Editorial Comment

Inhibition of Angiogenesis: Common Theme for Cancer and Atheromatosis?

ARISTOTLE BAMIAS, MELETIOS A. DIMOPOULOS

Dept. of Clinical Therapeutics, University of Athens, School of Medicine, Athens, Greece

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Address:
Aristotle Bamias

31 Komninon St., 124 62 Haidari, Athens, Greece
e-mail:
abamias@med.uoa.gr

Restenosis represents the primary weakness of percutaneous coronary intervention. The use of a coronary artery stent is an improvement over plain balloon angioplasty, because it provides a substantial reduction in the need for revascularisation. Nevertheless, 10-15% of patients will still require revascularisation after the placement of a bare coronary artery stent. The reason for this failure is the growth of proliferative neointimal tissue in response to strut-associated injury and inflammation. In order to counteract this mechanism, antiproliferative drug-eluting stents have been used. Both paclitaxel- and sirolimus-eluting stents have been shown to reduce the need for revascularisation further,[1,2] thus proving the importance of proliferative tissue growth in the process of restenosis.

An important factor in the development of atheromatosis is angiogenesis, which results in a dense net of vasa vasorum and can also potentiate intraplaque haemorrhage.[3] One could also speculate that angiogenesis might be responsible for restenosis of revascularised lesions through the same mechanisms. Angiogenesis has been more extensively studied in the context of the development and growth of human malignancies[4] and certain antiangiogenic factors, such as thalidomide, are already used in the treatment of human cancer.[5] Vascular endothelial factor (VEGF) has a central role in the regulation of this process.[6] VEGF stimulates the respective receptors (VEGFR-1, VEGFR-2 and VEGFR-3) of endothelial, lymphendothelial or haemopoietic cells, thus activating proliferation, migration, survival and vascular permeability. Similar pathways have recently been described in experimental models for the endothelium of carotid arteries,[7] suggesting that inhibition of this factor might be beneficial for preventing coronary artery stenosis.

In the context of the previously discussed data, the study of Stefanadis et al in this issue of the Hellenic Journal of Cardiology[8] represents a logical step in the sequence of preclinical and clinical studies aiming to reduce the incidence of restenosis after coronary angioplasty. Their study attempts to combine the recent knowledge that VEGF may play an important role in the procedure of restenosis with the progress in the use of drug-eluting stents. The drug they used was bevacizumab, an anti-VEGF monoclonal antibody, which is the most well studied anti-VEGF agent in the medical literature. As already mentioned, their choice was based on the anti-cancer efficacy of this agent. Bevacizumab is already approved in Europe and the USA for the treatment of metastatic colorectal cancer in combination with chemotherapy, because it was shown to prolong survival in a recent randomized phase III study.[9] This antibody has also shown promising anti-tumour efficacy in a variety of other tumours, including

non-small cell lung cancer and renal cancer.[10] Stefanadis et al have demonstrated that a bevacizumab-eluting PC coated stent can be safely implanted in atheromatic iliac arteries of rabbits.[8] This procedure was compared with the implantation of a non-eluting stent. The artery diameter did not differ (in fact it was strikingly similar) between the two procedures. This result in itself cannot be used as a predictor of the efficacy of these stents in humans but it can serve as a basis for the extension of these studies to the human setting.

Clearly, more research is necessary in order to answer several questions related to the mechanisms of angiogenesis in coronary endothelium. One of the most interesting issues is the identification of the importance of each of the VEGF receptors in this process, which could be different from those involved in the neoplastic diseases. The more advanced study of bevacizumab in oncology could also help cardiologists use such agents more efficiently. For example, it is accepted that the most successful use of this agent is in combination with chemotherapy. Could it be used in the same way for preventing vascular restenosis? Paclitaxel is a chemotherapeutic agent, already used successfully on drug-eluting stents. If it is technically feasible, a bevacizumab+paclitaxel eluting stent might represent an improvement over single-drug eluting stents. On the other hand, the toxic effects of these agents on the coronary endothelium should be carefully considered: bevacizumab has already been associated with hypertension,[10] perforation[9] and serious bleeding.[11] Well designed, prospective clinical studies are certainly necessary to address these issues. The study of Stefanadis et al may represent the first step towards further research into the value of antiangiogenic agents in preventing restenosis after coronary angioplasty.

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