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Applications of scaffolds: Tools for enhancing the immunomodulation of mesenchymal stromal cells

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Abstract: Exogenously delivered mesenchymal stromal cells (MSCs) are therapeutically beneficial owing to their paracrine effect; they secrete various cytokines, nucleic acids, and proteins. Multiple bioengineering techniques can help MSC cultures to release secretomes by providing stem cell niche-like conditions (both structurally and functionally). Various scaffolds mimic the natural extracellular matrix (ECM) using both natural and synthetic polymers, providing favorable environments for MSC proliferation and differentiation. Depending on material properties, either topographically or elastically structured scaffolds can be fabricated. Three-dimensional scaffolds have tunable substrate rigidities and structures, aiding MSC cultivation. Decellularized ECM-derived hydrogels are similar to the natural ECM, thus improving the paracrine effects of MSCs. Here, we discuss recent research on the application of scaffolds to maximize the immunomodulatory function of MSCs.

Introduction

Mesenchymal stromal cells (MSCs) are defined by the International Society for Stem Cell Research (ISSCR) as fibroblast-like non-hematopoietic cells (Ullah *et al*., 2015). They are multipotent but are CD40, CD80, and CD86 negative and have low major histocompatibility complex (MHC) I/II values; thus, they are less immunogenic than other stem cells. MSCs are therefore increasingly being utilized for tissue engineering and immunotherapy applications. In particular, MSCs have the potential to modulate inflammatory or immune-activated circumstances by secreting immune modulation factors, nucleic acids or proteins (Li *et al*., 2019). These immune-modulating factors include indoleamine 2,3-dioxygenase (IDO), heme oxygenase-1 (HO-1), transforming growth factor-β (TGF-β), TNF-α stimulated gene/protein 6 (TSG-6), cyclooxygenease 2 (COX2), prostaglandin E2 (PGE2), hepatocyte growth factor (HepGF), galectins-1 (Gal-1), iNOS, interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Rag), interleukin-10 (IL-10) and human leukocyte antigen-G (HLA-G) (Pittenger *et al*., 2019). Additionally, secretome from MSCs can regulate the proliferation, differentiation, and activity of most immune cells, including T cells, B cells, natural killer (NK) cells, dendritic cells (DCs), and macrophages (Lee and Song, 2018). MSCs can therefore alleviate inflammatory or immune-related diseases. Emphasis regarding regenerative medicine using MSCs has been shifting toward either producing cytokines or other factors (termed the paracrine effect), rather than the differentiation and rebuilding of damaged tissues using MSCs themselves. The potentiation of the immunomodulatory function of MSCs means that they constitute an emerging and potentially important tool for cell therapy.

To enhance the capacity of the immunomodulatory function of MSCs, multiple bioengineering techniques can be employed during their cultivation. Scaffolds can be utilized during cell culturing to preserve the tissue architecture and provide a three-dimensional (3D) biomimetic milieu to MSCs, similar to a stem cell niche. It has been known that the dimensionality, physical characteristics, topographical cues, surface chemistry of biomaterials, and micro-structure of scaffolds can regulate the immunomodulatory function of MSCs. Here, we review the link between the immunomodulatory function of MSCs and the properties of scaffolds, particularly topographical cues or substrate elasticities of biomaterials.

Scaffolds with Topographical Features

The ECM consists of networks of fibrous proteins, collagens, and elastic fibers, which are immersed in a viscoelastic gel

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that is rich in proteoglycans (Mecham, 2011). Thus, diverse synthetic polymers and natural polymers have been used to generate scaffolds with fibrous structures, so as to mimic the natural ECM. Synthetic polymers such as polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), and polylactic acid (PLA) can be utilized to generate fine-tuned fibrous structures via electrospinning. Su *et al.* (2017) reported that electrospun PCL scaffolds promoted pro-angiogenic and anti-inflammatory paracrine factors in adipose-derived stem cells [MSCs(A)]. They also further analyzed the effects of aligned, randomized, or meshed patterns fabricated with PCL on MSCs(A), revealing that meshed scaffolds best enhanced their paracrine effects. This finding indicates that the orientations of the fibers and the substrate rigidity might also be important factors for controlling the functions of MSCs. biocompatible material that can be used to fabricate several forms, including fibers, gels, and films (Qi *et al.*, 2017). A recent study demonstrated that the meshed scaffolds comprising silk fibroin nanofibers strongly elevated the levels of immunomodulatory factors such as IDO-1, COX2, and PGE2 in bone marrow-derived stem cells [MSCs(M)] (Kim *et al.*, 2019a). Furthermore, MSCs(M) on mesh form of silk fibroin nanofibers reduced mouse mortality from polymicrobial sepsis through their improved immunomodulatory functions than MSCs(M) only (Kim *et al.*, 2021). ECM like structured silk fibroin seems to provide a favorable environment for MSC cultivation through its structural and material properties. Vallés *et al.* also demonstrated the effect of topographical cue on immunomodulatory function of MSCs (Vallés *et al.*, 2015). MSCs(M) on 3D polystyrene scaffolds showed smaller cell bodies, but secreted a higher level of soluble factors than MSCs(M) on two-dimensional (2D) polystyrene scaffolds, indicating that topographical cue affects cell function differently. The pore size in hydrogel-based scaffolds also can make a critical difference even in the same hydrogel. For example, sponge or foam porous scaffolds contain connected pore structures that favorably transport gas and nutrients into cells. Hydrogels made of natural materials such as fibrin, alginate, or silk fibroin have been used as scaffolds for cells to promote cell growth and function (He *et al.*, 2020). However, if the pores are too small, the cellular penetration, ECM deposition, or neovascularization can be inhibited (Shruti *et al.*, 2013). Meanwhile, pores that are excessively large can decrease the cell-to-cell contact ratio, as the cells exhibit 2D growth patterns on the substrate rather than adopting a 3D organization (Marrella *et al.*, 2018). The effective pore sizes for cellular function in tissue engineering applications are listed in Table 1. The micro-architecture supporting MSCs seems to be an important cue to manage the paracrine effect of MSCs.

Substrate Stiffness and Biochemistry of Scaffolds

Since the effect of matrix elasticity on the MSC function and fate was demonstrated by Engler *et al.* (2016) for the first time, many studies have been performed to find the optimal substrate rigidity for MSC cultivation. Hydrogels are favorable for MSC cultivation as they can be tuned regarding to their substrate rigidity. Drzeniek *et al.* (2021) reported that a microporous 3D hydrogel composed of collagen significantly improved the paracrine effects of MSCs, compared with a 2D collagen-coated polystyrene. They used a customizable collagen I-hyaluronic acid (COL-HA)-based hydrogel to encapsulate MSCs for mimicking stem cell niches. Compared with a 2D surface coated with COL-HA, the 3D hydrogel comprising COL-HA elevated the secretion of angiogenesis-, immunomodulation-, hemostasis-, and ECM remodeling-related cytokines from MSCs. Similarly, Wong *et al.* (2020) also demonstrated that soft extracellular matrix (~2 kPa) mimicking bone marrow maximized the ability of MSCs(M) to produce paracrine factors and induce chemotaxis upon inflammatory stimulation. In addition to matrix elasticity,

TABLE 1

Cellular function and pore size of scaffolds

Cellular function	Scaffold	Pore size (nm)	Reference
Vascularization/angiogenesis	Fibrin	100–11,000	Francis *et al.*, 2008
	Collagen	1,000–11,000	Francis *et al.*, 2008
	Cellulose acetate	800–8,000	Brauker *et al.*, 1995
	Mixed esters cellulose	1200–8000	Brauker *et al.*, 1995
	Polytetrafluoroethylene (PTFE)	1000–15000	Brauker *et al.*, 1995
	Acrylic copolymer	800–5000	Brauker *et al.*, 1995
	Chitosan	>90,000	Lim *et al.*, 2008
	Poly(ethylene glycol) (PEG)	100,000–150,000	Chiu *et al.*, 2011
Wound healing	Collagen-glycosaminoglycan copolymers	20,000–120,000	Yannas *et al.*, 1989
Paracrine activity	Alginate hydrogel	5 or 120,000	Qazi *et al.*, 2017
	Alginate hydrogel	10 or 125,000	Qazi *et al.*, 2020
Proangiogenic, immunomodulatory, paracrine factors, neuroprotective	Collagen I-hyaluronic acid (COL-HA)-based hydrogel	30,000–40,000 90,000–100,000	Drzeniek *et al.*, 2021
Differentiation	Photo-crosslinked oligo[(polyethylene glycol) fumarate] (OPF) hydrogels	100,000–400,000	Dadsetan *et al.*, 2008

composite scaffolds that mimic natural conditions may greatly enhance the paracrine effect of MSCs. In order to maximize the similarity to the natural ECM, decellularized ECM (dECM) from various tissues and organs have been investigated and applied via a number of techniques that utilize chemical, enzymatic, or mechanical disruption. As the ECM is an essential non-cellular component of the tissue microenvironment, decellularized scaffolds composed entirely of ECM can help to reconstruct stem cell niches *in vitro*. Hydrogel forms of dECM can both affect stem cell differentiation and exert a functional effect, according to the origin of the organ or tissue in question. One disadvantage of ECM-derived hydrogels, however, is their poor self-supporting ability, which arises from their low viscosities and mechanical properties as scaffolds. Due to this characteristic, which hinders the possibility of making large and complex 3D structures with hydrogels (Yi *et al*., 2019), the combination with other ECM components, such as collagen, can be applied for enhancing the stiffness of hydrogels. There are, however, limitations to the use of dECM in standard clinical treatments, since there is no standard process for the dECM (Kim *et al*., 2019b) and the current process is unable to completely remove all cell materials in a practical setting (Gilbert *et al*., 2009). Thus, the general standard guideline for processing dECM will accelerate the clinical trials of MSCs and dECM-derived scaffolds.

Apart from the above mentioned factors, some reports have indicated that the cell source might affect the immunomodulatory function of MSCs, as they can be harvested from various adult tissues as well as neonatal tissues. Although MSCs(M) seem to be designated as the gold standard of MSCs (Hall *et al*., 2013), MSCs(A) and cord blood-derived MSCs [MSCs(CB)] have also been widely used in clinical studies due to their easy accessibility. Although it is hard to conclude which MSCs are more appropriate to use, it has been reported that human MSCs(A) are more genetically and morphologically stable in long-term culture, display a lower senescence ratio, show a higher proliferative capacity, and retain differentiation potential for a longer period in culture compared with human MSCs (M) (Elman *et al*., 2014). Further, the yield of MSCs(A) is approximately 500-fold greater than that of MSCs(M) when isolated from an equivalent amount of adipose tissue and bone marrow stroma, respectively (Strioga *et al*., 2012). Nonetheless, more intensive studies about the cell source are needed for arriving at a conclusion. The functions of the MSCs from different sources are listed in Table 2.

In conclusion, many methods for preparing scaffolds with various materials have been developed. In particular, scaffolds with favorable properties for improving MSC functions are actively being fabricated. Furthermore, enhancing the

TABLE 2

Immunomodulation of MSCs by different origin

Origin	Type of scaffold	Immunomodulation	References
Human bone marrow	Alginate/hyaluronic acid hydrogel	MSCs were hypoimmunogenic and could exert immunosuppressive effect on HLA-mismatched PBMCs.	Du *et al*., 2016
	Woven poly(ε-caprolactone) (PCL)	Enhanced glycosaminoglycans (GAGs) and collagen production by IL-1Rα-expressing scaffold in inflammatory conditions, and the level of PGE_2 was elevated	Glass *et al*., 2014
	Alginate micro-encapsulation	MSCs in 3D culture decrease the expression of TNFα level and PGE_2 level increase in rat organotypic hippocampal slice coculture	Stucky *et al*., 2015
	Fibrin hydrogel	MSCs in fibrin hydrogel increase PGE_2 secretion, and enhance macrophage polarization	Murphy *et al*., 2017
	Collagen	Promotes the activation of M2 macrophage, and reduced IL-10	Rashedi *et al*., 2017
	Silk fibroin nanofiber	MSCs on silk fibroin elevate the expression of IDO-1, COX2 and PGE_2	Kim *et al*., 2019a
	Grid-like square cavities from thermoplastic polyurethane	MSCs on grid-like structure induce secretion of PGE_2 and IL-1Rα	Roger *et al*., 2016
	Porous synthetic scaffold	MSCs in scaffold decrease the secretion of IL-6, MCP-1, and RANKL than 2D culture, and increase PGE_2 and TSG-6 level	Vallés *et al*., 2015
Human adipose tissue	Alginate hydrogel	ASCs in alginate hydrogel enhance their potential to inhibit proliferation of PBMCs	Follin *et al*., 2015
	Elecrospun PLLA fibrous scaffolds with random or aligned fiber alignment	MSCs on aligned fibers had enhanced expression and secretion level of TSG-6 and COX2	Wan *et al*., 2018
Human umbilical cord	Decellularized pig ECM scaffold	Molecular IDO, PGE_2, TGF-β1, IL-10, and HGF increased in the scaffold concentration group	Liu *et al*., 2012
	Exosome and collagen scaffold	M2 macrophage polarization, reduced inflammation(IL-1β, TNFα, IL-6), increased anti-inflammation(IL-10, TGF-β)	Xin *et al*., 2020
Human dental pulp	bFGF-heparin hydrogel	Attenuated the proinflammatory (IL-6, TNFα)	Albashari *et al*., 2020

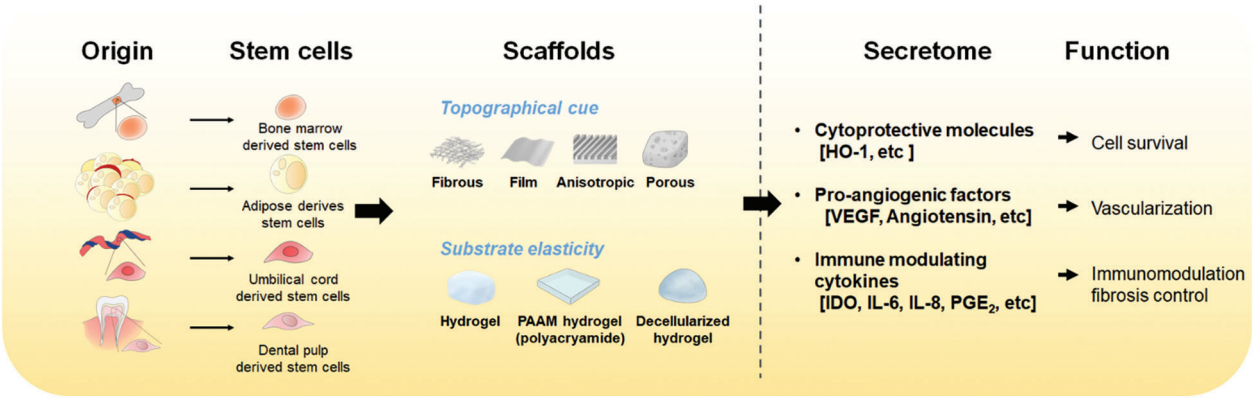

FIGURE 1. The effect of scaffolds on MSC cultivation and the function of secretome from MSCs. MSCs can be cultivated on various types of scaffolds. The optimal topographical cue and substrate elasticity of scaffolds provide a better environment than regular culture plates for MSCs to improve their paracrine effect. Secreted factors from MSCs include cytokines, nucleic acids, and proteins which play roles in improving cell survival, vascularization, or immunomodulation.

similarity of these substrates (in terms of their structures and properties) for MSC cultivation can improve both the paracrine effect and the differentiation of stem cells, thus enhancing the feasibility and efficacy of MSC therapies for clinical applications (Fig. 1). Now, it is important to consider how the improved function of MSCs can be maintained sustainably within scaffolds or how long the injected MSCs can survive after *in vivo* transplantation. Thus, thermo-responsive or injectable hydrogels and adhesion-related ligand-containing hydrogels are being actively developed (Hong *et al.*, 2019). In this regard, more biocompatible scaffolds need to be further developed to take advantage of the paracrine products of MSCs. Such studies could help to promote cell therapy and achieve efficient translational research.

Availability of Data and Materials: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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