



Extracellular Matrix Plays an Important Role in Stem Cell Biology

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Introduction

In vivo stem cells live in a complex microenvironment called stem cell niche [1-3]. Stem cell niche can affect stem cell behavior and regulate stem cell fate by multiple signals. These signals may be structural, physical, electrical or biochemical. In the human body, the stem cell microenvironment can maintain adult stem cell in a quiescent state. But after the tissue injury, the surrounding microenvironment actively sends out signals to promote self-renewal and differentiation of stem cells to form new tissues. Some factors are significant to their properties in the microenvironment, such as interactions between stem cells, interactions between stem cells and surrounding differentiated cells, interactions between stem cells and adhesion molecules, extracellular matrix, oxygen tension, etc. Extracellular matrix (ECM) is an important component of stem cell niche, which involved in almost all of these signals [4,5]. Cells elaborate their ECM by secreting proteins, which in turn regulate cell behavior and influence the remodeling of ECM [6,7].

There are many kinds of macromolecules in the ECM, which can be generally classified into different main groups: fibrous proteins, including collagen, elastin, fibronectin, and laminin; proteoglycans (PGs), and glycosaminoglycans (GAGs) [8]. Collagen is the most abundant protein in humans, which accounts for more than 30% of the total protein. It is located in a variety of organs and tissues in the body and it is a frame structure in the ECM, which can be synthesized and secreted by fibroblasts, chondrocytes, osteoblasts and some epithelial cells. It is designed to provide strength and resiliency to tissues, and able to regulate cell adhesion, chemotaxis, and migration, and to guide tissue development [9,10]. Fibronectin (FN) has plenty of functions that ensure the normal function of vertebrate organisms. It is involved in cell adhesion, growth, migration, and differentiation. Cellular fibronectin is assembled into the extracellular matrix, an insoluble network that separates and supports the organs and tissues. FN is involved in many diseases, such as cardiovascular disease and tumor metastasis [9,11]. Proteoglycans (PGs) are a major component of the animal ECM. They are involved in binding cations (such as sodium, potassium and calcium) and water, and also regulating the movement of molecules through the matrix [12]. Evidence also shows that they can affect the activity and stability. PGs can interact with growth factors, cytokines and chemokines, and interact with other ECM molecules in the process of different cell functions, which is beneficial to the formation of ECM scaffold [13].

ECM plays an active role in cell life: survival, motility, and communication. ECM not only provides structural scaffold for cells, but also promotes the function of cells and organs. Besides, ECM is of significance in regulating cell function in different ways, such as mechanical stimulation which can change the stiffness of the matrix

components, thereby directly affecting cell differentiation [14-18]. Moreover, ECM can regulate the availability and activity of soluble factors by combining its own components with many soluble factors (e.g. BMP). In addition, ECM proteins can interact with cell adhesion molecules, thereby affecting chemical signals and intracellular signals, as well as stem cell differentiation. Thus, ECM affects cell processes, and even gene expression through different stimulus [19]. In addition, it is worth mentioning that, ECM is also involved in cell death process. In fact, programmed cell death, also known as anoikis, is due to a decrease in the interaction between the cells and ECM which is resulting from detachment between cells and ECM [20].

It is demonstrated by Lynch and Pei [21] that the age-associated changes in proliferation and differentiation ability of mesenchymal stem cell (MSC) and the use of the ECM derived from young cells can rejuvenate old cell. In conclusion, the stiffness of ECM gradually increases with age, collagen and GAG accumulation, as well as the accumulation of other proteins. Their laboratory also showed that young ECM can promote MSC proliferation to a greater extent compared with mature ECM. Therefore, it is concluded that fetal ECM may promote the proliferation of stem cells in a manner similar to how adult ECM can direct MSC differentiation. What is more, Sun et al. [22] believed that ECM can maintain the function of MSC under normal circumstances, but aging can negatively affect the formation of ECM. When cultured on the young- ECM, the aged MSC can be rejuvenated.

Wang et al. [23] reported how ECM and its interaction with integrin receptors affect embryonic stem cells (ESC) differentiation. A more reasonable understanding of integrin-mediated interactions between cells and ECM and integrin signaling pathways in ESC differentiation may improve the effectiveness and specificity of ESC differentiation in research and clinical applications.

Interestingly, Marinkovic et al. [24] proposed that ECM is tissue-specific. They used bone marrow-BM-derived and adipose (AD) - derived stromal cells to prepare BM-ECM and AD-ECM which are decellularized to mimic the cellular niche of these tissues. Each ECM can influence the BM and AD-derived cells proliferation, cell stretch, and direct proliferation on the surface of tissue culture polystyrene (TCP) surface. Also, they found that the effect of proliferation of BM-derived MSC is more remarkable than the AD-derived MSC, and vice versa. In addition, BM-ECM and AD-ECM have significant effects on the osteogenic and adipogenic differentiation of MSC respectively, indicating that ECM has tissue specificity. Moreover, each ECM has an ability of affecting cell morphology, regardless of cell origin, and the results further suggested that ECM is tissue-specific.

ECM has great prospects in the field of tissue regeneration, because it has immune tolerance, thereby it comes about minimal immune

rejection in the receptor [25]. Besides, ECM provides a physical and functional environment for cells. Therefore, the purpose of using ECM as scaffold in tissue engineering is to mimic the ECM structure of the target tissues as much as possible. For instance, Ott et al. [26] decellularized lungs and seeded scaffolds with epithelial and endothelial cells to regenerate gas exchange tissue. After transplanted, the ventilation function regenerated lung was restored. With these technologies from laboratory to clinical applications, ECM is bound to create a broad field of medical transplantation tissue engineering. Taking into account the impact of these technologies on the quality of life of patients, the ECM-based regeneration technology needs to be continually re-evaluated.

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