Smooth Muscle Cells for Vascular Engineering

Y. Eugene Chen, Changqing Xie, Milton Hamblin

In the first decade of this century, ever-increasing scientific and technological advances are revolutionizing our approaches to developing therapies that bring about the promise of personalized medicine and the possibility of regenerative interventions. Multidisciplinary research has led to a better understanding of four key areas of scientific and technological knowledge that are essential to the development of such innovative therapies for cardiovascular disease: (1) increased understanding of normal development and cell differentiation processes in vivo; (2) elucidating signaling pathways involved in these processes; (3) uncovering new technological approaches that can efficiently mimic these processes in vitro; and (4) most importantly, the identification and characterization of adequate sources of precursor cells that serve as the starting material for regenerative undertakings.

See accompanying article on page 2938

A normal vasculature is crucial for maintaining homeostasis and providing the necessary nutrients to cells of the human body. Therefore, impairment to the integrity of blood vessels will lead to various complications. Cardiac and peripheral vascular diseases have been the major causes of morbidity and mortality in the Western world. Currently available therapies rely on the implantation of stents or grafts for reconstruction of blood conduits. However, the availability of suitable venous and arterial grafts for implantation is a challenge, and furthermore these therapies may not be sufficient for complete recovery of function and integrity of the injured vasculature. Thus, alternative vascular drains that have the ability to mechanically and biologically fulfill the properties of native vessels are in high demand. Engineered cell-based vascular therapies, which include a combination of vascular cells, scaffolding, and signaling to form biologically active vessels, offer the possibility of permanent and effective treatments for many vascular diseases.

Vascular smooth muscle cells (SMCs), in addition to playing an important role in maintaining viability and activity of the vascular endothelium, also regulate blood pressure in response to various stimuli. Therefore, the tunica media, the tissue layer containing functional SMCs, is critical for the successful regeneration of damaged vascular tissue (Figure). Mature vascular SMCs isolated from donor tissue have been used for the construction of tissue-engineered blood vessels. However, primary SMCs from native vessels have a limited capacity for proliferation and expansion, making it necessary to explore alternative sources of SMCs or smooth muscle-like cells.

Through fate-mapping studies, at least 8 independent origins of vascular SMC progenitors have been identified in the developing embryo, indicating substantial variation in derived SMCs and features within the vascular system. In addition to the numerous independent origins of vascular SMCs, there are several adult stem cell sources of vascular SMCs for vascular engineering. Those stem cells include (1) mesenchymal stem cells (MSCs) from bone marrow, umbilical cord, adipose tissue, vessel wall, and placenta; and (2) endothelial progenitor cells from bone marrow, peripheral blood, umbilical cord blood, adipose tissue, and vessel wall (Figure).

Biopsied skin samples may serve as alternative vascular SMC sources for vascular engineering, as indicated by recent studies. Specifically, in this issue of ATVB, Steinbach et al provided detailed evidence that skin-derived precursor cells (SKPs) can be manipulated to differentiate into SMCs. In this study, adult SKPs derived from different species were differentiated in response to transforming growth factor (TGF) signaling, which is known to direct neural crest stem cells to a SMC lineage. Interestingly, under serum-free conditions, TGFβ-stimulated human SKPs can differentiate into SMCs with high efficiency. However, with respect to enhanced SMC differentiation, rat and human SKPs appear to have different responses to TGF signaling. Most studies have shown that TGF-β reduces MSC proliferation but does not enhance SMC differentiation from MSCs. For example, TGF-β was shown to differentiate rat bone marrow MSCs into SMCs. Furthermore, human MSCs cultured in the presence of TGF-β1 were also able to differentiate into SMCs. However, in terms of directed SMC differentiation, neural crest derived SKPs, when compared with MSCs, may respond differently to TGF-β stimulation, in which c-Myb may partially contribute to this differential response. The study by Steinbach et al shows that TGF-β not only enhances SMC marker expression in human SKPs, but also promotes SMC proliferation, thus providing a promising source for efficient high-throughput SMC generation and the potential for future application in vascular engineering (Figure).

However, the detailed molecular mechanisms that initiate and control TGFβ-stimulated SKP-directed SMC differentiation are unclear. Thus, a detailed investigation of TGF-β function and expression profiles during the SKP to SMC differentiation process will lead to novel insights into the signaling pathways driving toward SMC differentiation. In addition, the effects of TGF-β on SKP telomerase activity and telomere length, which

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tive to determine the in vivo short-term and long-term responses of reconstructed vessels containing SKP-derived SMCs and determine whether SKP-derived SMCs retain SKP epigenetic memory. This may impact the physiological processes necessary for proper vascular repair. Moreover, SKP-derived SMCs have yet to be studied for their biocompatibility within appropriate bioactive scaffolds, which will be the next logical step toward translating these findings as a viable therapy for patients afflicted with vascular diseases.

Additionally, other lines of ongoing technological approaches and alternative sources of SMC production for vascular engineering have become increasingly reliant on the utilization of pluripotent stem cells, which include embryonic stem cells and induced pluripotent stem cells (iPSCs) cells. Recent proof-of-principle studies involving second-generation iPSC technologies and patient-specific transplantation treatment despite the undeniable remaining challenges regarding the application of personalized iPSC cells.

**References**


**Figure.** Schematic of vascular engineering in vitro using stem cells for eventual application of engineered vessels to patients. ECs indicates endothelial cells; SMCs, smooth muscle cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.


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