Materials Science and Engineering R 119 (2017) 1–35

Contents lists available at ScienceDirect

Materials Science and Engineering R

journal homepage: www.elsevier.com/locate/mser

Spatially and temporally controlled hydrogels for tissue engineering

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ARTICLE INFO

Article history:
Received 17 March 2017
Received in revised form 5 July 2017
Accepted 6 July 2017
Available online xxx

Keywords:
Hydrogel
Tissue engineering
Microfabrication
Bioprinting
Cell-biomaterial interaction
Biomaterials
Cellular microenvironments

ABSTRACT

Recent years have seen tremendous advances in the field of hydrogel-based biomaterials. One of the most prominent revolutions in this field has been the integration of elements or techniques that enable spatial and temporal control over hydrogels' properties and functions. Here, we critically review the emerging progress of spatiotemporal control over biomaterial properties towards the development of functional engineered tissue constructs. Specifically, we will highlight the main advances in the spatial control of biomaterials, such as surface modification, microfabrication, photo-patterning, and bioprinting, as well as advances in the temporal control of biomaterials, such as controlled release of molecules, photocleaving of proteins, and controlled hydrogel degradation. We believe that the development and integration of these techniques will drive the evolution of next-generation engineered tissues.

Contents

Abbreviations: 2D, two dimensional; 2PP, two-photon hydrogel polymerization; 3D, three-dimensional; AFM, atomic force microscopy; AgNP, silver nanoparticles; AuNP, gold nanoparticle; α-SMA, alpha-smooth muscle actin; RGD, Arg-Gly-Asp; BMP, bone morphogenetic protein; CNTF, ciliary neurotrophic factor; DMD, digital micromirror device; ECM, extracellular matrix; ESC, embryonic stem cell; FBR, foreign body reaction; FGF1, fibroblast growth factor 1; GelMA, gelatin methacryloyl; HUVEC, human umbilical vein endothelial cell; HA, hyaluronic acid; hESC, human embryonic stem cell; hiPSC, human induced pluripotent stem cell; hMSC, human mesenchymal stem cell; HSC, hepatic stellate cells; IL, interleukin; IPN, interpenetrating polymer network; MSC, mesenchymal stem cell; MMP, matrix metalloprotease; NF-κB, kappa-light-chain-enhancer of activated B cells; NIL, nanoimprint lithography; NIR, near infrared; NorHA, norbornene-functionalized hyaluronic acid; PHEMA, poly(2-hydroxyethyl methacrylate); PA, polyacrylamide; PAA, poly(acrylic acid); PBT, poly(butylene terephthalate); PCL, polycaprolactone; PDMS, polydimethylsiloxane; PDPA, poly(2-(diisopropylamino)ethyl methacrylate); PEG, poly(ethylene glycol); PEGDA, poly(ethylene glycol) diacrylate; PEI, polyethyleneimine; PLGA, poly(lactic-co-glycolic acid); PNIPAAm, poly(*N*-isopropylacrylamide); PMMA, poly(methylmethacrylate); PMPC, poly(2-(methacryloyloxy)-ethyl phosphorylcholine); PVA, poly(vinyl alcohol); PTFE, poly (tetrafluorethylene); RGD, Arg-Gly-Asp; ROMP, ring-opening metathesis polymerization; SHH, sonic hedgehog; SWGA, surface-wettability-guided assembly; SPAAC, strain-promoted alkyne-azide cycloaddition; UV, ultraviolet; VEGF, vascular endothelial growth factor.

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http://dx.doi.org/10.1016/j.mser.2017.07.001
0927-796X/

1. Introduction

Recent advances in biomaterials have allowed for deeper understanding of fundamentals of cell biology and fueled further development of novel pharmacological *ex vivo* models by recapitulating native physiological processes [1]. Moreover, biomaterials play a fundamental role in tissue engineering, which is aiming to fabricate living replacements to restore the functions of affected tissues and organs. The last decades have underlined the essential role of biomaterial design and engineering to improve the function of engineered tissue constructs [2]. Here, we critically review the emerging progresses of spatiotemporal control over biomaterial properties towards advanced biomaterials that facilitate the development of functional tissue-engineered constructs.

Traditionally, research directions on biomaterials have centered on the development of biomaterials with novel compositions and properties [3]. In parallel, an intense effort has been made towards the chemical modification of known biomaterials to endow them with improved performance or specific new functions. Moreover, conventional research has focused on the static behavior of biomaterials, while recent findings suggest that spatial and temporal control of biomaterials provides unique opportunities to recapitulate the dynamic nature of the microenvironments in native tissues, which play a key role in controlling cell behaviors and functions.

In addition to advances in biomaterial chemistry, numerous engineering techniques have also been developed to fabricate biomaterial constructs with unique spatial modifications and complex architectures [4]. We review the recent developments in biofabrication techniques including, but are not limited to, micromolding, photolithography, and spinning techniques for the fabrication of spatially defined biomaterials. The use of constructs fabricated with these technologies has revealed how the geometrical and topological factors of scaffolds can influence the proliferation, migration, and differentiation of cells in contact with engineered scaffolds. Also, we introduce the recent rapid developments in three-dimensional (3D) bioprinting techniques, which have provided practical methods for fabricating biomaterials into relevant sizes, shapes, and compositions for regenerative medicine [5].

We also review the recent achievements in temporal control over biomaterials. While conventional approaches have focused on controlled release of growth factors and drugs, recent studies have been dedicated to transforming passive and static scaffolds into responsive and dynamic matrices [6]. For example, cell-adhesive peptides can be presented in synthetic matrices upon on-demand photo-activation with precise spatial control, while biophysical characteristics such as matrix elasticity or stiffness can also be dynamically changed. Such new approaches are expected to play a major role in recapitulating the unique dynamic features of native extracellular matrix (ECM) to direct multistep biological processes, such as stem cell differentiation and functional tissue regeneration.

We conclude by providing a perspective on the future challenges and opportunities in the development of biomaterials for tissue engineering applications. Specifically, we discuss the