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Review article

Polymer microarray technology for stem cell engineering ☆

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ABSTRACT

Stem cells hold remarkable promise for applications in tissue engineering and disease modeling. During the past decade, significant progress has been made in developing soluble factors (e.g., small molecules and growth factors) to direct stem cells into a desired phenotype. However, the current lack of suitable synthetic materials to regulate stem cell activity has limited the realization of the enormous potential of stem cells. This can be attributed to a large number of materials properties (e.g., chemical structures and physical properties of materials) that can affect stem cell fate. This makes it challenging to design biomaterials to direct stem cell behavior. To address this, polymer microarray technology has been developed to rapidly identify materials for a variety of stem cell applications. In this article, we summarize recent developments in polymer array technology and their applications in stem cell engineering.

Statement of significance

Stem cells hold remarkable promise for applications in tissue engineering and disease modeling. In the last decade, significant progress has been made in developing chemically defined media to direct stem cells into a desired phenotype. However, the current lack of the suitable synthetic materials to regulate stem cell activities has been limiting the realization of the potential of stem cells. This can be attributed to the number of variables in material properties (e.g., chemical structures and physical properties) that can affect stem cells. Polymer microarray technology has shown to be a powerful tool to rapidly identify materials for a variety of stem cell applications. Here we summarize recent developments in polymer array technology and their applications in stem cell engineering.

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1. Introduction

Stem cells hold remarkable potential for applications in regenerative medicine and disease modeling. They have the unique ability to undergo self-renewal in an undifferentiated state and have the potential to differentiate into multiple cell types [4–7]. Adult stem cells, such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), have been thoroughly investigated and their clinical benefits have been well established [8–10]. The recently derived human pluripotent stem cells (hPSCs), including both human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), have the ability to self-renew indefinitely and differentiate into all of the human cell types in *in vitro* culture [11–14]. With these characteristics, hPSCs provide an ideal source for the large number of cells (>10^9 cells/patient) needed for cell replacement therapies [15–17].

To direct differentiation of hPSCs, many of the early advances were accomplished through the study of embryology, with the intent of replicating embryonic development [18–20]. By using soluble inductive factors (e.g., growth factors and small molecules) to recapitulate embryonic stage cell signaling, hPSCs can be differentiated into a desired cell phenotype. One textbook example is to modulate Wnt signaling in a temporally defined manner to produce functional cardiomyocytes from hPSCs [21]. In addition to this rational design-based strategy, high throughput approaches have been utilized to screen small molecules, growth factors and their combinations to direct hPSC differentiations [22]. For example, Borowiak and coworker screened 4000 small molecules and identified two molecules that can direct hESCs into endothermal cells [23]. With these advances, soluble factors have been extensively utilized to differentiate hPSCs into various functional cells.

In addition to soluble factors, insoluble factors (e.g., cell culture substrates and 3D scaffolds) have been shown to exhibit controlling effects on stem cells [19,24,25]. While soluble factors can modulate specific target(s) in signaling pathways to influence stem cells via chemical interactions, insoluble factors can provide both chemical and physical cues to direct stem cell fate [19,26–29]. As shown in Fig. 1, signals provided by the materials can be separated into two categories: surface bound chemical structures and material physical properties [30]. Surface bound chemical structures can engage a variety of cell membrane-bound proteins and receptors to initiate various cellular signaling cascades and influence stem cell activities [31]. These surface bound bioactive molecules can be derived from a variety of sources. Some studies have utilized naturally derived ECM proteins (e.g., fibronectin and laminin) due to their biological functions and abundant presence in the extracellular space within the human body [32]. Other research has suggested that it is advantageous to utilize the effective groups of these proteins in order to increase efficiency [33]. This has led to the popularity of peptide-mediated stem cell adhesion and fate determination. One example is the RGD peptide sequence that is known for its ability to induce cell adhesion [34,35]. Though certain integrin has a high affinity for RGD, the resulting interaction alone is not sufficient to control cell fate. As a result, it is inadequate to simply use RGD, requiring a combination of different ligands to elicit an optimized response from the cell membrane [36,37].

Within the last decade, studies assessing the effects of material physical properties on stem cells have received significant attention. One facet is the use of nanoscale topographical features to modulate cell adhesion and direct stem cell fate [38,39]. Due to the high-binding affinity of integrin, and its ability to produce focal adhesion points through cell-surface interaction, cells can bind surfaces of varying roughness and patterned geometries. It has been shown that nanotopographic features of materials surface can influence the key steps in cell adhesion (e.g., integrin clustering) and influence stem cell fate determination through self-renewal and directed differentiation [40–42]. In addition to nanotopographic features, it has been shown that cells are sensitive to the microscale features and stiffness of the materials [43,44]. Both the microscale features and materials stiffness can alter cellular cytoskeletal structures, affecting stem cell fate [44–46]. Due to the large number of variables of chemical and physical properties of materials that can influence cell behavior, it is necessary to develop a highly tunable platform that can be used to direct stem cells.

The traditional model for discovering effective factors for materials-directed cell activity and fate determination utilizes a methodical approach, where only a few conditions can be thoroughly investigated at a time [47]. Given the complexity of the interactions between stem cells and materials, there is a growing need for the development of high throughput approaches for the quick and efficient determination of optimal materials properties. One such strategy is the use of surface gradients, where the material is spatially arranged into regions of gradually varied chemical concentrations or physical properties [48–51]. These methods can allow for rapid establishment of the relationship between one or two materials properties and (stem) cell behaviors. Other studies leveraged the recent development in robotic liquid-dispensing technology and microfabrication to develop polymer microarray systems for the rapid examination of a variety of tunable testing conditions [47,52–56]. These polymer arrays can facilitate the simultaneous screening of a variety of factors, allowing for side-by-side analysis and small-scale experiments that require relatively few resources.

In this review, we will firstly give a brief overview of the technologies used to fabricate polymer microarrays. Secondly, we will discuss the recent development of polymer microarrays to screen the effects of material chemical structures on stem cells. Thirdly, we will describe the development of polymer microarrays to examine the effects of materials physical properties on stem cells with a focus on surface topography and elastic modulus. Lastly, we will review microarrays capable of examining combinatorial effects of materials chemical structures and physical properties as well as recent developments in 3D hydrogel microarray fabrication. We will conclude with an outlook on the field.

2. Polymer microarray fabrication

Polymer microarrays have been fabricated using a variety of patterning technologies. In general, these technologies can be categorized into two groups: (robotic) liquid-dispensing systems and microfabrication technologies [52,57]. The (robotic) liquid-dispensing systems include both contact printing and non-contact printing (i.e., ink-jet printing) [58]. After liquid dispensing, sometimes a crosslinking step (e.g., UV crosslinking of monomers) is needed [54,59]. The contact printing often uses a pin to load the "ink" (e.g., monomer and polymer solutions) and then deposits the "ink" onto a substrate by direct or close contact. The non-contact printing can directly eject "ink" droplets through a nozzle onto substrates [60]. Liquid-dispensing technologies can allow for accu-

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