Endothelial plasticity
Moonen, Johannes Antonius Jacobus

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It is well established that endothelial cells (EC) play critical roles in vascular physiology. Originally regarded as a passive barrier, the endothelium has become appreciated to be a complex tissue with multiple functions, with EC acting as vascular transducers of physical and chemical stimuli within the circulation. EC regulate coagulation and vasomotor tone, and modulate immune and inflammatory responses by acting as a selective permeability barrier. Besides, EC direct vascular development. As such they are crucial for shaping health which requires a high degree of adaptation and plasticity. This is reflected in the remarkable heterogeneity of the endothelium along the vascular tree. Adverse stimuli such as pro-fibrotic and pro-inflammatory cytokines or reactive oxygen species, induce endothelial injury and dysfunction, characteristic of vascular pathology and causally related to onset and progression of atherosclerosis. Persistent adverse stimuli push this dysfunction towards endothelial-to-mesenchymal transition (EndMT) which contributes to fibro-proliferative disease. Hence, EC plasticity can also shape disease.

In this thesis we have investigated how local environmental cues dictate endothelial plasticity. We have shown that chronic inflammatory disease impacts endothelial progenitor cell (EPC) biology, through a reduction of their circulating numbers and by impairing their function. Both mature EC and EPC were shown to be highly plastic in vitro, as evidenced by their capacities to undergo TGF-β-driven EndMT. Also we have shown how biochemical stimuli, i.e. pro-fibrotic and pro-inflammatory cytokines, can act in synergy in induction of EndMT. And finally, how hemodynamic forces modulate EndMT both through inhibition, and stimulation of this process. Thereby providing insights in the regulation of EndMT in vivo, and its potential involvement in disease.

Most importantly, our studies have shown that endothelial cells retain a remarkable plasticity during adult life. These insights open new horizons for vascular regenerative medicine and challenge current dogmas on the pathophysiology of fibro-proliferative vascular disease. Three major questions need to be answered over the next years: on the one hand how endothelial plasticity, in particular EndMT, contributes to vascular regeneration and on the other hand how dysregulation of this process results in vascular disease, and finally whether EndMT is reversible in vivo.

A role for EndMT as a physiological mechanism in endothelial and vascular regeneration in adult life, has to be uncovered yet. Analogous to epithelial-to-mesenchymal transition (EMT), which is essential for wound healing and tissue regeneration [1], EndMT likely plays an important role in vascular repair. Cellular dedifferentiation, typical for EndMT, facilitates proliferation and confers stemness, two important requisites for tissue regeneration. This opens an interesting new perspective on the long debated origin of endothelial progenitor cells (EPC). Over the past years, many different circulating EPC subpopulations have been described which are generally believed to be bone-marrow-derived [2]. In contrast, others have suggested circulating endothelial cells (CEC) to be no more than detached vascular endothelial cells as the result of vascular damage [3]. However, endothelial dedifferentiation, followed by proliferation and subsequent detachment, might in fact be an active physiological process to supply circulating progenitor cells for vascular repair. This notion is supported by the presence of EPC in the vascular intima [4].
In this respect so-called vascular wall-resident stem cells have also gained increased interest over the past years. The adventitial, or outermost layer of larger veins and arteries, forms a niche that protects stem and progenitor cells during early development and in adult life [5;6]. Several studies have shown that these adventitial progenitor cells contribute to vascular remodelling and neointimal hyperplasia [7;8]. Human vessels also contain adventitia-localized vascular progenitor cells [9;10] which bear the EC markers CD34, VEGFR2 and Tie2, but lack PECAM-1/CD31 [10]. Intriguingly, this phenotype is consistent with EC which are undergoing EndMT. The reversibility of EndMT has been poorly studied as yet, but adventitial progenitor cells can differentiate to mature endothelial cells. In analogy, this suggests that re-differentiation to EC after EndMT is possible too and is a physiological process. Interestingly, to date, the embryonic origin of adventitial progenitor cells is undetermined, but these cells were shown not be derived from either bone-marrow or the neural crest [7;11]. A challenging hypothesis is that dedifferentiated endothelial cells traffic from the intima to these vasculogenic zones to replenish the progenitor cell population. Stem cell niches are often characterized by (relative) hypoxia. In this regard, it is also highly relevant to study the influence of hypoxia on EndMT.

Besides this vasculogenic zone, which contains progenitor cells for vascular regeneration, the concept of a vascular niche for organ-specific stem and progenitor cells has emerged [7;12]. Although highly speculative, recent insights in the capacity of endothelial cells to differentiate to multiple mesenchymal lineages after EndMT [13] sheds an interesting new light on a possible role for endothelial cells in providing these organ-specific stem-like cells.

On the other hand, pro-fibrotic and pro-inflammatory stimuli including oxidized LDL and ROS, provoke endothelial dysfunction which might propel this dedifferentiation in the wrong direction. Adverse EndMT would result in a population of fibro-proliferative cells, which characterize the neointimal lesions present in atherosclerosis. An endothelial origin of neointimal cells would challenge the longstanding dogma of a key role for media-derived smooth muscle cells in this process. More importantly, if physiological re-differentiation to endothelial cells is possible, with the right switches, these fibro-proliferative cells might be reconverted to endothelial cells. Reversion of adverse EndMT (MEndT) is highly relevant in clinical perspective, as this drives novel therapeutic approaches for hitherto virtually incurable vascular diseases. Yet, the molecular mechanisms by which adult and embryonic EndMT differ have to be elucidated first. Remarkably, the reversion process is well established in epithelial cells, where it is known as mesenchymal to epithelial transition (MET) [1]. Mechanistic insights in how hemodynamic forces modulate endothelial plasticity will likely provide us with these clues. For example, in this thesis we uncovered a novel role for shear stress-induced ERK5 signalling in inhibition of EndMT. Besides, shear stress induces endothelial differentiation of embryonic stem cells [14;15], mesenchymal progenitor cells, and vascular smooth muscle cell lines [16;17] and induces endothelial differentiation of adipose-derived mesenchymal stem cells [18], often in synergy with biochemical stimuli [19]. Epigenetic factors, and especially chromatin dynamics are important in the regulation of stemness and cellular differentiation. Likewise, chromatin remodelling was shown to regulate shear-stress induced gene expression.
[20], and stabilization and activation of histone deacetylase 3 (HDAC3) by shear stress was essential for endothelial differentiation of ES cells [15].

Taken together, over the past years it has become increasingly clear that endothelial cells are not terminally differentiated cells but retain a remarkable, likely reversible, plasticity. In the years to come, it will become clear how endothelial plasticity can further shape health through contributing to vascular regeneration, but also shape disease by differentiating to fibro-proliferative cells. In the process, new insights will help design therapeutic strategies specifically aimed at modulation of endothelial plasticity and guiding it in the proper direction e.g. by endothelial ERK5 activation.
REFERENCES