Following vascular injury, endothelial cells become activated in the attempt to repave the damaged luminal surface. In addition, a physical interaction is established not only among the denuded subendothelial matrix, activated platelets, and circulating inflammatory cells but also with the progenitor cells (PCs).1 Endothelial survival, proliferation, and migration, necessary for re-coverage of exposed lamina, are aided by CD34+ PCs that express the vascular endothelial growth factor (VEGF) receptor-2/kinase-insert domain receptor (KDR). However, whether these cells enter the peripheral circulation as a predefined population or acquire their final antigenic phenotype on homing to the peripheral vasculature remains a matter of debate.

One puzzling aspect of the study by de Boer et al is represented by the remarkably low levels of KDR expression on the surface of CD34+ cells from healthy controls. Although KDR was found to be variably expressed, previous reports showed values 10-fold higher than the figure reported in de Boer’s study. Furthermore, a large body of evidence indicates a reduction rather than an increase in KDR expression in diabetes.3–5 A recent metaanalysis of 4 longitudinal studies including 1,057 patients showed that low abundance of CD34+ KDR+ PCs is associated with a higher risk of major adverse cardiovascular events.5 On the other hand, we found that in type-1 diabetic patients free from cardiovascular complications except mild background retinopathy, the number of circulating CD34+ KDR+ PCs is similar to that of age-matched controls; nevertheless, functional deficits were detected in the fraction of diabetic cells that migrate toward a chemoattractant.7 Thus, functional analysis might provide useful information at an early stage, before the antigenic profile becomes altered. One possible explanation for the apparent discrepancy in KDR+ counts is that pharmacological treatment can confound the final readout. However, apart from statin and aspirin, common cardiovascular drugs reportedly do not have an influence on CD34+ KDR+ numbers.8 Another aspect, the resistance to VEGF signals in diabetes, was recently studied by Tchaikovski et al in monocytes.9 Because of the preactivation of intracellular signaling pathways in cells derived from diabetic donors, VEGF was unable to induce further specific cellular activation. Directly equating cell function with KDR expression on CD34+ PCs might therefore be misleading.

The proposal that cellular interaction induces KDR surface expression on CD34+ cells raises further questions (Figure). If CD34+ KDR+ cells are more adhesive than CD34+ KDR− cells, why are the former augmented in the circulation of diabetic patients rather than remaining adherent to the vessel wall? In a broader context, can detached PCs carry messages from tissues and the vessel wall back to the circulation and finally the bone marrow (BM)? Are adhering/circulating cells in dynamic equilibrium with cells continuously released from
Figure. As presented by de Boer et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, platelets on a vascular lesion may stimulate KDR externalization in CD34⁺ cells (black arrows). However, several questions remain open (grey arrows and numbers). (1) Can BM cells acquire KDR while passing the vascular sinusoid barrier to reach the circulation? (2) Can endothelial-associated transcription factors and microRNAs, among other factors, deliver messages that induce KDR expression? (3) Can platelet-derived KDR be transferred to CD34⁺ cells? (4) If CD34⁺/KDR⁺ cells firmly adhere to the activation site, why are they found augmented in diabetes? (5) Can CD34⁺/KDR⁺ cells carry messages back to the BM? (6) Are cells in dynamic equilibrium between circulation and BM? (7) Does the analysis of the circulating cells truly reflect what is happening at the vascular level?

the BM? To enter the circulation, BM cells have to pass the endothelial sinusoid barrier. Is this an additional site for KDR induction on transmigrating cells? The authors show that the abundance of KDR⁺ on CD34⁺ cells does not increase after active mobilization with granulocyte colony-stimulating factor, which is supportive of KDR being a peripheral addendum. However, granulocyte colony-stimulating factor–induced mobilization could be rapid enough to minimize KDR translocation on CD34⁺ cell surface during transendothelial migration. A recent study from our group showed an increased adhesion of BM-derived PCs to diabetic BM endothelial cells under static conditions and after introduction of shear flow.10 This enhanced adhesive contact may facilitate the acquisition of endothelial antigens like KDR by transmigrating CD34⁺ cells. It would be relevant to investigate whether aspirin treatment results in a more rapid transmigration of KDR⁺ PCs into the circulation.

Furthermore, alternative mechanisms might also explain the presence of KDR on adhering CD34⁺ PC surface. It was proposed that platelet-derived microparticles start to cover PCs immediately after their entry into the bloodstream from the BM and thereby enhance the adhesive capacities of PCs.11 Putative endothelial markers, such as CD31 and von Willebrand factor, are also abundant on platelets. In addition, platelets contain cryptic VEGF receptors, including KDR, which become exposed on the platelet membrane following stimulation by VEGF. It is therefore possible that, as shown for other endothelial antigens, KDR is exchanged from platelets to adherent PCs.12 Finally, transcription factors, small molecules, and microRNAs could be delivered during transient or firm interactions with the endothelium, thereby inducing specific responses, including expression of surface antigens, in target cells.13 The capacity of recipient cells to selectively elaborate the donated material suggests that these are close encounters that leave a sign.

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References

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Close Encounters of the Third Kind: Progenitor Cells Land on the Platelet-Enriched Vascular Surface

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