Growing, Tracking, and Directing Bone Marrow Derived Stem Cells From Two-Dimensional and Three-Dimensional Cell Culture Microenvironments

Tiffany Miller [1]

[1]USF

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Abstract

Bone marrow derived stem cells express biomarkers capable of facilitating adhesion to the cell culturing microenvironment, thereby, influencing their proliferation, migration, and differentiation. In particular, biological biomarkers of mesenchymal stem cells include, but are not limited to, CD14-, CD19-, CD34-, CD45-, CD29, CD44, CD73+, CD90+, CD105+, CD106, CD166, Stro-1, and HLADR. The relationship between the stem cell biology and the materials and methods forming a cell culturing microenvironment serves as a critical aspect in the successful adhesion and growth within two-dimensional cell culture microenvironments such as polystyrene, laminin, fibronectin, or poly-L-lysine and within three-dimensional cell culture microenvironments such as hydrogel, ceramic, collagen, polymer based nanofibers, agitation, forced floating, and hang drop systems. Further, electrical stimulation of the stem cells may be implemented during the cell culturing process to measure stem cell growth and to determine stem cell viability. In addition, electrical stimulation of implanted stem cells may facilitate tracking by measuring stem cell migration distance and travel area. Although many biochemical and inflammatory biomarkers are expressed based on severity in stroke including, but not limited to, Interluken-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and glutamate (Glu), current methodologies of stem cell directing lack localization and biological effector specificity. Biological effector bound magnetic particle stem cells may serve as a potential treatment method in ischemic stroke. In particular, a stem cell biomarker may be configured to communicate with inflammatory biomarkers, thus, more efficiently delivering the stem cells to site specific areas having the most severely affected *in-vivo* biochemical microenvironments.

Specific Aims

Scientific evidence demonstrating the safety and efficacy of stem cells in animal models of focal cerebral ischemic stroke provides the basis for transplantation of human bone marrow mesenchymal stem cells (hBMSCs) as a treatment strategy in reducing the stroke secondary cell death [12]. In the laboratory, these hBMSCs are routinely grown in an artificial environment during the cell culturing process. The health of*in vitro* cultured hBMSCs is measured by including, but not limited to, the success rate of stem cell proliferation, migration, and differentiation, collectively referred to as stemness, which can be measured via microscopy [2]. We posit that introduction of electrical stimulation to the cell culture system enhances stemness. Accordingly, we will probe the role of electrical stimulation as a putative stemness enhancer under ambient and pathological condition.

Specific Aim 1: To test the hypothesis that finding the optimal regimen of electrical stimulation will enhance stemness of hBMSCs grown under ambient condition.

Specific Aim 2: Next, using the optimal electrical stimulation regimen from Aim 1, we will test the hypothesis that electric stimulation will enhance the therapeutic effects of cultured hBMSCs against an experimental stroke.

Investigations on the effects of electrical stimulation on proliferation, migration, and differentiation of cultured hBMSCs will likely provide the optimal microenvironment conducive for amplifying the stemness and therapeutic properties of stem cells as a safe and effective donor cells for transplantation therapy. Understanding the key stemness-relevant factors may guide the cell culture optimization process. In particular, we are interested in electrical stimulation, as studies have revealed that brain injury resulting from central nervous system disorders such as stroke may be treated with transplantation of hBMSCs and then applying electrodes into the brain to deliver electrical stimulation [11]. Moreover, electrical stimulation of the brain resulted in an increased stemness potential of the transplanted hBMSCs [11]. To date, however, the direct link between electrical stimulation and cell culture microenvironment remains unexplored and represents a major gap in knowledge about stemness. Thus, we propose to elucidate the involvement of electrical stimulation in the cell culture microenvironment in an effort to gain insights on enhancing stemness of hBMSCs.

We hypothesize that electrical stimulation in the microenvironment facilitate stemness of hBMSCs under ambient condition.. Further, such electric stimulation when applied under stroke setting will not only enhance stemness but also exert neuroprotection. Our overarching hypothesis is that enhancing the stemness of hBMSCs via electrical stimulation will enhance their therapeutic effects against stroke and relevant neurological disorders.

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