Endothelial Progenitor Cells, Neointimal Hyperplasia, and Hemodialysis Vascular Access Dysfunction

Novel Therapies for a Recalcitrant Clinical Problem

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Vascular stenosis as a result of neointimal hyperplasia is a major clinical problem that has an impact on multiple and diverse disciplines, including cardiology (coronary restenosis), cardiothoracic and vascular surgery (saphenous vein and polytetrafluoroethylene [PTFE] graft failure), neurology (carotid stenosis), nephrology (dialysis access dysfunction), and transplant medicine (chronic allograft rejection in hearts and kidneys). The traditional response to injury hypothesis on the pathogenesis of neointimal hyperplasia focuses on the migration of medial smooth muscle cells from the media into the intima.1 Recently, there has been a great deal of excitement about the role of circulating smooth muscle progenitor cells in the pathogenesis of neointimal hyperplasia. These cells have been identified in a variety of experimental models of vascular injury,2 and interventions that reduce the number of these cells can attenuate neointimal hyperplasia. In marked contrast to the deleterious effects of smooth muscle progenitor cells on neointimal hyperplasia, circulating endothelial progenitor cells (EPCs) are believed to play an important role in vascular repair and in the inhibition of neointimal hyperplasia.3

Placement of anti-CD34–coated grafts in an arteriovenous graft rejection in hearts and kidneys). The traditional response to injury hypothesis on the pathogenesis of neointimal hyperplasia focuses on the migration of medial smooth muscle cells from the media into the intima.1 Recently, there has been a great deal of excitement about the role of circulating smooth muscle progenitor cells in the pathogenesis of neointimal hyperplasia. These cells have been identified in a variety of experimental models of vascular injury,2 and interventions that reduce the number of these cells can attenuate neointimal hyperplasia. In marked contrast to the deleterious effects of smooth muscle progenitor cells on neointimal hyperplasia, circulating endothelial progenitor cells (EPCs) are believed to play an important role in vascular repair and in the inhibition of neointimal hyperplasia.3

Placement of anti-CD34–coated grafts in an arteriovenous model of PTFE graft stenosis by Rotmans et al resulted in almost complete endothelialization of the grafts (both at 3 days and at the end of the experiments at 28 days). Endothelialization, however, did not result in a decrease in neointimal hyperplasia, as expected. Rather, the endothelialized grafts demonstrated a paradoxical increase in neointimal hyperplasia at the graft-vein anastomosis, which is the end point for this model.

The article by Rotmans and colleagues comes at a particularly opportune moment, as it addresses 3 issues of current interest: (1) it recognizes that the combination of recent advances in biomedical engineering, drug delivery, and molecular biology has resulted in a fertile substrate for investigators in this field; (2) it challenges conventional wisdom about the inverse association between endothelial repair (endothelialization) and neointimal hyperplasia; and (3) it draws attention to the huge but often ignored clinical problem of hemodialysis vascular access dysfunction. This editorial addresses each of these issues in turn.

There have been great advances in the past 5 to 10 years in the in vivo application of both experimental and clinical therapies for vascular stenosis and neointimal hyperplasia. These advances have been made possible through a fusion of advances in biomaterials, drug delivery techniques, and molecular and cell biology. A few examples of such technologies include a multitude of drug-eluting coronary stents,6 the use of perivascular drug-releasing or cell-containing polymers in experimental models of neointimal hyperplasia,7 and exciting new advances in the generation of nitric oxide–releasing polymers.8 All of these approaches share a common thread in that they are local therapies applied directly to the site of vascular injury. In particular, the remarkable success of the drug-eluting coronary stents against the background of multiple unsuccessful clinical trials of systemic therapies for neointimal hyperplasia suggests that local therapy could be the delivery mode of choice in the setting of vascular stenosis.

For many years the unattainable goal for vascular access interventions has been the complete endothelialization of the region of vascular injury after surgery or angioplasty to prevent both thrombosis and stenosis. The recent identification of EPCs has allowed us to come another step closer to this goal. EPCs were initially identified by Asahara and colleagues,10 who demonstrated that a subset of CD34+ cells could be differentiated ex vivo into an endothelial phenotype (which expressed both the stem cell marker CD34 and the endothelial marker protein VEGFR2). Other groups have since demonstrated enhanced endothelial coverage and a reduction in neointimal hyperplasia after an infusion of EPCs in animal models of carotid angioplasty injury.11,12 In all of these experiments, an increase in endothelialization of the region of vascular injury invariably translated into a reduction of neointimal hyperplasia. In the article by Rotmans et al,
however, endothelialization of PTFE graft with anti-CD34 antibodies was accompanied by an increase rather than a decrease in neointimal hyperplasia. What could be the possible reasons for this paradox?

Previous studies have demonstrated that it is possible to obtain endothelial coverage of prosthetic stent or graft material by isolating or expanding EPC cultures ex vivo and then using these cells to coat prosthetic material. Unfortunately, these approaches tend to be time consuming, labor intensive, and expensive. In marked contrast, the ability to store anti-CD34–coated graft or stent material in the cardiac catheterization laboratory, interventional radiology suite, or operating room clearly lends itself to current clinical practice.

The Rotmans group, very appropriately, did not attempt an ex vivo endothelialization of their prosthetic graft material but instead tried to achieve this in vivo through the use of anti-CD34–coated grafts. As alluded to by the authors, the reason for the dichotomy between endothelialization and intimal hyperplasia in these experiments could be linked to the fact that CD34 is a hematopoietic stem cell marker. The antibodies to CD34, therefore, could have attracted CD34+ cells that still had the potential to transform into smooth muscle cells and myofibroblasts, as has been previously reported. Why was there no evidence of smooth muscle cells on the actual PTFE graft material, which was covered only by cells that had an endothelial phenotype? One explanation could be that the transformation of CD34+ cells preferentially into smooth muscle cells may require additional stimuli such as turbulence or low shear stress, which would be present only at the graft-vein anastomosis. Alternatively, true EPCs/endothelial cells themselves may have the plasticity to dedifferentiate into smooth muscle cells at the graft-vein anastomosis in response to hemodynamic and surgical stress. Finally, it needs to be mentioned that these studies were performed in a model of venous (rather than arterial) stenosis, which is characterized by continuous ongoing hemodynamic stress and compliance mismatch at the graft-vein anastomosis. Whether the results would have been different in an arterial interposition or angioplasty model is open to speculation.

Despite its surprising results, the study by Rotmans et al is critically important because it is an important step forward toward the application of EPC technology to the problem of vascular stenosis in a manner that is clinically relevant. Further refinements to this approach could include an antibody coating that has the specificity to bind to circulating cells that only have the potential to differentiate into lining endothelial cells. To do this, however, we will need to learn more about the biology and plasticity of EPCs. For example, it is likely that what we consider to be EPCs are in fact a diverse population of different cell types with different functions. Clearly, many more studies are needed for us to learn how to tweak this fascinating cell so that it can be effectively used to prevent vascular stenosis in the clinical setting.

Finally, by using an arteriovenous model of PTFE graft stenosis, the authors draw attention to the huge clinical problem of hemodialysis vascular access dysfunction. There are ≈300 000 hemodialysis patients in the United States, a number that is expected to double by the year 2020. The 2 main forms of dialysis access are the arteriovenous fistula (32% prevalence rate in the United States) and the PTFE arteriovenous graft (50% prevalence rate in the United States), both of which have dismal survival rates as compared with other vascular procedures—between 50% and 75% 1-year survival at best. The single most important reason for hemodialysis vascular access dysfunction is a stenosis at the graft-vein anastomosis of PTFE dialysis access grafts or in the proximal vein of an arteriovenous fistula as a result of venous neointimal hyperplasia. At a histological level, we and others have demonstrated that venous neointimal hyperplasia in the setting of dialysis access grafts and fistulae comprises smooth muscle cells, myofibroblasts, microvessels within the neointima, and a peri-graft macrophage layer. In marked contrast to arterial stenoses, venous neointimal hyperplasia is difficult to treat with angioplasty (nonthrombosed PTFE grafts have a 50%, 6-month primary patency, whereas thrombosed grafts have a 40%, 3-month primary patency after angioplasty). The reasons for this poor survival rate are unclear, but they include (1) anatomic and physiological differences between veins and arteries, (2) the presence of continuous hemodynamic stress in the form of turbulence and possibly low shear stress at the graft-vein or artery-vein anastomosis, (3) recurrent needle damage during the dialysis procedure, and (4) the presence of uremia, which could predispose a patient to endothelial dysfunction.

Regardless of the cause, the aggressive natural history of neointimal hyperplasia in the setting of hemodialysis vascular access translates into a financial cost of $1 billion per year. More important, it results in tremendous morbidity and is responsible for 20% of all hospital admissions in the hemodialysis population. Despite the huge clinical, economic, and social impact of hemodialysis vascular access dysfunction, there are no truly effective therapies available for this clinical problem. Percutaneous angioplasty and surgical revision are commonly used, but in marked contrast to the cardiac literature, these are not accompanied by interventions to prevent restenosis. Even more disappointing, when compared with the multitude of clinical trials in the setting of coronary stenosis, is that there are very few ongoing clinical trials targeting hemodialysis vascular access dysfunction. The lack of focused clinical research in this area is all the more surprising because dialysis access grafts and fistulae could be the ideal clinical model for testing novel local therapeutic interventions for vascular stenosis in general. This is because (1) the aggressive nature of vascular stenosis in hemodialysis patients could result in clinical trials being conducted with a smaller sample size and in a shorter time; (2) dialysis access grafts and fistulae are superficially located and away from important anatomic structures, making these patients ideal candidates for the delivery of local therapies either through the percutaneous approach or at the time of surgical placement; and (3) patients on hemodialysis have large-bore needles placed within 3 to 6 cm of the site of venous stenosis 3 times per week for dialysis, which could allow for the repeated delivery of novel therapies (including endothelial progenitor cells) during the dialysis procedure itself.
In summary, the article by Rotmans et al brings out both the advantages and the pitfalls of using EPCs to reduce vascular stenosis. Regardless of its final outcome, this study has brought us one step closer to the use of EPCs in the setting of clinical vascular stenosis. Perhaps most important, this article draws attention to hemodialysis vascular access dysfunction, a huge clinical problem that is lacking in effective treatments but at the same time could be ideally suited to the application of novel local therapeutic interventions.

Acknowledgments
This work was supported by National Institutes of Health grant DK-61689 and by a grant from Satellite Dialysis Clinics.

References


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_Circulation_. 2005;112:3-5
doi: 10.1161/CIRCULATIONAHA.105.548651
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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