Letter to the Editor

Mouse Models of Vein Grafts

To the Editor:

A recent article published in Arteriosclerosis, Thrombosis, and Vascular Biology by Sata and Nagai1 provided a commentary on mouse models of vein grafts based on our mouse model1 and another model by Cooley.3 Although it is not a peer-reviewed article, it is expected to be a fair and accurate expert view. However, I feel that there are several issues which are not fair or fully accurate. Firstly, our article concerning smooth muscle cells (SMCs) in vein graft atherosclerosis demonstrated both donor and recipient origins, using our model in which SM-LacZ transgenic mice were crossed with apoE−/− animals, rather than ROSA26 (expressing LacZ in all tissues).4 Because the LacZ gene only expresses in SMCs in our model, it generates more reliable data for studying SMC origins than that using ROSA26 mice. Thus, the correct citation should be the data derived from using SM-LacZ mice.4 Secondly, our results of SMC origins in vein grafts have been confirmed by another laboratory.5 Zhang et al.4 in an article published in Arteriosclerosis, Thrombosis, and Vascular Biology, demonstrated that 66±6% SMCs in vein graft lesions were derived from donor vessels and 56±7% from recipients, results which are similar to our findings. Unfortunately, the authors ignored this article on mouse vein grafts. In addition, many laboratories are using our mouse models of vein grafts, and a number of articles have been published from other laboratories.6–10

Thirdly, I feel that the citation is unbalanced, for example, regarding the description and comparison of the surgical procedure in the two models. The authors should have compared Cooley’s model3 with another4 using the suture technique. However, the authors cite articles from their own work although these articles do not directly describe vein grafts. Fourthly, a question was raised regarding the vessel of choice for grafting, in relation to the diameter size and the equivalent human procedure. We have calculated the diameter match in humans and mice. The difference in the diameter between vena cava and carotid artery in mice is similar to that between human saphenous vein and coronary arteries. Sata and Nagai’s Figure1 shows a three-fold difference, which is inaccurate. The Figure also implies that the grafted vessel in our model was ballooned, not straight, which, as shown by the in vivo image of the actual procedure (Figure), is not true. Additionally, quantitative data as to the contribution of donor versus recipient cells in Cooley’s model3 is not provided. That is, the contribution of donor cells was indicated in a figure but the contribution of recipient cells was not excluded. In the Table of the editorial,1 it seems that all lesion cells are derived from the donor vessels.

In summary, because of a number of issues with incorrect or inaccurate article citation or data interpretation, it is difficult to accept the opinions expressed in this article. The two models are different both in terms of the vessels used and the mechanism of surgical procedure (for example, 10-mm length graft vessel [vena cava] in our model versus 2-mm [branch of the jugular vein] in Cooley’s), therefore slightly different results may be obtained yet be equally valid. Thus, I suggest that the authors might address and clarify these issues and publish a correction where necessary.

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In response:

We thank Dr Xu for his comments on our editorial concerning mouse models of autologous vein graft. First of all, we express our respect to Dr Xu and his colleagues for their pioneer works to develop a murine model of vein graft.1–4 We acknowledge that the model has been accepted as a standard murine model of vein graft disease.5–7,11 The model greatly contributed to our understanding of the pathophysiology of vein graft disease5,6,8 and development of therapeutic strategies.4,9,11 With this model, Dr Xu’s laboratory...
reported that both donor and recipient cells contribute to reendothelialization and neointima formation in the vein graft.\textsuperscript{2} The experiments were well done, and the data were convincing. Their main conclusion has been confirmed by another laboratory using another model of vein graft.\textsuperscript{12} We regret not citing the literature in the editorial,\textsuperscript{13} because we were unaware of the article published in March\textsuperscript{12} when we were preparing the draft. It is clear that recipient cells do contribute to neointima formation in these models.

Contrary to these compelling results, Dr Cooley proposed a different concept in \textit{Arteriosclerosis, Thrombosis, and Vascular Biology}.\textsuperscript{14} Using his new model, the author concluded that most of the neointimal cells and endothelial cells were derived from the donor vein graft. Our editorial was written to illustrate the main concept and to draw attention to this article among investigators in the area of research, who are not familiar with the experimental methods of transplantation.\textsuperscript{15} In this editorial, we intended to highlight the crucial issue that different models lead to quite different conclusions on the origin of neo-intimal cells in vein graft. In the figure and the table,\textsuperscript{13} we fairly cited the main conclusion made by Dr Cooley based on his experiments, although there still remained possibility that recipient cells also contributed to neointima formation and reendothelialization.

Dr Xu and his colleague used SM22-LacZ, SM22-LacZ/ apoE\textsuperscript{−}/−, ROSA26 mice, and wild-type mice.\textsuperscript{2} Eventually, any combination of these genetically altered mice produced consistent results regarding the origin of the neointima of vein graft. Thus, we illustrated the method and result of transplantation from wild-type mice to ROSA26 mice, which were used by Dr Cooley,\textsuperscript{14} because we did not have enough space to describe all the mice used in the sophisticated experiments by Dr Hu et al.\textsuperscript{2} Regarding anastomosis technique, we highlighted the difference between suture and cuff-mediated method. We assumed that difference in anastomosis procedure may account for the different results, at least in part. The references 12 to 17 in our editorial were cited to demonstrate that different models lead to completely different cellular constituents of neointima after mechanical vascular injuries.

We made the figure based on the sizes of vena cava and common carotid artery reported in human. The diameter of adult common carotid arteries is 6 to 7 mm,\textsuperscript{15} whereas the diameter of inferior vena cava (IVC) of healthy controls is reported as 14±4 mm\textsuperscript{16} or 8 to 11.5 mm/m\textsuperscript{2}.\textsuperscript{17} To prepare this response to the letter, we harvested a 9-week-old C57BL/6 mouse to compare the sizes of the two vessels in a mouse. When we isolated the vessels, the IVC appeared \textsim 1.5- to 2-fold larger than the right carotid artery (Figure A). After excision, the IVC seemed to shrink; the difference in diameter became less (Figure B). In human aortocoronary bypass surgery, the saphenous vein graft is \textsim 1- to 2-fold larger than coronary arteries.\textsuperscript{18} We acknowledge that the diameter difference between vena cava and carotid artery in mice is analogous to human aortocoronary saphenous vein graft procedure. We corrected the figure in the editorial\textsuperscript{13} as Figure C.

It is clear that no animal model would represent exact pathophysiology of human autologous vein graft disease.\textsuperscript{15} Particularly, vein grafts used in all murine models are isogenic, but not autologous.\textsuperscript{1,2,12,14,19} It is not clear whether genetic manipulation and/or forced expression of transgenes affect host immune reaction to isogenic vein grafts, although genetic backgrounds are identical so that no acute rejection may take place. As Dr Xu addressed in his recent review article, caution must be advised when extrapolating from mouse mode data to supposed human equivalents.\textsuperscript{2} For better understanding of vein graft disease, we should compare molecular processes of neointima hyperplasia in different models with regard to clinical analogy.

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