Give your heart a chance: match the muscle to the vessel

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This editorial refers to ‘Serum-free differentiation of function-al human coronary-like vascular smooth muscle cells from embryonic stem cells’ by El-Mounayri et al., pp. 125–135, this issue.

Trace lineage studies have provided strong evidence that vascular smooth muscle is a mosaic tissue deriving from multiple independent developmental origins including the neuro-ectoderm-derived neural crest, lateral plate mesoderm, and paraxial mesoderm.1 However, the differences between vascular smooth muscle cells (VSMCs) of different origins remain largely unexplored, especially for human cells. In addition, the relationship between pericytes surrounding the vessel wall and VSMC is not well understood. It is also widely recognized that blood vessels in certain anatomic locations are more likely to develop vascular disease despite the systemic nature of risk factors such as hypercholesterolaemia or diabetes.2 The different origin of VSMCs is thought to be a possible contributor to this site-specific pre-disposition to vascular disease, suggesting that development of site-specific treatment(s) might provide more effective therapeutic options. Finally, donor ageing and culture senescence were shown to impair both the proliferation and contractile function of VSMCs,3 necessitating the development of novel approaches to restore their regenerative potential.4

These reasons led several investigators to explore ways to derive VSMCs from embryonic stem cells (ESCs) and human induced pluripotent stem cells (hiPSCs),5–8 which provide an ideal system for re-adding to impair both the proliferation and contractile function of VSMCs,3 pre-disposition to vascular disease, suggesting that development of this issue.

In this paper, El-Mounayri et al. took on the challenge of generating tissue-specific SMCs that exhibited unique molecular and functional signatures resembling coronary-like SMCs.10 In a step-wise protocol, they first derived a population of primitive streak-like hESCs using a combination of activin A, bone morphogenetic protein 4 (BMP4), and basic fibroblast growth factor (bFGF). Further specification into cardiovascular mesoderm via lateral plate mesoderm was achieved by endothelial growth factor (VEGF) and dickkopf homolog 1 (DKK1). Subsequent expansion in the presence of both bFGF and VEGF was required to transition from cells exhibiting a mixed phenotype to two distinct populations of cardiomyocytes (CM) or VSMC, as verified by expression of troponin (TNNI3) or α-actin (ACTA2), respectively. Interestingly, the resulting VSMCs exhibited similar contractile function as coronary artery-derived SMCs but were significantly different than aorta- or bladder-derived SMCs. Finally, using GFP-expressing hESC-derived VSMCs, the authors demonstrated that these cells integrated into the newly formed mouse vasculature by 3 weeks post-implantation, similar to native mature VSMCs. These results clearly demonstrated that developmentally inspired strategies can recapitulate in vivo developmental pathways to generate tissue-specific SMCs.

The ability to generate coronary-like cells from patient-specific hiPSCs may be particularly useful in studying disease pathophysiology in vitro by providing a basis for evaluation of various environmental stressors, including hypercholesterolaemia, hyperglycaemia, or oxidative stress in disease development. Comparison of cellular responses using cells from cohorts of patients may have the potential to offer novel insights into the relative importance of genetic vs. environmental (epigenetic) factors in the development of coronary artery disease. Consequently, such systems may facilitate development of personalized medicine, by providing a patient-specific platform for drug screening. Finally, patient-specific coronary-like
VSMCs may serve as an abundant source of autologous cells for tissue engineering and regenerative medicine. After all, matching the muscle cells to the diseased blood vessel that must be regenerated may improve remodelling and reduce long-term complications, ultimately enhancing the therapeutic benefit of bioengineered vascular grafts.

The study by El-Mounayri et al. was the first study that reported tissue-specific SMCs using a developmentally inspired differentiation strategy. Consequently, it raises many interesting questions that will need to be answered in the future: (i) Is this strategy generalizable to other blood vessels? Given the limited number of diffusible signals that regulate cell fate, what other strategies can be developed to establish lineage commitment? (ii) Can this strategy be adapted to other SMC-containing organs, e.g., airways, intestine, uterus, bladder, or oesophagus? (iii) How about other cell types that may also display molecular and phenotypic differences depending on anatomic location, e.g., endothelial cells of arterial, venous, or lymphatic vessels?

Answers to these questions may require broad collaboration between developmental biologists, bioengineers/tissue engineers, and clinicians to bear fruit. Evidently, developmental biology provides the guiding principles for the development of similar strategies. On the other hand, engineering of three-dimensional (3D) tissue constructs may facilitate evaluation of tissue-specific cells in a 3D context using appropriately designed molecular and functional assays. This approach will provide a more physiological platform for addressing developmental questions as well as for drug screening. It may also facilitate the success of regenerative medicine. Matching the right cells to the right organ might provide site-specific remodelling leading to tissue-tailored attributes, e.g., biomechanics, ultimately enhancing the likelihood of long-term success of cellular therapies.

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References