Role of Biomaterial Scaffolds in Tissue Engineering and Stem Cell Therapy

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Biomaterials form a powerful and indispensable tool in the study of stem cells and their application to regenerative medicine.

It has long been recognized that stem cells hold tremendous therapeutic potential for a variety of diseases and injuries, particularly for numerous ailments that have no effective treatments, but restoring tissue and organ functions with stem cells has also posed several challenges that remain to be overcome. One approach for surmounting many of these limitations and significantly advancing capabilities of stem cells in therapeutic applications is the use of biomaterials with stem cells. Biomaterials offer numerous advantages and expand capabilities that generally cannot be achieved with stem cells alone, particularly in the case of implanting cells and reconstructing damaged tissue.

Synthesis of Form and Function

Tissue engineering aims to restore the function of damaged or diseased tissue by the use of stem cells and biomaterials. Biomaterials generally include forms of natural or synthetic matrix molecules that replicate aspects of innate extracellular matrix in various tissues. This biomaterial scaffolding can serve many functions, such as supporting structural organization of cells, providing cell signaling and differentiation cues, providing attachment points for cells and aiding anchorage-dependent survival, as well as preventing cells from being washed away from implantation sites in the body [1]. Many types of biomaterials have been shown to influence the survival and function of developing stem cells, and biomaterial designs can recapitulate the cellular interactions, matrix characteristics, biochemical gradients, and signaling events that occur in development, in addition to supporting cell survival, differentiation, and integration into innate tissue.

Anatomical Organization

The suspension of biomaterial polymers in an aqueous medium enables cells to be cultured in 3D configurations, which helps form unique structures and functions found in many types of organ tissues. This was shown in cerebral organoids, where clusters of pluripotent stem cells were cultured in spheres of proteinaceous Matrigel to create numerous types of neural structures and cell types [2]. 3D hydrogel cultures of stem cells have been shown to enable the formation of other advanced anatomical structures, including various gastrointestinal, hepatic, pancreatic, renal, retinal, and cerebral tissues. The cells themselves appear to possess innately-programmed capabilities to self-assemble at least some aspects of important anatomical structures even in unpatterned hydrogel constructs. For example, neural tissue organoids have demonstrated various aspects of ventricular, hippocampal, retinal, spinal, and cortical regions [2–4]. The use of biomaterials in clinically-relevant testing has also shown promise in enhancing cell survival [5], promoting a favorable regenerative environment [6], and extending neural connectivity through neural lesions [7].

Architectural Effects on Cells

Advancing technologies may also enable biomaterials to provide detailed guidance of cellular and even subcellular architecture. For example, inclusion of functionalized polymer nanofibers within hydrogels can serve as cell attachment scaffolding that directs neurite outgrowth along the fibers [8]. Even characteristics like biomaterial stiffness, density, and cross-linking capability can influence the cell differentiation and function [9]. In addition, a wide array of tissue types and cell states can be achieved within the same choice of biomaterial, either by means of intrinsic cell signals or by means of various growth factors and differentiation factors that can be supplied within the biomaterials. Thus much research remains to be done on the optimal combinations of biomaterials, signaling factors, scaffolding architectures, and culture medias needed to optimally prepare cells for transplantation and integration into specific tissues of the body.

Biocompatibility

In addition, biomaterials may help enhance the biocompatibility of certain tissue implants. Certain types of matrix molecules may inhibit inflammatory and scarring reactions that arise from disrupting tissue or introducing a foreign body into the tissue, either by interacting with cellular receptors or by absorbing and diffusing reactive cell signaling factors. If the biomaterial takes too long to degrade or has too great of stiffness compared with the innate tissue, it may trigger foreign body reactions that prevent functional integration of the implanted cells; conversely, if the biomaterial degrades too quickly or is too elastic or friable, it may not adequately support functional integration of implanted cells into the tissue. Biomaterial polymers can be designed to facilitate integration into host tissue, minimize foreign-body reactions, and enhance the permissive environment of the tissue.

The Role of Diffusion

Recent research has also suggested that the inherent diffusion limitations of gasses and nutrients through 3D tissue cultures can specifically affect cellular organization, differentiation state, and metabolic characteristics of cells [10]. Biochemical signaling factors included in the 3D tissue construct can form diffused concentration gradients that direct differentiation, axis patterning, and other cellular identities and functions at distinct regions of the tissue construct. Understanding these diffusion processes will better help deliver specific controllable concentrations of ions, nutrients, and growth factors to specific regions of the cellular tissue constructs, which in turn will enable tight control of cell state and differentiation processes. Evidence suggests that stem cells implanted into the body may have better survival if they are cultured and prepared under certain conditions of stress or exposure, a form of “preconditioning” the cells [11], and culturing cells in 3D conditions with limited diffusion is one way of achieving the preconditioning effect.

Conclusions

Altogether, it can be seen that when attempting to design ideal cellular constructs for implantation, numerous aspects must be carefully considered in the context of the specific tissue type and the desired functional effects. Restoring function in tissues and organs—whether brain, heart, lung, liver, kidney, nerve, muscle, or other tissues—is likely to require reconstructing functional architecture of the tissue rather than simply integrating isolated cells. Recent stem cell research has therefore focused on the application of biomaterials along with stem cells to enable desired patterning and organization of more accurate and complete tissue structures, and this work is of great import to regenerative medicine efforts.

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