Human models for smooth muscle cell differentiation. Focus on “A novel in vitro model system for smooth muscle differentiation from human embryonic stem cell-derived mesenchymal cells”

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THE STRUCTURE AND FUNCTION of smooth muscle cells (SMC) may be very similar from the vascular system to the gastrointestinal tract to the respiratory system, but they are known to react to stimuli in precise ways to enable tissue-specific actions to occur. The rationale for such differing responses is still largely unknown, and some of the most recent data suggest that they may originate from different progenitor populations. Perhaps the most well-studied smooth muscle progenitor cell is in the cranial neural crest of the embryo. Lineage tracing experiments have also shown that progenitor cells exist in the secondary heart field, somites, mesangioblasts, proepicardium, splanchic mesoderm and mesothelium; other circulating stem cells are also able to give rise to SMC. It is difficult to study intracellular mechanisms governing the heterogeneity in the differentiation of SMC from these different progenitor populations without good in vitro models.

Over the past decade several groups have focused on the mechanisms of differentiation to SMC utilizing both adult and embryonic stem cell populations (2–4, 6–9). The advent of induced pluripotency provides an unlimited source of human cells, and robust differentiation protocols are now in place to derive neural and mesenchymal stem cells from induced pluripotent stem cells (iPSC). The work by Guo and colleagues (1) featured in the current issue of American Journal of Physiology-Cell Physiology utilized iPSC-derived mesenchymal stem cells (iPSC-MSC) as a renewable source of cells to study the differentiation of MSC to SMC (1). This study follows their previous work where they modeled SMC differentiation from iPSC-derived neural stem cells (NSC; 8). Understanding the differentiation mechanisms of SMC may be critical in elucidating the cellular and molecular changes that occur during the development and progression of diseases where SMC dysregulation is prominent: such diseases include cardiovascular diseases like atherosclerosis and hypertension.

It is well established that transforming growth factor-β (TGF-β) is capable of inducing SMC-like differentiation. In rat bone marrow–derived MSC the mechanism involved Smad2 binding to the CaRG box in the SM22α promoter (10). This mechanism is similar to that described in the Guo article, where upregulation of smooth muscle-dependent genes was shown to be dependent on serum response factor (SRF) and myocardin binding CaRG. When investigating the signaling pathways responsible in human iPSC-MSC, inhibition of the p38 MAPK, PI3K, and Smad2/3 pathways all impacted SMC differentiation (1). In a similar investigation using mouse embryonic MSC, increased phosphorylation of ERK, JNK, p38 MAPK, and PI3K was observed; however, only disruption of the PI3K/AKT pathway prevented generation of SMC (7). Like the human iPSC-MSC in the Guo study, the mechanisms involved nuclear binding of SRF to CaRG (7).

Interestingly, the mechanisms discovered in Guo’s study differ from those already discovered in neural crest progenitors and adipose-derived mesenchymal stem cells. TGF-β is integral for the upregulation of SMC markers, SM22α, calponin-1, and smooth muscle myosin heavy chain (SM-MHC) and the assembly of stress fibers in all progenitor cells. In neural crest cells, the signaling pathway involves response gene to complement 32 (RGC-32) binding to polyomovirus enhancer element (PEA3) and SBE, leading to SMC gene transcription (2), and in adipose-derived MSC, angiotensin II is able to upregulate the transcription of SMC genes via induction of TGF-β and activation of a MEK/ERK/Smad2-dependent pathway (4). More recently, the adipose-derived MSC differentiation has been shown to involve a TGF-β-dependent upregulation of ADAM12, a metalloprotease family member, localized to lipid rafts in adipose cells; disruption of the ADAM12/lipid raft complex severely attenuated the differentiation to SMC (5). In adipose-derived MSC, sphingosylphosphorylcholine (SPC) can induce SMC differentiation via a Gαo-ERK-dependent autocrine secretion of TGF-β, which subsequently activates the Smad2-SRF/myocardin-dependent pathway (3).

It appears that the cellular pathways governing SMC differentiation are complex. In MSC, RhoA, for example, is known to regulate the nuclear/cytoplasmic localization of myocardin-related transcription factors (MRTFs), and Notch signaling, via TGF-β-induced upregulation of Notch ligand Jagged-1, is dependent on SMAD3 and RhoA signaling (6). The latter pathway also is involved in human embryonic stem cell differentiation to SMC. While Guo and colleagues investigated the TGF-β-dependent activation of SMAD2/3 and binding of SFR and its coactivator, myocardin, to the CaRG domain in Acta2 and Tagln promoters, they did not extend their study to look at potential roles for Notch or RhoA (1). Figure 1 provides a diagrammatical summary of the currently known differentiation mechanisms from iPSC-MSC, neural crest progenitors, and adipose-derived MSC.

It may be that such intricacies in the differentiation mechanisms correspond to the mature SMC subtypes; many more studies will be necessary to fully elucidate this. Mouse- and rat-derived cells can shed much light on SMC differentiation pathways; however, there are many known differences in the development and differentiation of cells in comparison to humans; studies like the current one by Guo and colleagues, utilizing iPSC-derived progenitor cells, will be at the forefront of understanding the mechanisms in human SMC differentiation. Furthermore, given the number of diseases where a myofibroblast phenotype is acquired by cells, contributing to vascular remodeling and scarring, an understand-
ing of the acquisition of a SMC phenotype in a variety of human cells may identify novel mechanisms and therapeutic targets for these diseases.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

A.L.F. and J.X.-J.Y. prepared the figure; drafted the manuscript; edited and revised the manuscript; approved the final version of the manuscript.

REFERENCES


