Plasticity of adult endothelium: how frequent and to what extent?

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This editorial refers to ‘Endothelial-to-mesenchymal transition contributes to fibro-proliferative vascular disease and is modulated by fluid shear stress’ by J.-R. Moonen et al., pp. 377–386.

In most healthy blood vessels, average endothelial cell turnover is very low, with cell lifespan estimates of up to many years—hardly indicative of a cell type that might be expected to undergo substantial proliferative and phenotypic changes in response to external stimuli. This contrasts with the relatively rapid and continuous turnover of many epithelial cell linings, with replacement by generation from local progenitor cells, such as in the skin or gut. However, this perspective needs to be balanced by our knowledge of significant and rapid alterations in endothelial cell behaviour in the control of vascular homeostasis, for example in response to altered shear stress or to pro-inflammatory mediators. And, indeed, there are also clear examples of the ability of adult endothelium to chronically adapt its phenotype. One of these is the generation of so-called high endothelial venules at sites of chronic inflammation, where the thickened endothelial cells are specialized to enhance lymphocyte trafficking and the phenotype is maintained by paracrine interactions between the two cell types.1 An early elegant and innovative experimental demonstration of a chronic switch in endothelial cell function in response to an external stimulus was provided by Aird et al.,2 using transgenic mice carrying in all (endothelial) cells a reporter cassette in which a section of the von Willebrand factor (vWF) promoter sequence is tagged to a reporter gene. Native vWF is variably but essentially ubiquitously expressed in all endothelium, but the reporter gene was only active in some vascular beds. Tissue transplantation demonstrated that reporter activity was specifically dependent on factors secreted from neighbouring tissue cells. Similarly, local paracrine cues are primarily responsible for the differentiation of primitive endothelium into distinct arterial, capillary, venous, or lymphatic lineages and for the maintenance of specialized fenestrated endothelium such as in the renal glomerulus.3,4 Finally, endothelial cell phenotype is chronically, but reversibly, adapted to altered conditions of local blood flow and shear stress.5

None of these types of phenotypic differentiation involves migration away from the endothelial monolayer and transition into an alternative mesenchymal cell type. In contrast, such a transition in epithelial cells (‘endothelial-to-mesenchymal transition’ or EMT) is well documented. Mouse embryo primitive streak epiblast cells undergo EMT in vivo during development. In vitro maintenance of an epithelial morphology or transition to a fibroblastic morphology in these cells is dependent on exposure to different cell matrix proteins.6 Miettinen et al.,7 exploring the phenotypic alterations of cultured mouse mammary epithelial cells in response to TGFβ, showed decreased expression of epithelial cell marker proteins including E-cadherin and ZO-1, novel expression of fibroblastic markers such as fibronectin, and change of cell shape and behaviour consistent with EMT, implicating TGFβ as one driving stimulus. The phenomenon of EMT also is critical in the development and metastasis of many epithelial cell-derived tumours. Recent research emphasizes that the process involves de-differentiation of the epithelial cells before trans-differentiation; activation of specific transcription factors including Hippo, Slug, Snail, Twist, and Zeb; and the involvement of growth factors including TGFβ, EGF, and FGF.8,9

The concept that adult endothelial cells may undergo a similar transition to a mesenchymal cell type (EndMT) is less well documented. During development, a few examples have been robustly demonstrated, notably in the formation of heart valves where the cells of the endocardial endothelium proliferate and undergo EndMT to generate the final valve structure.10 There have also been indications for some time that EndMT contributes in the adult particularly to the generation of myofibroblasts in pathological fibrogenesis. Although initial studies were not definitive, since they did not involve cell lineage tracking, more recent work has done so.11–13 As in EMT, TGFβ is a stimulus for EndMT and signalling pathways leading to the activation of similar transcription factors are involved. Welch-Reardon et al.14 have in addition recently drawn attention to features of EndMT that accompany sprouting angiogenesis.

The prevailing views of atherogenesis, however, do not suggest any role for EndMT in neointimal lesion formation. These are challenged in this issue of Cardiovascular Research by Moonen et al.15 They show that intimal cells displaying both an endothelial marker (PECAM or endocan) and a smooth muscle marker (α-actin, transgelin, or calponin) can be detected in human and porcine atherosclerotic plaques, and in mice where neointima formation is induced by aortic constriction. In vitro experiments showed that TGFβ treatment of endothelial cells induced induction of mesenchymal marker genes, an effect that was inhibited when cells were cultured in laminar flow conditions. Knowing that endothelial ERK5 signalling is activated by laminar flow, Moonen

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et al. knocked down ERK5 and observed that this alone was sufficient to induce features of EndMT in their cultured cells, some of which were exaggerated in the presence of TGFβ. Transduced expression of constitutively active MEK5 (an upstream activator of ERK5) inhibited the ability of TGFβ or disturbed flow to induce features of EndMT in vitro.

These results are interesting and provocative. The actions of TGFβ on endothelial cells are multiple, complex, and context dependent (e.g. growth inhibitory in vitro but pro-angiogenic in vivo). The novel demonstration that endothelial cells whose basal phenotypes differ according to their exposure to flow respond differently to TGFβ provides a further example of this complexity. However, whether the action of TGFβ on cells under static conditions in vitro is a robust model for studying EndMT requires further analysis, in particular of the transcription pathways being activated. Similarly, the detection of some cells in vivo within the expanded intima or atherosclerotic plaque that apparently have both endothelial and mesenchymal marker expression, while suggestive, falls short of providing definitive evidence that EndMT is occurring (or of its importance) in atherogenesis. Future in vivo studies using lineage tracing are required to substantiate this claim.

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References