

Use of Adult Stem Cells in Biomaterials Research

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All mature cells in the human body originate from stem cells. Stem cells are generally defined as cells that can renew themselves in addition to possessing potential to differentiate in one or multiple lineages. Current studies indicate great possibilities for use of both embryonic as well as adult stem cells in regenerative medicine. The more easily available adult stem cells, especially mesenchymal stem cells have led to extensive application of their use in a variety of topics in regenerative medicine. The self-renewal characteristic of MSCs occurs through symmetric and asymmetric cell divisions [1]. Specific criteria are laid out by the International Society for Cellular Therapy for the identification of MSCs [2]. The potential for use of stem cells in regenerative medicine is tremendous and progress in recent years suggests an advent of transformational improvement in regenerative medicine capabilities through engineering design of stem cell use in comparison to transplant technologies. The use of stem cells opens many challenges that are of clinical, scientific and ethical nature. Adult stem cells are being extensively studied for application in replacement of tissues. Human Mesenchymal Stem Cells (hMSCs) derived from the bone marrow are adult stem cells that are easily available and are used in tissue generation including tissue engineering methodologies. Tissue engineering, a field pioneered by Langer and Vacanti [3] utilizes 3D porous structures called scaffolds that are seeded with human cells. These scaffolds are provided appropriate growth factors and life-like conditions often inside bioreactors. The materials of the scaffold degrade as the seeded cells grow and proliferate (and differentiate) and make new tissue. Many advances have been reported recently, in all areas of the scaffold design and fabrications [4], materials design of scaffold [5], parameters of bioreactors such as flow rates of media as well as the choice of growth factors and their delivery methods. Rapid prototyping techniques show much promise in development of custom designed tissues and organs [6,7]. The role of porosity (sizes and connectivities) in scaffolds in appropriate differentiation, proliferation and eventual role on vasculature formation is also an important design parameter [8]. Nanominerals such as hydroxyapatite in combination with various synthetic [9,10] and biobased polymers [11-13] are extensively investigated as materials for scaffolds. Efforts in experimental investigation of degradation of these composites in their solid and scaffold forms are extensive. Recently, nanoclays have been demonstrated as a potential new material system for scaffolds in tissue engineering [14,15]. For MSCs applications in tissue engineering, the MSCs cells seeded on the scaffolds need to adhere to the scaffold materials and also easily migrate to the interior regions of the macroscopic scaffold. The role of integrins and focal adhesions of the cells are significant in the adhesion and migration of the cells. Integrins are the most important receptors responsible for cellular adhesion processes with the extracellular matrix as well as with other cells. It is paramount that the materials used in tissue engineering, and the nano-micro-meso structure of the scaffold provides an environment that is conducive to cell-scaffold adhesion. The mechanism of the integrin activity is through binding to a range of ligands on the cell surface and the extracellular matrix [16]. This binding enables the receptors ability for signal transport between inside of the cell and outside.

Further advantage of use of MSCs involves their ability to avoid allogenic rejection in humans and animals [17]. Problems associated

with immune rejection are avoided with use of MSCs due to the immunomodulatory effects of MSCs in tissue engineering. Currently, during *in vitro* expansion of MSCs an important issue encountered is senescence resulting in permanent arrest of cell division due to a permanent growth arrest phase during the cell cycle [18]. On some occasions, loss of multipotentiality is also observed in the MSCs. The controlled and effective *in vitro* expansion of MSCs remains an important area of research that needs to be pursued for extensive applications of MSCs in tissue engineering. In addition both electrical and mechanical stimuli are potentially useful for influencing behavior of MSCs and their use in tissue engineering [19-21].

One area of research that is most promising and currently least developed is *in silico* design of biomaterials as well as scaffold design. Although much work has been done on use of finite element and other continuum based approaches to model scaffold characteristics [22,23], degradation of the scaffold-cell constructs over time is not well understood and investigated. Scaffold degradation behavior is primarily modeled through existing degradation models of polymers, while the nanocomposite scaffold materials exhibit degradation mechanisms, fairly different from those of pristine polymers. Further, extensive molecular models of materials of scaffolds present a significant design parameter that would require extensive studies in multiscale modeling to develop robust predictive capabilities of scaffolds over the time scale of degradation and cellular attachment, migration, proliferation and differentiation. In addition, computational approaches that enable predictive capability to scaffold degradation as well computational materials science [24,25] for design of nanocomposite scaffolds has shown much promise.

The vast and extensive literature on use of hMSCs in tissue engineering has certainly led to high expectations on the potential of use of hMSCs in tissue engineering primarily due to large numbers of successes in achievement of vasculature, enhanced differentiation capabilities etc. reported. Fundamental cell biology studies in behavior of hMSCs their interaction with engineered materials are still a challenge. Additionally advanced characterization tools that enable characterization of the living-nonliving interface *in situ*, such as nano mechanical characterization and scanning probe microscopy appear promising based on a few recent studies [26]. The promise of successful clinical possibilities in this area is a real possibility. Multiscale computational studies as well as fundamental cell biology studies are key to fulfillment of the promise. Advances in materials design and manufacturing techniques aided by the above two factors, is likely to revolutionize and increase exponentially the use of stem cells for regenerative medicine in the coming decades.

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