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NEWS AND COMMENTARY

Electroporation-based DNA therapy

DNA electrotransfer to the skin: a highly translatable approach to treat peripheral artery disease

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The *Gene Therapy* article 'Increased perfusion and angiogenesis in a hindlimb ischemia model with plasmid FGF-2 delivered by noninvasive electroporation' by Ferraro *et al*. (this issue) reports on a novel noninvasive and potentially therapeutic approach for peripheral artery disease (PAD)-related limb ischemia. The approach uses electroporation to enhance delivery of plasmid DNA encoding fibroblast growth factor-2 (FGF-2) to the skin to induce neovascularization as a therapy for ischemia in a rat model. Specially designed electrodes were used to accomplish effective delivery to the skin and a single treatment was shown to be sufficient to induce vascularization in an ischemic limb.

PAD is a potentially debilitating disease that typically results in the reduction of blood flow to the lower extremities and can lead to intermittent claudication or critical limb ischemia. Current treatment options include risk factor reduction, physical therapy and training, pharmacological treatment or open surgical procedures to revascularize the ischemic limb. These approaches can be limited by associated comorbidities, such as diabetes, coronary artery disease or stroke.[1,2] Alternative approaches are being investigated for PAD, including therapeutic angiogenesis.[3]

Delivery of angiogenic growth factors, including vascular endothelial growth factor and FGF, are being evaluated as potential therapeutic approaches for PAD, particularly when direct revascularization is not possible.[4] Administration of recombinant FGF-2 protein has shown promise for the treatment of PAD-related symptoms. There are disadvantages to the use of recombinant protein in a clinical setting, particularly its short half-life[5,6] and poor bioavailability, which necessitates frequent administration to sustain lasting effects. In light of this, gene therapy approaches seem extremely attractive. Both viral and nonviral gene therapy approaches have been used to deliver angiogenic factors. Although viral vectors can result in high levels and long-term expression compared with nonviral delivery, the use of these vectors has caused inflammatory responses, formation of antibodies to the viruses, transient fever[7] and hepatotoxicity.[8] Although most nonviral approaches have yielded much lower expression, electroporation has been used effectively to enhance nonviral delivery. Previous PAD studies delivered plasmid FGF-2 by intramuscular injection with electroporation and demonstrated improved ischemic hindlimb blood flow and increased angiogenesis.[9]

The strategy reported in the current paper is an improvement over these other approaches. In contrast to muscle delivery, targeting the skin allows for control of the localized expression level and duration. This noninvasive approach to deliver FGF-2 to an ischemic limb is also an attractive alternative to viral and recombinant protein approaches because it reduces the potential of adverse side effects of viral delivery and the practicality issues associated with recombinant protein. Although this approach will still need to be further developed before it can be tested in the clinic, the study presented evidence that it could be used as a therapy for ischemic limbs. It has the advantages of decreased possibility of side effects, local control of expression and minimally invasive delivery. These factors, coupled with the recent success of a phase I clinical trial for metastatic melanoma using electroporation-mediated delivery of interleukin-12 plasmids to the skin with no significant adverse effects, make this approach intriguing.[10]

Conflict of interest

The author declares no conflict of interest. ■

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1 Robeer G, Brandsma J, van den Heuvel S, Smit B, Oostendorp R, Wittens C. Exercise therapy for intermittent claudication: a review of the quality of randomized clinical trials and evaluation of predictive factors. *Eur J Vasc Endovasc Surgery* 1998; **15**: 36–43.

2 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surgery* 2007; **33**: S1–S75.

3 Aviles RJ, Annex BH, Lederman RJ. Testing clinical therapeutic angiogenesis using basic fibroblast growth factor (FGF-2). *Br J Pharmacol* 2003; **140**: 637–646.

4 Bobek V, Taltynov O, Pinterova D, Kolostova K. Gene therapy of the ischemic lower limb—therapeutic angiogenesis. *Vasc Pharmacol* 2006; **44**: 395–405.

5 Lazarous DF, Unger EF, Epstein SE, Stine A, Arevalo JL, Chew EY *et al.* Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. *J Am Coll Cardiol* 2000; **36**: 1239–1244.

6 Bush MA, Samara E, Whitehouse MJ, Yoshizawa C, Novicki DL, Pike M *et al.* Pharmacokinetics and pharmacodynamics of recombinant FGF-2 in a phase I trial in coronary artery disease. *J Clin Pharmacol* 2001; **41**: 378–385.

7 Ylä-Herttuala S, Alitalo K. Gene transfer as a tool to induce therapeutic vascular growth. *Nat Med* 2003; **9**: 694–701.

8 Muruve D, Barnes M, Stillman I, Libermann T. Adenoviral gene therapy leads to rapid induction of multiple chemokines and acute neutrophil-dependent hepatic injury *in vivo*. *Hum Gene Ther* 1999; **10**: 965–976.

9 Fujii T, Yonemitsu Y, Onimaru M, Inoue M, Hasegawa M, Kuwano H *et al.* VEGF function for upregulation of endogenous PlGF expression during FGF-2-mediated therapeutic angiogenesis. *Atherosclerosis* 2008; **200**: 51–57.

10 Daud AI, DeConti RC, Andrews S, Urbas P, Riker AI, Sondak VK *et al.* Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma. *J Clin Oncol* 2008; **26**: 5896–5903.