All Arteriogenesis Is Local? Home Boys Versus the Newcomers

To the Editor:

The article by Khmelewski et al1 raises an important question in the field of arteriogenesis: do circulating (mononuclear) cells play a functional role during the adaptive proliferation of preexistent collateral pathways? Khmelewski et al propose that local vascular macrophages, rather than circulating monocytes, are crucial during early phases of arteriogenesis. Several important aspects, however, have not been addressed in the report by Khmelewski et al, and several other points made by the authors are contradictory to the experimental findings of others.

The experimental-induced depletion of monocytes under in vivo conditions is cumbersome and error-prone. Cyclophosphamide (CY) indeed is used as a chemotherapeutic agent. However, it is also a strong macrophage-activating agent. Remarkably, after CY treatment, ED1+, ED2+, and ED3+ macrophage subpopulations, in general, exhibit signs of cellular activation, such as an increase in the number and size of cells. In addition, there is an upregulation of the ED1, ED2, and ED3 reactive surface molecule expression in all organs.2 Hence, the pretreatment with CY might very well explain the increase in the number of tissue resident macrophages. We propose to study such effects in a nonpharmacological model of monocyte deficiency, eg, under osteopetrotic conditions.3 Khmelewski et al used only a surrogate marker for arteriogenesis, the proliferative index of collateral arteries. The effects of the cell infusion and MCP-1 infusion, respectively, on collateral dependant tissue perfusion have not been investigated. Thus evidence about the functionality of the leukocyte and CC-chemokine infusion is lacking.

The results of Khmelewski et al are rather contradictory to previous reports, and critical methodological aspects have not been addressed in detail. In 1976, histological evidence for monocyte adhesion and migration to the endothelium of newly recruited collateral arteries in dog hearts was found by Schaper et al.4 More recently, functional studies have shown that arteriogenesis directly correlates with (1) the concentration of circulating monocytes5 and (2) the amount of accumulating monocytes/macrophages in the perivascular tissue.6 Conclusively, arteriogenesis is reduced when monocyte deficiency, eg, under osteopetrotic conditions.3 It is noteworthy that functional data are indispensable to elucidate the multiplex mechanism of regenerative cytokine/cell therapies.

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