Origin of Smooth Muscle Progenitor Cells: Different Conclusions From Different Models

To the Editor:

We read with interest the recent article by Hu et al,1 who investigated the origin of smooth muscle cells (SMCs) in transplant atherosclerotic lesions. The authors proposed that SMCs in graft vasculopathy derive from non-bone marrow cells of host origin.1 On the other hand, recent evidence suggests that bone marrow cells also differentiate into the SMCs that substantially contribute to vascular diseases, including graft vasculopathy.2–4

We are concerned that such opposite conclusions are drawn using different experimental systems to test the hypothesis. Hu et al1 used a novel mouse model of arterial transplantation. The authors grafted a donor aorta to a recipient carotid artery using the cuff technique in the absence of immunosuppressants. The pathophysiology of vasculopathy in the authors’ model may differ from that of arteriosclerosis observed in immunosuppressed cardiac allografts, as many studies have suggested that immunosuppressants potentially affect the pathogenesis of transplant arteriosclerosis. By inducing 3 distinct types of mechanical vascular injuries to a single mouse, we found that recruitment of bone marrow-derived cells to vascular lesions depends largely on the type of model used (K. Tanaka and M. Sata, unpublished observation, 2002). We detected a robust contribution of bone marrow-derived cells after mechanical endovascular injury, whereas there were only a few marker-positive cells in the neointima after ligation of the common carotid artery. We seldom found bone marrow-derived cells in the lesion induced by perivascular cuff replacement. These results suggest that in certain types of models, we may underestimate the potential contribution of bone marrow cells in vascular remodeling.

Furthermore, Hu et al1 used a transgenic mouse that expresses LacZ in vascular SMCs under the transcriptional control of the SM22 promoter. Human vascular SMCs are quite heterogeneous in the expression of differentiation markers, although α-actin is abundantly expressed in all SMCs.2 Thus, some α-actin–positive cells may not express LacZ in the transgenic mouse. Consequently, although the transgenic mice are useful to identify SMCs, they may not be adequate to identify “SMC-like cells” in the neointima. Finally, we are aware that irradiation and bone marrow transplantation have tremendous effects on many tissues, even when the blood system appears to have been reconstituted.

Therefore, Hu et al1 might have underestimated the potential contribution of bone marrow cells to graft vasculopathy. We also believe that there are other sources of smooth muscle progenitors. We suggest caution before extrapolating the conclusions provided by Hu et al to the pathogenesis of graft vasculopathy.

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Response

We thank Dr Sata et al for their interest in our article1 and their comments with respect to the origins of smooth muscle cells (SMCs) in transplant atherosclerosis.

In the last several years, many reports have demonstrated with the use of bone marrow chimeric mice that bone marrow cells could differentiate into almost all types of cells. Several years after the first report, however, some of the results are proving hard to replicate and some show the opposite.2 Recently, Sata et al2 and Shimizu et al3 showed that a proportion of SMCs in transplant arteriosclerotic lesions originated from bone marrow cells. However, data from us1 and Li et al2 showed no evidence that bone marrow cells are a source of SMCs. How can we explain the contradictory conclusions?

Sata et al suggest that the controversial conclusions might result from using different models and techniques. However, existing data do not seem to support this explanation. First, our model using the cuff technique is comparable to the suture method, but simpler. A similar result concerning SMC composition in lesions was observed using either a cuff technique or a suture method. Second, immunosuppressants might not significantly influence SMC origins in transplant arteriosclerosis, because the conclusions from both papers,2,3 with or without immunosuppression, were almost identical. Third, results from other models of vascular diseases, eg, endothelial injury and perivascular cuff replacement, cannot be compared with transplant arteriosclerosis, because of the different pathogenic mechanisms. Fourth, even if a small proportion of SMCs express LacZ or LacZ mRNA, enzyme activity should be detectable in the lesions of chimeric mice with SM22-LacZ bone marrow using reverse-transcription polymerase chain reaction and series sections (>500 sections). Fifth, irradiation and bone marrow transplantation were used in all experiments studying SMC origins. Finally, a more convincing explanation comes from interpretation of the data obtained from double labeling. Double positive cells may have been in adjacent regions of SMCs and leukocytes that were too close to be separately recognized in sections of transplant vessel. Support for this issue is the fact that a proportion of double positive cells (yellow) were seen in sections of graft vessels labeled for α-actin (red) and MAC-1+ macrophages (green), which are known to be separately present in SMCs and macrophages (data not shown). On the basis of double labeling data, it was not possible to conclude that neointimal SMCs were derived from bone marrow cells. Therefore, we decided to use transgenic mice expressing LacZ gene specifically in vascular SMCs and provided the direct evidence that SMCs in lesions are unlikely to be derived from bone marrow stem cells.1

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