VEGF165 Gene-Mediated Arteriogenesis and Cardioprotection in Large Mammals With Acute Myocardial Infarction. Confirmation of Previous Results From Other Authors

To the Editor:

In a recent article, Ferrarini et al. report that direct intramyocardial transfer of the human vascular endothelial growth factor (VEGF) 165 gene in dogs with acute myocardial infarction exerts a beneficial effect by enhancing both arteriogenesis and cardiomyocyte viability in the infarcted myocardium.

With regard to the arteriogenic effects of the VEGF gene in large mammalian models of ischemic heart disease, we have previously demonstrated that the direct intramyocardial injection of a plasmid encoding human VEGF165 in pigs with Ameroid-induced circumflex artery occlusion (a model which combines myocardial infarction with peri-infarct ischemia) promotes a remarkable proliferation of arterioles measuring 8 to 50 μm in diameter.

In addition to this effect, VEGF165 gene substantially increased the mitotic index of adult cardiomyocytes and induces cardiomyocyte hyperplasia at 35 days posttreatment. So, the supposition of Ferrarini et al that “. . . VEGF might have an effect on resident cells, either by protecting the differentiated cardiomyocytes from apoptosis or by promoting their proliferation”, is likely true.

Moreover, in a study published concomitantly with Ferrarini’s article (and therefore not available at the time of resubmission), we showed that in sheep with acute myocardial infarction, in addition to the increase in adult cardiomyocyte mitosis, VEGF165 gene transfer increased the number myoblasts in the peri-infarct zone at 10 days after occlusion. Most of these precursors were undergoing mitosis and even cytokinesis. Consequently, Ferrarini’s speculation that “VEGF might have a role in the recruitment or activation of a putative population of cardiac stem cells, which could contribute to tissue repair after the onset of ischemia” is most probably a fact.

Besides confirming our previous observations, Ferrarini’s results extend them by showing that the protective effects of VEGF are active even when injecting the gene 4 hours after the infarct, which may be of uppermost clinical relevance, by showing the upregulation of VEGF receptors expression, and by demonstrating the feasibility, safety and efficiency of the use of an adeno-associated virus for VEGF165 gene vectoring in this setting.

We must disagree, however, with Ferrarini’s statement that “This is the first evidence that a VEGF-based gene therapy approach might be of important therapeutic value in the early phases of acute myocardial infarction and that its beneficial effect extends beyond the well-known angiogenic properties of VEGF”.

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