Estrogen-Related Receptor-γ: Conductor of Muscle Angiogenesis Through Conversion of Fast- to Slow-Twitch Fibers?

Alain-Pierre Gadeau, Jean-François Arnal

Tissue vascularization is tightly coupled to its oxidative capacity. This phenomenon is especially well characterized in skeletal muscle, which can be enriched in either oxidative slow-twitch or glycolytic fast-twitch myofibers. Slow-twitch muscles are characterized by high-oxidative-capacity fatigue-resistant (type I) fibers and dense vascularity. Conversely, fast-twitch (type II) muscles have lower oxidative capacity, with a less developed vascular network, and are fatigue sensitive. Different studies have well demonstrated that nuclear receptors including peroxisome proliferator-activated receptor-[alpha] (PPAR-α), PPAR-δ, and estrogen-related receptor-α (ERR-α), along with coregulators PPAR-γ coactivator-1α (PGC-1α), PGC-1β, and nuclear receptor-interacting protein 1 (RIPl40), control fatty acid oxidation, oxidative phosphorylation, and mitochondrial biogenesis in skeletal muscle4-10; however, the mechanisms linking the oxidative profile of the muscle to its vasculature remain a matter of major interest.

A large number of proangiogenic growth factors that coordinate endothelial cell activation, proliferation, and migration and pericyte recruitment have been described in the skeletal muscle (reviewed in Carmeliet11 and Ferrara and Kerbel12). Whether nuclear receptors orchestrate the vascularization of aerobic muscles was unclear until recently. Two factors, the coactivator PGC-1α and the AMP kinase (AMPK), have drawn attention. PGC-1α is induced by hypoxia and exercise13 and represents a potential target to stimulate vascularization; however, PGC-1α knockout mice are viable, retain oxidative muscle, and have normal vasculature13,14. Because the intrinsic enrichment of blood flow to aerobic muscles in the absence of exercise is unlikely to depend on PGC-1α induction, the existence of an alternative regulatory angiogenic pathway has been suspected. AMPK was shown both to enhance running endurance in the absence of exercise by inducing metabolic genes and to increase basal skeletal muscle capillarization and expression of vascular endothelial growth factor (VEGF).15,16 Thus, AMPK could be a performer in this alternative angiogenic pathway, but the upstream element that controls this gene was unknown.

ERR-γ: Missing Link and Major Conductor? ERR-γ is a constitutively active orphan nuclear receptor, and unlike ERR-α and -β, it is selectively expressed in metabolically active and highly vascularized tissues such as heart, kidney, brain, and skeletal muscles, as well as in a variety of tumors with hypermetabolic demand and abundant vasculature. It is described as a key regulator of multiple genes linked to both fatty acid oxidation and mitochondrial biogenesis.17,18 From these data, in a previous work, Narkar et al questioned how type I skeletal muscle inherently maintains high oxidative and vascular capacity in the absence of exercise.15 They found first that in skeletal muscle, ERR-γ is exclusively and abundantly expressed in oxidative (type I) slow-twitch fibers. Therefore, they explored the potential of ERR-γ to control the intrinsic angiogenic pathway in oxidative slow-twitch muscles (Figure). For this purpose, they produced transgenic mice overexpressing ERR-γ (ERRGO) in fast-twitch anaerobic type II muscle. Transgenic fibers triggered aerobic transformation with mitochondrial biogenesis and type I fiber specification, which was associated with a 100% increase in running endurance, all in the absence of exercise. Concomitantly, muscles in ERRGO mice displayed an activated angiogenic program that consisted of the secretion of proangiogenic factors and robust fiber vascularization. These intrinsic effects of ERR-γ did not depend on PGC-1α induction but were linked to activation of the metabolic sensor AMPK. Therefore, ERR-γ represents a previously
unrecognized determinant that specifies intrinsic vascular and oxidative metabolic features that distinguish type I from type II muscle.

**ERR-γ: A Potential Target for Ischemic Tissue Repair**

The ability to form new skeletal muscle capillaries in ischemic tissue is a major challenge. The concept that new blood vessels can grow to enhance tissue perfusion is now achieving widespread acceptance.\(^{20}\) Therapeutic angiogenesis is proposed as a complement or an alternative to surgical revascularization. To date, several proangiogenic factors, including VEGF and fibroblast growth factor, have been tested and have demonstrated convincing efficiency in acute and chronic experimental models;\(^{21,22}\) however, clinical trials to test VEGF or fibroblast growth factor angiogenic therapy in coronary and peripheral artery diseases were disappointing because their effects were inconsistent.\(^{21,22}\) One of the explanations for the lack of efficiency of angiogenic therapy probably comes from the use of individual factors, whereas angiogenesis is known to involve a plethora of angiogenic factors.

On the basis of their previous data, Matsakas et al.\(^{19}\) propose in this issue of *Circulation Research* a new and very interesting approach to treat muscle ischemia, taking advantage of the ability of oxidative muscle fibers to secrete a cocktail of angiogenic factors and thus allow recruitment of new blood vessels. This innovative approach takes into account the major physiological implication between metabolic characteristics of the muscle fibers and their capillarization, i.e., the perfect matching between metabolic demand and energy supply. As expected, the increased number of oxidative fibers in ERRG mice was associated with a strong acceleration of the recovery of blood perfusion and the promotion of a striking recovery from ischemic damage compared with wild-type mice.

Moreover, they provide additional evidence that the receptor is dispensable for the classic hypoxic response of VEGFα induction. The beneficial effect of ERR-γ in this model of limb ischemia is linked to the receptor-mediated transformation of the transgenic skeletal muscle to one that inherently expresses high levels of proangiogenic factors. Because ERR-γ is highly expressed in highly vascularized organs that are often prone to ischemia, such as skeletal muscle, heart, brain, and kidney, targeting ERR-γ to potentiate and orchestrate a reparative angiogenesis of ischemic muscle would be very powerful.

It remains to be determined to what extent these mechanisms that led to this spectacular effect in an acute ischemic model performed in normal mice are operative in animal models with metabolic or cardiovascular risk factors or diseases. In addition, it is not known to what extent this approach can provide a therapeutic benefit in chronic and complex pathophysiological clinical conditions, such as found in arthritic, diabetic, or elderly patients. The ischemic tissues of these patients are characterized by an impairment of many pathways and functions, including activation of the hypoxia-inducible factor-1α–VEGFα pathway\(^{23}\) and endothelial function.\(^{24}\) Furthermore, the consequence of limb immobility (in a plaster cast, for instance) is a switch of glycolytic fast-twitch myofibers to oxidative slow twitch, and the muscles of diseased patients could already have shifted toward a prominent oxidative slow twitch. Finally, even though nuclear receptors have proved to be major pharmaceutical targets, natural ligands or synthetic drugs that activate ERR-γ are still unknown, but studies should be conducted to search for such agents.

**Disclosures**

None.

**References**


Key Words: muscle fibers ■ muscle ■ angiogenesis ■ nuclear receptors ■ ischemia
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