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.6 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 the bone marrow? Are adhering/circulating cells in dynamic equilibrium with cells continuously released from the bone marrow?
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Close Encounters of the Third Kind: Progenitor Cells Land on the Platelet-Enriched Vascular Surface
Gaia Spinetti, Orazio Fortunato, Nicolle Kraenkel and Paolo Madeddu

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