site of proteins (48). In another study, the micro-topography architecture on quartz was used as cavities by pit diameter of 7, 15 and 25 μm and pit distance of 20 and 40 for determination of fibroblast behavior by Catherine C (49). Berry *et al.* reported that among the whole 2D curved groups, sized pit of 7:20 showed the higher proliferation rate, migration speed and more entering cells. In the following of bio-mimicry, the structured of 7 μm pitted substrate has considered in the mesh size of collagen from 14 to 5 μm (48). Additionally, OCT-1 osteoblast-like cell was analyzed by Wan *et al.* on the both pit and islands PLLA and PS surfaces and compared with non-islands patterned PLLA. This study showed that the cell stretching on pit or islands-patterned substrate by 2.2 and 0.45 μm made the cultured cells have more contact angle and cell height. On the other hand, SEM studies proved that cells extended pseudopods which inserted into the patterned islands with more proliferative potency(50).

The seeded cells on different aligned scaffolds are able to apply the cell distinguished arrangement. Similarly, the unpatterned direction of micro-channels influences to be disordered the cell orientation in contrast to the parallel alignment of micro-channels due to contact guidance. The micro-channels confinement could affect cell behavior through cell orientation is the same on patterned and unpatterned of micro-channels. The threshold value of micro-channels width was between 120 and 270 μm for prescription of the cell manner on a surface (51). More cell attachment and differentiation on nano-scaled texture could be due to the role of nanoparticles curvature on folding of adsorbed proteins i.e. albumin and fibrinogen (52). So it could be concluded that the behavior of some other proteins such as fibronectine, collagen and elastin may alter in the contact with nano-topography. Absolutely, the cell behavior on different topological surfaces is dependent on cell type. That is because the various cell spreading changes focal adhesion signaling and cytoskeleton contractibility by the alteration of actin and myosin assembly. In spite of this, the receptor proteins for cell attachment could be immobilized on the culture substrate. DDS technology stabilizes proteins with authentic folding and hampers their denaturation to facilitate the cell recognition (53).

Determination of the least number for adherent special proteins as RGD receptors should be studied into constitute of

equivalent focal adhesions. Thus the microstructured surfaces of gold nanoparticles were ranging the square from 6 to 3000 per adhesive patch and were activated by c (-RGDfK-)-thiol peptides. These gold nanoparticles within squares were made as ~58 nm as extent as focal adhesion sites and due to extension of paxilline domains based on applied surface force, sized square lower than 500 nm had the stabilized attachments. The highest actin-connected paxillin domain length was discerned on squares of 100 nm (8). On the contrary, the electrical conductivity influences the optimum reactions between the cells and substrate. Carboxylated SWNT can be entrapped in collagen matrices for the augmentation of electrical conductivity by MacDonald *et al.* Here is considered after the living cells were attached to collagen, they will be able to remodel the direction of SWNT embedded in the collagen matrix. As far as increasing the amount of SWNT, the percentage of the attached cells is decreased by the reduction of compact collagen (54).

The chemical properties of surface as a director to cell adhesion

Chemical treatment results in the surface endure a severe degradation that will lead to more roughness (55). Surface charge is known as a substantial factor that is able to change the cell fate. At a higher degree of surface charge density, the modulation of more cell attachment is expected as well as the adsorption of proteins. So, if the charge type, positive or negative, are changed by different functional groups, the spreading and differentiation rate of the cell will have another specific pattern (56). Chemical groups as carboxylic SAM are negatively charged and so provide a hydrophilic condition for the cell attachment (56). Thus the modification of the surface with OH-terminated SAMs acts similarly to the cell adhesion on phosphoryl-choline substrate (57). The self-assembly mono-layers of alkyl-thiols for modulation of the cell attachment and spreading was evaluated by McClary et al. The prepared hydrophilic surface with carboxyl-terminated groups provide less than 20° contact angle and support cell attachment via reducing of contact angle (58). Studying the extended filopodia on the animated substrate demonstrated that stronger adhesion could be resulted by hydrophilic groups (59). Other chemical groups similar to aminated PES along with various combinations of early acting cytokines exposed to which the positive charge promotes the cell adhesion. In this case, the surface with amine groups and CD34 antigens is capable to activate the signaling pathways into proliferative fate (59). In another study, Richert *et al.* reported the chemical modification on titanium alloy by H2SO4/H2O2 produced nano-micro textured surfaces during the different times of treatment. In addition, with increasing the treatment time from nano-topography to micro size, the three different cell lines will respond differently and the micro-structured surface will return to the result of the control group. Thus, here the chemical properties of substrate influence on the cell behavior rather than topography. Thus, the nanostructured surface could modulate cells as performance as ECM (60). The etching of silicon wafers using Ag-nanoparticles which followed by oxidation with SiOx was studied by Yang *et al* (2010). The substrate was modified by amino group (NH2), fluorine (F) and their surface treatment with oxygen plasma and seeded with Chinese hamster ovary (CHO) cells. Scanning electronic microscopy (SEM) test showed that the more extended morphology of the cells on amino groups represents to take the more hydrophilic chemistry. In addition, the contact angle is decreased with oxidized nanosponge. This study determined that the cells on hydrophilic substrate make actin filaments across the center of cells. But in contrast, actin bundles were aggregated in the peripheral edge of cells (23). Also, the different numbers of the side-chain CH2 groups were used for increasing the hydrophobicity by Ayala *et al.* There was no alteration on charge and the value of stiff. The seeded cells on C1 hydrogels had less sticky behavior because of random and rather fast movements. But the cells on C5 hydrogels had moved in more precise and slowly. Summary by the influence of shear-flow, the more force was needed for the detachment of the cells cultured on C5 hydrogels (for C1 group 4.3±0.8 nN and for C5 was 20.1±3.2 nN). Additionally, the more osteogenic differentiation were happened on C5 hydrogels by higher expression of alkaline phosphatase (ALP), collagen type I, calcium deposition and osteocalcin compare to other types of hydrogels. Their analysis was repeated for myoblasts and the results coordinated with osteogenic type. The parallel alignment of actin within the cytoskeleton was another reason for the optimum number of CH2 groups in C5 hydrogels (61). By increasing the usage of C5, the rate of adsorbed proteins would be higher. But the higher adsorbed proteins will not increase the cell attachments and that is because of steric inhibition or conformational changes. It is necessary to notify, for better interaction between the cells and surface, the balance of hydrophobicity and hydrophilicity is an emergent requirement (61).

Rebollar *et al.* reported that laser irradiation could make the new C=O containing chemical groups on PS surfaces. So the enhanced wetability could be proved by contact-angle measurements. But under the exposure of laser about 30 and 45, the cells aligned along the direction of chemical groups. Furthermore, the cell orientation are influenced not only by

surface hydrophilicity but also by the implied contact angle of surface chemical groups that has a most significant impact (62). Another methods like the hydrolysis process was performed on PLGA and enabled to break the ester bonds by Miller *et al.* The resulted from soluble oligomeric or monomeric glycolic acid fragments of polymer degradation produced a nanoscale roughnesses with a role of the cellular adhesion mediators. Then the cast nanostructured PLGA with coated vitronectin and fibronectin were cultured with vascular smooth muscle cells and lead more interactions with the cells in comparison to conventional PLGA (63). As a consequence, the preferential interactions between the cells and adhering proteins improved on the basis of surface topography with nanostructured architecture.

Conclusion

It is well established that cell fate is considered by the combination of the substrate surface, cells, and growth factors. Cell adaptation into a special environment is followed by changes in morphology, gene expression, and cell cycle. Thus the surface modification is applied in terms of the scale, physical properties and the kind of material. The bioengineering field is strikingly improving various branches of bio-mimicking. Many studies confirmed the considerable effect of cell spreading, appropriate attachment, and surface topography. The cell behavior during the cell cycle is influenced by contact angle and guidance of the adhesion potency and the extension of filopodia relative to the surface topography. Generally, the less contact angle has resulted under the stronger compatibility and hydrophilicity of a culture surface (2/3D) which should be proposed as an ideal cell culturing surface. The surface potency for cell attachment is markedly increased by the achievement of a higher surface area to volume ratio as an outcome of nanotechnology. Similarly, surface modification by using protein adsorption and chemical treatment plays as the desirable biological mimicry with a nanometer scale. Therefore, the management of cell behavior has been interested in researchers and experienced the actual improvements recently. Some techniques similar to molecular self-assembly (64, 65), plasma surface modification (66-69), laser irradiation(70), photochemical surface modification (71, 72) and lithographic techniques (62, 73) capable to afford the requirements of the cell fate. The patterned surfaces which are resulted by engineering methods render to specify the accessible area for cell focal adhesion sites. Typically, the controlled interactions between integrin and FAC molecules play a considerable role in folding and special architectural of membrane proteins and finally cell signaling. The anchorage of focal adhesions to the cytoskeleton stimulates the signaling pathways up to nuclear components that trigger a particular cell activity including growth, proliferation, and apoptosis. Although, not only surface properties act obviously on cell cycle, but also the ultimate fate depends on the presence of other unique parameters as same as proliferation or differentiating agents and cell function. Most of the current research on surface modification using different techniques focuses on augmentation of surface biocompatibility. It is well known that the cell attachment specifies the cell activity as an exclusive approach of surface modification studies. Surface modification as compared to non-modified surface improves the intrinsic properties of a surface which yield a convenience of the biocompatible environment. Therefore, the quality of noteworthy forces between cell and surface express the main role in regenerative medicine projects and subsequent can be led to high-quality cell-tissue based products.

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