Plasticity of Myocytes and Capillaries
A Possible Coordinating Role for VEGF

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Blood vessels in muscle proliferate or regress under the control of a variety of physiological and pathological stimuli. Therapeutic angiogenesis applied to the myocardium or to skeletal muscle seeks to exploit this phenomenon to treat disorders of inadequate perfusion. Early results obtained from uncontrolled human trials using angiogenic agents, for example, vascular endothelial growth factor (VEGF), were promising and led to exuberant expectations. However, of the four large placebo-controlled trials of therapeutic angiogenesis that have been published, all but one were negative, and results from a fifth trial that used an adenovirus-expressing FGF-4 have already been released as being negative. A number of reasons have been suggested to account for negative results from human angiogenesis trials: the dose of the factor, duration of expression, mode of delivery, multiple splice variants for agents, patient selection, preselected trial end-points, patient heterogeneity, endogenous angiogenesis inhibitors, and a strong placebo effect.

Thus, a potential for clinical benefit from administration of angiogenic agents cannot be excluded, and greater understanding of the biological consequences evoked by such factors may yet lead to meaningful clinical applications.

In skeletal muscles, both myocytes and capillaries undergo rapid and profound remodeling in the face of changing patterns of contractile work, environmental stresses, neurohormonal stimuli, or pathological conditions. Physical changes in myocyte size and biochemical changes in metabolic capabilities of myocytes are driven primarily by changes in expression of specific sets of genes controlled by signaling pathways that are beginning to be understood. This potential for clinical benefit from administration of angiogenic agents cannot be excluded, and greater understanding of the biological consequences evoked by such factors may yet lead to meaningful clinical applications.

The structure and function of the microvasculature of cardiac and skeletal muscles is also subject to rapid and profound remodeling responses driven by many of same stimuli that promote myofiber transformations. Changing patterns of contractile activity lead to proliferation of endothelial cells and formation of new capillaries. Limit muscles consisting primarily of fast-twitch, glycolytic myofibers can be converted entirely into slow-twitch, mitochondria-rich (oxidative) myofibers by changing patterns of neural stimulation in animal models, and directionally similar (although less complete) fiber type transformations are generated in animals and humans by exercise training. The density of capillaries within the microvasculature of skeletal muscles varies markedly among muscles of differing myofiber composition, and follows a similar course in response to neuromuscular activation or exercise: major angiogenic responses accompany myofiber remodeling evoked by such stimuli. Thus, it has been known for many years that mechanisms are in place by which skeletal muscles match capillary density and the resulting capacity for oxygen delivery to mitochondrial biogenesis and other biochemical properties of myofibers that determine capacity for generating ATP by oxidative phosphorylation.

The article by van Weel et al. in this issue of Circulation Research shows that VEGF administered by gene transfer techniques leads to an increase in capillary density in a murine model of ischemic limb disease, as observed previously in other animal models. However, they also noted that ischemic muscles expressing VEGF became deeply red in color, in the absence of changes in angiographic scores of collateral vessels. This observation mirrored changes that occur when fast-twitch glycolytic myofibers are transformed into mitochondria-rich oxidative myofibers by neuromuscular stimulation. Biochemical assays revealed a marked increase in active myoglobin and in a histochemical marker of mitochondrial content of myofibers (NADH-TR) in VEGF-transfected muscles. They also noted a correlation between expression of endogenous VEGF and myoglobin in ischemic segments of human limb muscles from amputees, and an induction of myoglobin mRNA expression induced by VEGF in cultured murine myotubes.

VEGF receptors are members of a family of tyrosine kinase receptors. When initially described, the accepted paradigm was that VEGF receptors are expressed only on endothelial cells thereby providing specificity to the consequences of VEGF activity. More recent data describe a somewhat broader spectrum of expression of VEGF receptors on hematopoietic and vascular smooth muscle cells. The article by van Weel et al. and other reports cited within the article, present evidence of expression of the VEGF receptor on cultured myoblasts and myotubes, and on skeletal myofibers from muscles from intact animals and humans. The presence of VEGF receptors on myocytes, and evidence for myofiber remodeling evoked by VEGF in cell culture and in intact animal models, suggest that VEGF may act directly to upregulate expression of genes encoding myoglobin and mitochondrial proteins in skeletal myofibers.

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Previous studies have demonstrated that stimuli promoting myofiber remodeling in skeletal muscles also lead to elaboration of angiogenic growth factors, including VEGF, thereby providing a plausible explanation as to how fiber-type plasticity can be linked to changes in capillary density. A variety of signaling mechanisms have been shown to transduce the effects of neuromuscular stimulation or exercise to the relevant target genes (e.g., myoglobin) in myofibers, the expression of which defines specialized myofiber subtypes. The major significance of the work of Van Weel et al is to suggest that VEGF participates as a signal to modulate remodeling as well as angiogenesis, thereby helping to match capillary density to the capacity of myofibers for oxidative metabolism.

Defining the mechanisms by which intracellular and extracellular signaling molecules control and match specialized properties of myofibers and microvascular adaptations in skeletal muscles holds considerable promise for the development of novel therapeutics. The biochemical and physiological properties of skeletal muscles are a major determinant of physical work capacity in athletes, in the capacity of normal individuals to perform activities of daily living without excess fatigue, and in the quality of life of individuals afflicted with heart failure, ischemic heart disease, renal failure, pulmonary disease, peripheral vascular disease, or advanced age. The biochemical and metabolic properties of skeletal myofibers also are important determinants of risk for the development and progression of diabetes. Indeed, van Weel et al may be correct in their interpretation that salutary effects of VEGF administered to humans could be based, at least in part, on remodeling of skeletal myofibers to function better during limited perfusion as a function of increased expression of myoglobin and mitochondrial proteins. Histological examination of skeletal muscles in cross-section shows myofibers ringed by capillaries in an intimate physical embrace. It is important that we understand how these partners communicate with each other and VEGF may be playing an important coordinating function in this interaction.

References


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