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Review Article

Emerging Stem Cell Controls: Nanomaterials and Plasma Effects

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Stem cells (SC) are among the most promising cell sources for tissue engineering due to their ability to self-renew and differentiate, properties that underpin their clinical application in tissue regeneration. As such, control of SC fate is one of the most crucial issues that needs to be fully understood to realise their tremendous potential in regenerative biology. The use of functionalized nanostructured materials (NM) to control the microscale regulation of SC has offered a number of new features and opportunities for regulating SC. However, fabricating and modifying such NM to induce specific SC response still represent a significant scientific and technological challenge. Due to their versatility, plasmas are particularly attractive for the manufacturing and modification of tailored nanostructured surfaces for stem cell control. In this review, we briefly describe the biological role of SC and the mechanisms by which they are controlled and then highlight the benefits of using a range of nanomaterials to control the fate of SC. We then discuss how plasma nanoscience research can help produce/functionalise these NMs for more effective and specific interaction with SCs. The review concludes with a perspective on the advantages and challenges of research at the intersection between plasma physics, materials science, nanoscience, and SC biology.

1. Introduction

Controlling the fate of stem cells (SC) is one of the most crucial issues in regenerative biology and medicine. This versatile type of cell, with promising applications due to their ability to renew their own population and become other types of cells (Figure 1(c)), constitutes the fundamental element of cell therapy. The approach depends upon isolation of SC cells from a tissue as is the case for adult or somatic SC or undifferentiated SC from a culture of pluripotent SC then culture *in vitro* to generate differentiated mature functional cells for use in regeneration of aged, injured, and diseased tissues. However, cell therapy presents challenges that goes beyond the usual tissue engineering—which combine high-performance materials and signaling factors with living cells to restore tissue functions. It involves cells which, when stimulated by specific growth/differentiation factors (e.g., soluble proteins, insoluble attached proteins, and extracellular matrix (ECM) molecules), give rise to a range of heterogeneous cell types (Figure 1(c)). The success of this approach relies on knowing which of these factors affects SC fate and how this interaction occurs. This is a very difficult task and also depends on how and when the factors are delivered, that is, affected by the growth factor presentation (conformation) and time dependent. Studies also show that it is not only the chemical factors but also the physical interaction between the biomaterials and SC that influence the behavior of cells in culture [1, 2] since it directs the forces exerted by cells on the ECM and are believed to trigger gene activation and suppression [3–6].

This suggests the important role of controlling the environmental material properties (density, stiffness, and architecture) as well as regarding how exactly the growth/differentiation factors are presented and delivered (Figure 2). For this task, biomaterials are being developed to contain and deliver combinations of factors in a controllable way. Gels that mimic the ECM, functionalized polymers, inert metals/alloys, calcium phosphates, nanoparticles, nanofeatured surfaces, and several others are just some examples

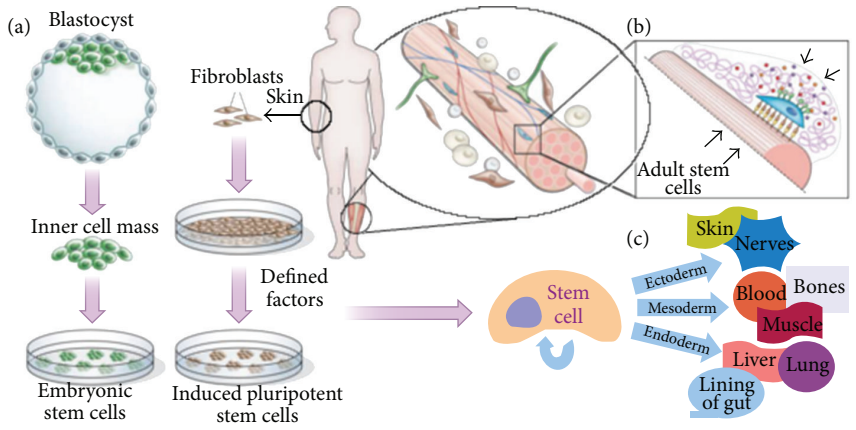

Figure 1: (a) The two sources of pluripotent stem cells. (b) Adult tissue as source of adult (multipotent) stem cell. (c) Differentiation path to each cell lineage. ((a) and (b) adapted from [7], reprinted with permission from Macmillan Publishers Ltd.: Nature, Copyright (2009).)

of functional materials that are currently used to study and control SC fate [1, 7–13]. Although there has been a considerable advance in the area of gels and scaffolds, here we focus on nanomaterials (nanoparticles, nanofibers, and nanostructured surfaces) that can influence selection, proliferation, and differentiation of SC.

To achieve a greater degree of control, reproducibility, scalability, and synthetic materials have gained a significant advantage over naturally occurring materials [1]. In order to precisely design nanomaterials' architecture, its mechanical properties and binding sites for the proper presentation of ligands, techniques to produce and functionalize these materials are required. As an attractive alternative to widely used lithography and chemistry processes, we discuss some of the new advances in self-assembled plasma-made nanomaterials [14]. Furthermore, the plasma environment can be used to produce building blocks for nanoscale assembly and reactive free radicals for surface modification and in addition can be used for controlled synthesis and processing of self-organized nanomaterials [15].

This review will briefly describe in Section 2 the biological role of SC and some of the known mechanisms by which they can be controlled. Section 3 will then highlight the benefits of using a range of nanomaterials to control the fate of SCs. Within Section 4, we discuss how plasma nanoscience has the potential to produce or functionalize these NMs to improve their interaction with SCs. The review will conclude with a perspective on the advantages and challenges of research at the intersection between cell biology, plasma science, materials science, nanoscience, and engineering.

2. The Biological Role of Stem Cells

2.1. Basic Information. Stem cells (SC) are present in mammals from the beginning of their life until their death. They form the first cell aggregates, during embryogenesis, and are able to self-renew their own population and, in order to form an adult animal, can differentiate into virtually any cell type; moreover, within the adult mammal tissue, specific adult SC are also responsible for regenerating mature injured tissues [1, 7–9]. Due to these two defining properties, namely, self-renewability and specific differentiation, SC play a pivotal role in cell therapy for treating/restoring damaged tissues by direct replacement of diseased cells [1, 8, 9, 17].

Stem cells can be divided into two broad categories: pluripotent (embryonic SC (ESC) or induced SC (iPSC)) and adult SC. Each of these different SC types is derived or obtained in different ways [7, 9] (Figures 1(a) and 1(b)). For example, ESC are derived from cells that are removed from the inner cell mass of the blastocyst (or embryoblast); iPSC are a reprogrammed adult cell (from any tissue cell back to pluripotent stem cells) [21, 22]; and the adult SC are found in adult tissues within specific anatomical locations and niches. Adult SCs are found in many tissues and organs such as the bone marrow, gastrointestinal tract, skin, and within the central nervous system where their physiological role is to provide an ongoing supply of mature cells or to facilitate tissue repair [1, 7–9, 23] (Figure 1(b)). Although adult SCs' ability to proliferate and differentiate decreases with the age of the donor and also with time spent in cell culture [24, 25], the use of this approach in cell therapy still remains of great importance as for some tissues it is relatively easy to isolate and manipulate their resident SCs. For example, hematopoietic stem cells are readily isolated from bone marrow or blood and are routinely used for transplantation [26].

Since 1981, when mouse ESC (mESC) were first isolated by Evans and Kaufman [27], the use of these cells in regenerative medicine has been the subject of great interest [8], especially in tissue engineering because of the major limitations of artificial implants [9]. The use of ESC as a cellular model also helps us to understand early developmental events at the molecular and cellular level and potentially models of disease progression and epigenetic regulation of cellular fate [28, 29]. This review will focus on, but is not limited to, SC fate control by use of synthetic nanomaterials, combined or not with the defined growth factors (rather than isolating SC or growth factors themselves). For a discussion of the isolation of SC from different adult tissues [30–32] and the generation of

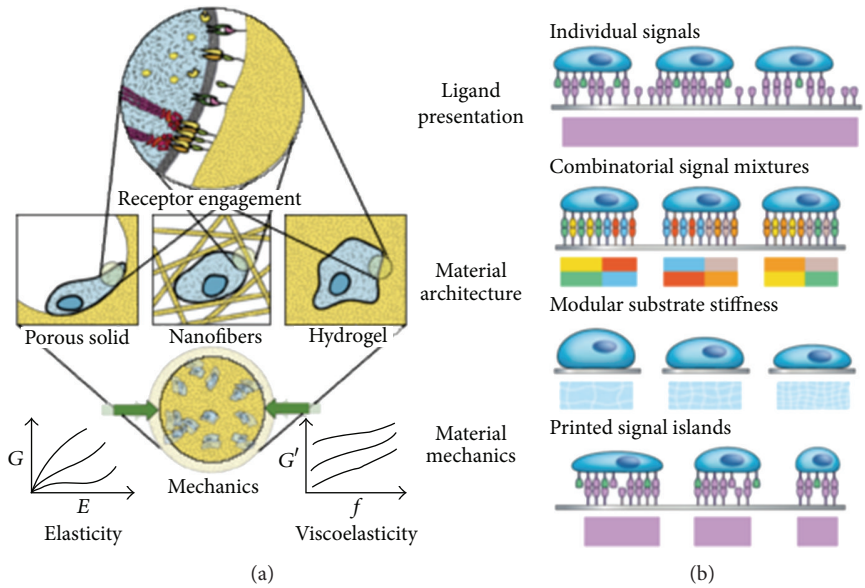

FIGURE 2: (a) Factors that control stem cell fate in 3D materials, namely, ligand presentation, material structure, and mechanical properties. (b) Four strategies to be used with 2D materials for controlling stem cells. ((a) is reprinted from [1] Copyright (2009), with permission from Elsevier. (b) is reprinted from [7] by permission from Macmillan Publishers Ltd.: Nature Copyright (2009).)

pluripotent cells from multipotent ones through reprogramming, we refer the interested reader to a number of other reviews [21, 22, 33, 34].

2.2. Controlling the Fate of Stem Cells. Growth factors, which for the remainder of this paper will include hormones, proteins, and cytokines, have been shown in numerous works to improve the control over either adult or pluripotent SC. The appropriate use of biochemical signals directly added into the culture medium can maintain or differentiate SC [35–38]. Retinoic acid (RA), activin-A, TGF-beta, and insulin-like growth factor 1 (IGF-1) are seen as being responsible for promoting differentiation of murine ESC (mESC) into lung epithelial progenitor cells and pancreatic endocrine cells (alpha, beta, gamma, and delta) [39, 40]. In addition to the great importance to choose which growth factor to use for SC control, the cellular niche—the specific tissue site responsible for regulation of SC fate in the body [9, 41, 42] (Figure 1(b))—helps us to understand the role of the growth factor availability and presentation time as well as the need for a material support for insoluble transmembrane receptor ligands, as well as its specific presentation to the cells. The material selection can be based on the desire to maintain an undifferentiated SC in a culture for a long time or to directly control cell differentiation [1, 9].

For proper application in tissue engineering or adult SC-based therapy, it is desirable to choose/manufacture a biomaterial that closely mimics the "robust spatial and temporal microenvironment of biophysical and biochemical signals" (such as chemokines, cytokines, and growth factors, membrane ligands, and ECM molecules) [7, 26]. Ideally, this microenvironment is an artificial version of the stem cell niche, promoting SC self-renewal or specific differentiation without loss of the key SC attributes [7, 41–45]. Therefore, to control SC behavior and achieve homogeneous and efficient cell differentiation, it is crucial to understand the effects of the identity, presentation, and density of the differentiation factors (e.g., ligands and signals), as well as the material micro- and nanoarchitecture and mechanical properties, which will be described in the next section [3, 9, 11].

The hydrogel is a well-established culture media that has been used for decades to mimic the microenvironment of stem cells in the human body [2, 8, 46–48]. This is due to its high water content, elasticity, biocompatibility, and the ability of nutrients and growth factors to diffuse through it [46–49]. Hydrogels, either natural or synthetic, closely resemble the consistency of the native body tissue by adjusting the hydrogels' crosslinks [8, 50]. Thus they provide efficient adhesion sites for cells and biological signals and also guidance for cell orientation and proliferation [3].

These materials can be used instead of feeder-cell layers for supporting hESC culture and maintenance and were first reported by Xu et al. [51–53] using natural hydrogels, with proven ability to differentiate hESCs [54]. Collagen is an example of a natural hydrogel which is capable of cell encapsulation [55], support of ESC-derived endothelial cells, [56] and, in high concentrations, inhibit the embryonic body (EB) apoptosis and enhance its differentiation [54]. Moreover, collagen in association with fibronectin or laminin was able to differentiate SC into endothelial and cardiomyocyte cells, respectively [54]. Furthermore, denaturated collagen becomes porous gelatin, and is also biocompatible and extensively used [57, 58]. Other important natural materials hyaluronic acid and alginate, are both able to encapsulate SC

and keep them undifferentiated [59] and also differentiate SC into cardiac [60] and hepatic lineage [61] (Figure 1(c)). Likewise, the commercial Matrigel, comprising multiple natural ECM components, has the ability to direct SC into endothelial cells [62] and enhanced neovascular formation [63].

2.3. Present-Day Challenges. The use of natural materials, however, presents some limitations, like batch-to-batch variations, weak mechanical properties, and manufacturing difficulties [64]. Synthetic hydrogels, however, are not usually subject to these limitations and instead offer relatively easy control over biochemical properties and represent risk-free media [7–9, 65, 66]. The most commonly used synthetic biomaterials include polyethylene glycol (PEG), polyvinyl alcohol (PVA), polylactic acid (PLA), and poly(L)lactic acid (PLLA), and polylactic-co-glycolic acid (PLGA), which are microfabricated to be active, degradable, porous, and/or stiff enough to induce SC differentiation both *in vitro* and *in vivo* [1, 8, 9]. The first biomaterial listed, PEG, is a polymer composed of nanofibers and is capable of cell encapsulation and differentiation in numerous tissues (e.g., bone tissue [67, 68]). Also being able to maintain a neural SC culture, PLA can be produced with aligned fibers and induce aligned neural cells [20]. The PLGA usually helps differentiating neural SC into neural cells [69]. Moreover, when mixed with PLLA, it also promotes differentiation of ESCs into numerous cell lineages [70–72].

All these results highlight some important factors about the medium architecture and applied forces, present in the natural cell niche, that mechanically control SC fate [2, 73]. Some limitations for the use of hydrogels in the mechanical control of SC fate, however, include an inability to be synthesised at a stiffness that mimics higher mechanical strength tissues such as bone, cartilage, and ligaments [8]. Moreover, although other studies show that hydrogels provide a 3D structure to support cells, this is not always in the right spatial dimension (e.g., nanoscale), as that conferred by nanofibrillar proteins secreted by cells (e.g., collagen) present in cellular niche [9, 69, 74].

Although the successful application of synthetic hydrogels modified with numerous growth factors (GF) to mimic the SC niche and control the SC fate has been demonstrated, the strict control of its chemical functionalization, degradation rates, ligand presentation, and mechanical properties still remain challenging. The strategies adopted nowadays involve the use of nanomaterials [75, 76]. For example, some growth factors can be adsorbed on nanoparticle surfaces and then controllably released in the culture medium. Nanomaterials can also be added to hydrogels in order to control stiffness. Micro- and nanoscale patterning is now capable of building materials with specific topographies in order to control the cell focal interaction in different scales and shapes as well as providing spots for the attachment of localized ligands and preventing diffusion [77]. New technologies also provide better control over the surface chemistry of biomaterials. For example, functionalization with chemical radicals allows the attachment of biological factors or may lead to hydrophilic properties depending on the specific applications.

3. Materials Science Approaches for Stem Cell Control

3.1. Brief Overview and Critical Factors. Substantial research efforts in micro- and nanoscale science and technology are aimed at controlling material topography, surface biochemistry, and mechanical properties, in order to mimic and understand the natural cellular environment. In this way, many techniques (e.g., chemical vapor deposition, lithography, and sputtering) have achieved high fabrication resolutions which made it possible to study the effects of material properties on cell-material interactions [78–81]. These techniques may be used to fabricate nanomaterials, such as nanoparticles, nanodots, nanostructured surfaces, and nanoarchitectured scaffolds composed of nanofibers which can directly affect the cells' focal attachment and apply forces that change the cell shape and alignment—important factors in controlled cell differentiation [2, 73]. Furthermore, some of these techniques are used to chemically modify the surface with reactive radicals [82, 83], control degradation rates, hydrophilicity [84], and ensure proper presentation of the growth factors, either soluble or attached, thereby directly influencing SC behavior [7–9, 85].

As extensively reported, the ECM plays a significant role in controlling cellular behavior by different factors (forces, topography, growth factors, and ligands) at different levels—from macro- to nanoscales [1, 7, 9–11, 86]. Here we emphasize that materials science approaches hold a major potential for the recreation of diverse cellular environments, which can control these factors in order to better mimic and understand the natural physicochemical ECM features, any relevant spatial, and temporal scales [7, 8, 10]. The most advanced approach is to reduce the complex *in vivo* system to a controllable simplified system where the desirable factors (e.g., density, porosity, surface energy, topography, chemical radicals, surface ligands, and soluble factors) are combined with the custom designed nanostructures, surfaces, or scaffolds [15]. This approach is very promising to increase our understanding of the most relevant factors for SC control [7].

In the following, we will discuss engineered biomaterials with nanofeatures, either functionalized or functionalized with the specific growth factors. This approach helps to maintain SCs "stemness," which is essential for stem cell therapy or, alternatively, to differentiate the SCs, which is crucial for tissue engineering. Nanomaterials will be discussed in order of increasing dimensionality (from 0D to 3D).

3.2. Zero- and One-Dimensional Nanomaterials. Having at least two dimensions in the nanoscale, 0D and 1D materials have huge surface/volume ratios which enable properties that are different compared to film/bulk materials. These properties are mainly guided by the materials' composition, size, and shape, crystallinity, and how they emerge as a surface property [76, 87–89]. Depending on the media, some characteristics, such as the surface charge, hydrophobicity, particle aggregation, and dissolution, are of great importance for biological applications. Moreover, these properties regulate the interaction of nanomaterials with proteins dispersed

in the media [75, 76, 90, 91] and with cells (e.g., binding receptors, blocking pores, and membrane rupture) [92–94].

Nanoparticles, nanodots, nanowires, carbon nanotubes (CNT), graphene flakes, and many other zero- and one-dimensioned materials have found numerous applications in biomedicine. For example, quantum dots and CNTs have been used for *in vivo* imaging [95, 96], and nanofibers and nanoparticles have been used for gene/drug delivery [97, 98]. Moreover, magnetic nanoparticles were also used to induce hyperthermal tumor reduction [89]; Ag and Au nanoparticles [99] have bactericidal properties (Ag, Au [99]) whereas TiO_2, ZnO, and organic [100] nanoparticles have been shown to have high UV absorbance. Recently, other versatile materials have been designed for high-precision sensing [101, 102].

Despite many biomedical-related applications of this class of nanomaterials, only a few applications on direct SC differentiation and maintenance have been reported in the literature. Meanwhile, these small building blocks can dramatically change the media properties, like hydrogels' stiffness and polymers' conductivity. Recently, it was reported that a hybrid hydrogel-CNTs reinforced scaffold induced a rapid hMSC proliferation [103]. Their effect was due to the suitable mechanical properties of the scaffold. These properties could be achieved by controlling the CNT quantity, for the formation of specific tissues (e.g., cardiac [104]). The CNT were also incorporated in polymer matrices to fabricate electrically conductive scaffolds, aiming at differentiation and interaction with neural and cardiac cells via electric signals [103, 105, 106].

It is well known that nanomaterials in a biological fluid bind with proteins differently from plain substrates [75, 76, 90], forming an organized and complex (e.g., time-dependent) structure called the "protein corona." Some common proteins, like albumin, immunoglobulin, and fibrinogen, are found to bind strongly to CNTs, iron oxide, and polymeric particles. The properties listed above (e.g., surface composition, hydrophobicity, and charge) influence the protein adsorption and mediate cell-NP interaction (e.g., binding, uptake). Therefore, the understanding of the formation of the protein corona is seen as one of the important objectives in bio-nanoscience [76, 90–93].

Ranging from microseconds to days [91], the duration of protein-nanoparticle interaction can be used for controllable protein delivery through to SC control. It can be directly introduced into nondegradable (or with difficult degradation rate control) scaffolds [10, 103] or *in vivo* [3], as was done before with other biochemical factors loaded into microspheres [107, 108]. Nanoparticle-protein interaction also represents a promising application of protein presentation in diversified conformations [1, 7, 76, 86, 109], which is an important issue in the SC fate selection.

Using nanomaterials, it is also possible to produce unique thin films. For example, TiO_2 nanoparticles increase MSC attachment by altering surface roughness [110]. In another study, the use of TiN nanoparticles also promotes hMSCs attachment. More than merely cell attachment, applications of these nanomaterial films can be extended, targeting protein binding and presentation as well as controllable hydrophobicity.

3.3. Two-Dimensional Nanomaterials. Biomaterial designed surfaces are the simplest, more controllable- and well-explored model for probing factors for controlling the cell fate (different ligand presentation strategy can be found in Figure 2(b)). The development of building and patterning techniques has made it easier to improve the understanding of cell biology over the smallest scale of the interaction between the cells and their natural niches. Furthermore, this development made it possible to mimic such niches by appropriate material patterns—from hydrogels using soft embossing technique to hard ceramics by electron beam lithography (EBL). The EBL technique—just one example among many useful techniques—can provide virtually any topographical nanoarchitecture desired (e.g., cones, tubes, pitches, and domes) in order to mimic the cell niche.

Cells have the ability to sense and adapt to these environmental nanofeatures, using their filopodia [17, 111–113]. Although this has been known, at least since 1952 [114], the improvement of fabrication techniques over the last decade has allowed the study of interactions at markedly smaller scales. Topography combined with material composition and hardness was shown to exert spatially resolved forces over the cells' cytoskeleton [2, 16–18, 115–117], thereby modifying the cell shape and possibly controlling their fate. Chen et al. showed that smaller ECM islands change cell morphology (leading to a more rounded shape), profoundly altering the actin cytoskeleton and the organization of focal contacts [115, 116] (Figures 3(a) and 3(b)).

More examples of the options for nanoscale control over different cell types can be found elsewhere related to the dimensions and type of the nanostructure (e.g., grooves, pits, and pores) [16, 18, 112, 113, 118]. For example, an increase in the apoptotic response of endothelial cells was related to a decrease in the diameter of the cell's culture size [16]. Cell fate is therefore controlled by complex intracellular mechanisms affected not only by the size and type of nanostructure but also by symmetry. Highly ordered square nanoarrays produced by EBL induced low fibroblasts adhesion (Figure 4) [113]. Moreover, normalised array data show broad downregulation of genes in fibroblasts cultured on hexagonal pattern, indicating that mechanical forces lead to changes in gene regulation [117]. However, the same hexagonal symmetry of gold nanodots binding with integrin receptors has shown that separation between dots is an important factor to control cell adhesion and proliferation [119].

These and many other mechanisms can be used to direct SC growth and differentiation [120]. The same mechanisms to control the cell shape, alignment, and adhesion using mimic-designed biomaterials were studied in order to control stem cell proliferation and differentiation [17]. A similar effect of low adhesion induced by highly ordered nanotopographies was reported by Dalby et al., where they demonstrated significantly increased hMSC osteogenic differentiation [18]. Mesenchymal stem cells also show clear alignment and elongation when cultured on a surface with nanogrooves [121, 122]. Yim et al. also reported that the upregulation of neuronal markers (SOX2, MAP2, neurofilament light peptide, and tyrosine hydroxylase) was observed and enhanced if the surface was coated with retinoic acid [121].

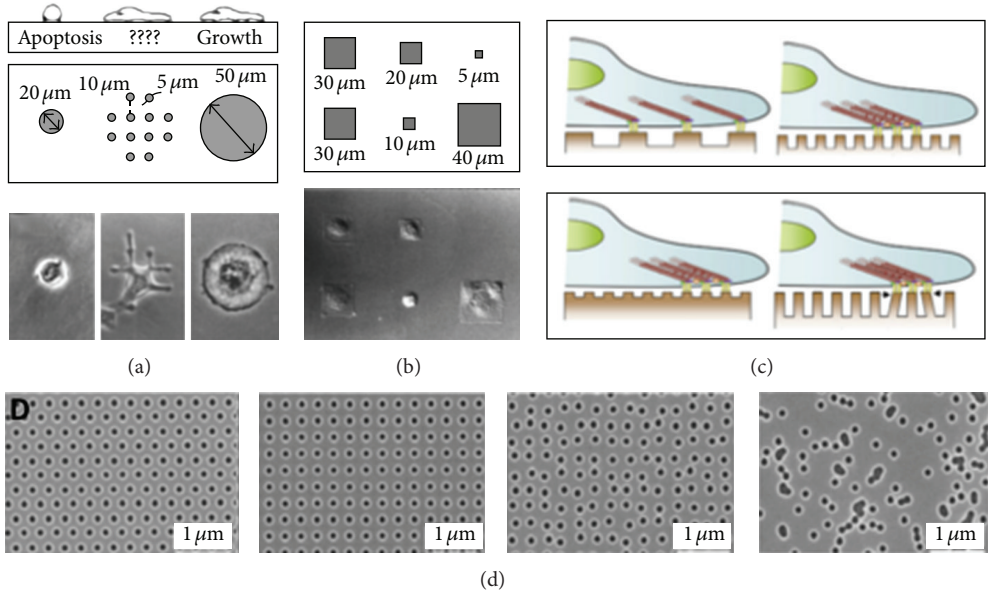

Figure 3: (a) Substrate controlling the cell shape and fate. (b) The signal islands strategy being applied to control stem cells. (c) Different nanostructured surface exerts different forces over the cytoskeleton of the cell. (d) Example of nanostructured organization (hexagonal, square, dislocated square, and disordered). ((a) and (b) reprinted from [16] with permission from AAAS. (c) reprinted from [17], Copyright (2009), with permission from Elsevier. (d) reprinted by permission from Macmillan Publishers Ltd.: Nature Materials [18], Copyright (2007).)

The above studies suggest that nanotopological cues may be used to direct hMSC and hESC into specific cell lineages. Acting as a component of the ECM, they change the cell shape—that is, modify the cytoskeleton structure—by controlling the number and density of focal adhesion sites in response to nanostructures shape, size, and symmetry (Figures 3(c) and 3(d)). A direct consequence is the change in the cell's cytoskeleton's structure which in turn activates specific genes via mechanotransduction mechanisms (Figure 3(c)), which are presently not fully understood. Moreover, nanotopography can be used as a spatially well-defined platform to exert proper presentation of immobilized biochemical factors (e.g., proteins, ligands, and radical groups) in order to control cell adhesion, migration, and differentiation [66, 123]. Furthermore, surface nanoarchitecturing can dramatically change the surface properties, for example, hydrophilicity [18] and biocompatibility [101].

Graphene is another 2D material being actively studied for SC support. Although it is a relatively new material, its surface properties were shown to promote growth and proliferation of hMSC on a range of graphene-coated substrates [124] and to enhance the differentiation of human neural stem cells (hNSC) [125]. Moreover, graphene and graphene oxide were shown to stimulate hMSC differentiation toward the osteogenic lineage [126–128]. These materials were also studied as a platform for induced pluripotent SC and induced differentiation of these cells into an endodermal type [129].

3.4. Three-Dimensional Nanomaterials. The natural niche for tissue-specific adult SCs is not a plane surface. In contrast, it is three-dimensional and presents biological cues at different scales and directions (Figure 1(b)) [1, 7–9, 130]. Moreover, cells are not static and can "feel" the presence of tension and electrical signals in media. A 3D fibrous scaffold is a viable model to use as a mimic of body tissue when studying the proliferation and differentiation of SCs [131–133]. Whilst 2D materials represent a simple model for isolating the control factors for SCs in fundamental research, 3D materials possess a more complex architecture which can be tailored more precisely for real tissue engineering. The combination of these scaffolds and adult cells (e.g., fibroblasts and osteoblasts) for the regeneration of connective tissues is well documented [9, 134–138].

Commonly made of biopolymers, nanofibrous scaffolds (NFS) are used to support SC growth (attachment, proliferation, and organization) and differentiation [8, 10, 11, 70]. Recent studies reported that NFS can promote the differentiation of hMSCs even without intentional addition of growth factors [139]. However, similar to other nanoarchitectured surfaces, nanofibers can also be designed for molecule/ligand presentation and delivery [140–142]. In addition to surface composition and mechanical properties, diffusion of GFs and migration of cells should be taken into account.

Nevertheless, the results previously discussed for 2D materials, such as cell alignment to substrate and controlling cell size and shape, also hold for 3D materials. For example, using the electrospinning technique, Li et al. produced and used polymer NFS to induce differentiation of hMSC into the chondrocyte lineage in order to substitute for the micromass cell pellet culture [143]. The same group reported the differentiation of hMSCs from a single patient into adipogenic, chondrogenic, and osteogenic lineages utilizing

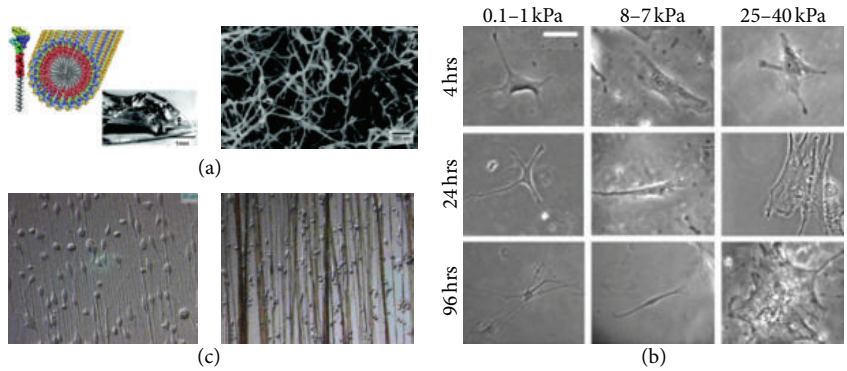

Figure 4: (a) Self-assembled peptide, micro- and SEM view of the produced scaffold. (b) Matrix elasticity controlling the stem cell fate. (c) Cells growing on nano- and microfibers scaffolds with visible evidences of cell alignment with fibers produced via electrospinning. ((a) reprinted from [19] with permission from AAAS., (b) reprinted from [2], Copyright (2006), with permission from Elsevier., (c) reprinted from [20], Copyright (2005), with permission from Elsevier).

the same NF matrix [144]. The same technique was also used to produce aligned nano- and micro-FS [20]. Neural SCs cultured on that media grew such that they were aligned with the fibers, independently of their diameter (Figure 4(c)). However, the differentiation rates were higher (as evidenced by a strong protein expression) on the nanofibrous rather than on the microfibrous scaffolds [20]. Importantly, not only differentiation but SC proliferation was reported using synthetic polyamide NF matrix [133].

A notable advantage of these materials is the reasonably high level of control over elasticity, an important characteristic due to the strong influence over the SC fate [2, 145]. This property is hard to control when using 2D materials and can be set closer to the elasticity of biological tissues using nanofibers [7]. Moreover, introduction of carbon nanotubes/fibers into polymeric matrices can lead to an increase in mechanical properties, electrical conductivity, and reactivity of the biomaterials [146, 147]. Recently, Subramony et al. [134] showed the time control of mechanical stimulation during MSC growth and its effects on cell differentiation. Mechanical tension combined with the matrix alignment led to the development of fibroblasts *in vitro* without any significant chemical influence.

Instead of polymers, another two classes of materials that are used for NF 3D scaffolds deserve specific attention, namely, carbon nanotubes/fibers and self-assembled peptide nanofibers (Figure 4(a)). Carbon nanomaterials have already been discussed in this review. Nevertheless, nanofibers of this abundant and nontoxic material have been effective in differentiating neural stem cells as well as offering good electrical conductivity, high reactivity [146], and increased absorption of laminin [148]. On the other hand, some peptide sequences known to direct SC differentiation can self-assemble in order to form a high-density NF scaffold [19]. Some useful characteristics of these peptide scaffolds are the high water content and the diffusion of nutrients, bioactive factors, and oxygen sufficient for the survival of large numbers of cells for extended periods of time [19].

4. Potential Use of Plasmas for Materials for Stem Cell Control

4.1. Plasma-Based Process Overview. Plasma-based synthesis and processing of nanomaterials are an interdisciplinary research field [14, 15, 149]. A wide range of applications resulted from the control over the properties involved in plasma-based systems such as source power, frequency, and chemistry. A range of species such as ions, electrons, atoms, and radicals are present in a plasma discharge. The principal property of plasma processes is the capability to deliver these species at a desired substrate with controllable energy, thus enabling nanoscale self-assembly [150–155] and deterministic fabrication of nanomaterials [14, 15, 152, 156–164]. Some examples of plasma-produced nanomaterials are presented in Figure 5. Interestingly, these carbon-based nanostructures—vertically aligned graphene and carbon nanotubes—can only be obtained via plasma-based processes [165].

The focus on direct medical applications of plasmas—where the related substrate can be a living tissue—is also increasing [166, 167]. For example, low-temperature plasmas have been used for treating diseases in animal models [88, 168, 169]. Reactive species produced in low-temperature plasma (e.g., free radicals as well as reactive oxygen and nitrogen species (ROS/RNS) such as O, OH, H_2O_2, O_3, NO, and NO_2) [169, 170]) have a fundamental role in chemical reactions, as they can be used to regulate the level of ROS and RNS in intracellular space in order to control cell fate [88, 167]. The role of ROS and RNS in cell control is widely studied; amongst other things they have been shown to influence cell "stemness" [171] and proliferation [172, 173].

Recently, atmospheric-pressure plasma jets showed a special selectivity, killing cancer cells without affecting normal cells [174]. These and similar (e.g., dielectric barrier discharges) devices were also used under different doses to inactivate pathogens and microorganisms such as bacteria, fungi, and viruses [168, 169, 175]. This type of plasma has found numerous applications in medicine and several others such as sterilization of surgical instruments, skin,

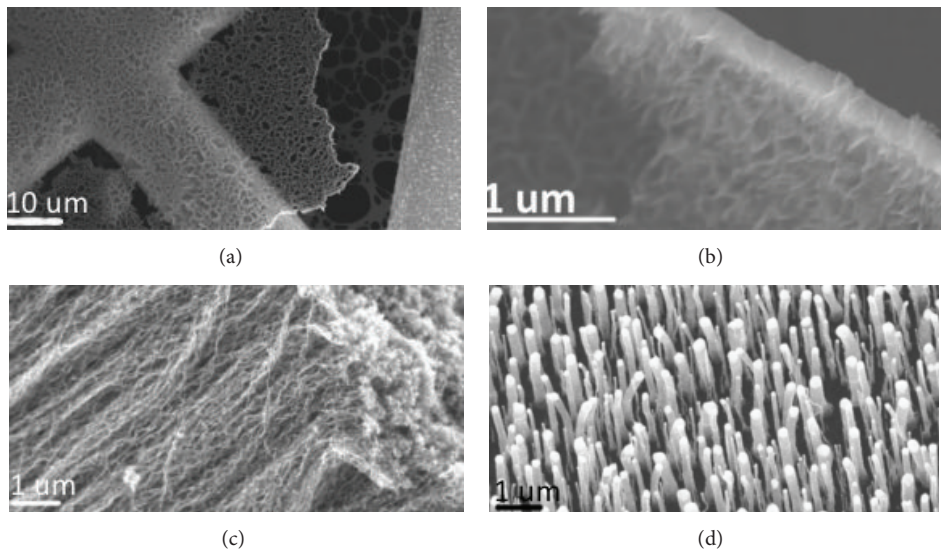

Figure 5: SEM of plasma-produced carbon nanostructures. (a) Vertical aligned graphene (VAG) on a TEM grid. (b) Detail of VAG. (c) Side view of high-density vertical aligned carbon nanotubes (VACN). (d) Top view of low-density VACN tips. Original research results from the Plasma Nanoscience Laboratories at CSIRO.

and wound disinfection/healing [88, 176–180]. Atmospheric pressure plasmas have also been demonstrated to support "plasma bullets" [181, 182]; such exotic structures are likely to lead to a range of promising medical applications and should be the subject of further investigation.

Control over SC fate mediated by plasmas is also possible; for example [183], atmospheric-pressure room-temperature plasmas can effectively induce *in vitro* differentiation of neural stem cells (NSCs) predominantly into neuronal lineage. After plasma treatment, the murine NSC exhibited rapid proliferation and differentiation into neurons with high efficiency.

There are, however, potential disadvantages associated with the use of plasmas for direct medical application; these are largely related to the presence of plasma-generated energetic ROS/RNS and UV radiation [184]. Studies have shown that, depending on the specific conditions (i.e., plasma dose/irradiation and cell type), plasmas may affect cell properties (i.e., adhesion, membrane permeability, migration, and apoptosis/necrosis) and possibly damage DNA and modify proteins [184]. Further study and clinical trials are required before practical use of plasmas as direct medical tools.

Plasmas may also be used to fabricate micro- and nanostructures (see Figure 5) as well as appropriately functionalized surfaces, suitable for SC control. The aim of the rest of this section is to track where plasma technologies have an implication over materials production and modification for stem cell control and highlight where it could have potential uses.

4.2. Plasma-Based Nanofabrication. The existence of energetic species in plasmas makes it suitable for dry etching applications and many other materials synthesis and processing [152, 157, 159, 163, 185]. These techniques can produce patterns in hard materials at micro- and nanoscales. These patterns in turn can be used to control the alignment and shape of SCs. The material removed from a target using plasmas can also be used for functional thin film deposition, with almost no restriction over the target composition or substrate shape—which is an advantage for coating 3D materials [14, 15, 149, 186]. Moreover, the properties of these thin films can be precisely tailored, for example, to enable degradation after use [159, 187]. Other considerations for biological applications are the production time and cost [16], which can be reduced in plasma processes [151, 153, 188].

The applications, namely, etching, deposition and, surface modification, are the most common in literature, although plasma-based processes are capable of producing a variety of nanomaterials [151, 189], namely, nanoparticles [190, 191], nanodots [155, 192], and various allotropes of carbon (e.g., nanodiamond [15], nanotubes [158, 189], nanocones [193], nanowalls, and graphene [102, 160, 161, 194]). Plasma techniques also provide the control over the properties of these nanomaterials (e.g., size, shape, and surface reactivity) [99, 152, 157, 162, 163, 195]. As discussed above, these properties are essential to bind proteins and cells, as well as for the delivery of specific (e.g., differentiation) factors in order to control the SC fate. Moreover, due to the unique ability to dissociate molecules (e.g., hydrogen), the control over some properties is not achievable by other techniques such as neutral gas-based CVD or by wet chemistry routes [165].

The control over the nanostructural properties is related to the plasma ability to generate and concentrate building units (BU) of nanoscale matter [15, 99]. Moreover, these BU can be directly delivered to a substrate and build a wide range of complex architectures discussed previously to mimic the SC natural niche and control cell fate. The plasma environments have specific features and control self-assembly of nanostructures into patterns and arrays (often termed "mask-less"). Plasma processes have also been reported to

lead to a sustainable energy saving and reduction of greenhouse emissions. Interestingly, carbon nanotubes and other one-dimensional nanostructures show pronounced vertical alignment which is not common to thermal CVD [165].

For the same reason, plasma-based technologies have long been reported as an effective route for surface treatment [15]. The importance of this fact is, for example, the ability to chemically improve the biocompatibility of the surface by increasing its hydrophilicity, which in turn increases the cell proliferation [8, 158, 163]. Moreover, several limitations (e.g., control over chemical properties and difficulties in sterilization) could be overcome by plasma-based techniques. Furthermore, plasma-based techniques were used to functionalize important nanomaterials such as CNTs leading to better substrates for the enhancement of cell growth and proliferation [196].

Regarding the control of SC fate, it is well known that the proliferation (without differentiation) or the differentiation to desired lineages requires both growth factors and, for some specific SC, mechanical stimulation. Several strategies can be followed to reach this goal, for example, production of specific tailored nanostructures with or without bound/immobilised growth factors that directly promote SC expansion or controlled differentiation. These nanostructures can be added to hydrogels/nanoscaffolds in order to temporally control the delivery of GFs and migration of cells. Surfaces can also be plasma-tailored with desired nanostructures to mechanically guide the SC via focal contact or be used as binding point to ligands/chemical radicals or both, leading to SC proliferation/differentiation according to the input stimulus.

An example involving a plasma-treated nanostructure coated with a specific GF was reported by Arnold et al. [119]. In order to understand the role of a precise molecular arrangement on cell response, a substrate was patterned with Au nanodots (<8 nm), highly ordered with controllable distances, via self-assembly of diblock copolymer micelles. After the assembly of the nanodots, the polymer was completely removed by the plasma treatment and the dot-patterned substrate was functionalized with a specific peptide (c(RGDfK)), which has a high affinity to the $\alpha v\beta$-integrin. Due to the small surface area of the nanodot, only one integrin can attach to each dot and the effect of the arranged binding sites could be studied. Such an approach is powerful as it enables control over the presentation of mass amounts of specific signals/ligands at precise spatial locations and size scales and therefore an ability to dissect how cells respond to variations in ligand density. There is great potential to exploit this approach to critically examine the presentation of defined amounts of combinations of biological signals to stem cells. We predict that sophisticated nanoengineering based on plasma generated biomaterials will underpin a new era in cell culture.

5. Conclusions and Challenges for Future Research

In this review, we have discussed sources and applications of SCs and the mechanisms by which they can be controlled and subsequently, the use of nanomaterials to control SCs. We have pointed out the properties that make low-temperature plasmas a suitable tool to use in the production and functionalization of these NMs for more effective and specific interaction with SCs, both through direct treatment and as a versatile nanofabrication tool [15].

Due to the many unique characteristics of low-temperature plasmas, we believe that the direct use of plasmas, especially atmospheric plasmas, should be considered as a viable strategy to direct SC differentiation. Plasmas as a nanofabrication tool should be focused on developing "lab on a chip" devices as suitable platforms for the differentiation of SCs into any cell lineage through mechanical and/or electrical stimulus.

Tissue engineering and SC biology can benefit greatly from advances in plasma nanoscience [15]. Nanomaterial design is leading to a greater degree of control over cell attachment and migration in order to grow multilevel tissues (or organs, e.g., skin). This control also contributes to basic studies on mimicking ECM properties and ligands quantity and presentation as well as elucidating the role of time in growth factors delivery.

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