Vascular endothelial growth factor (VEGF) is well known as an important molecule in angiogenesis. Its inhibition is pursued as an anti-cancer therapy; its enhancement as therapy for tissue ischemia. Here its role in skeletal muscle is explored, both at rest and after exercise. Muscle VEGF mRNA and protein are increased several fold after heavy exercise. While global VEGF knockout is embryonically lethal, muscle-specific knockout is not, providing models for studying its functional significance. Its deletion in adult mouse skeletal muscle: 1) reduces muscle capillarity by more than 50%, and 2) decreases exercise endurance time by about 80%, and 3) abolishes the angiogenic response to exercise training. What causes VEGF to increase with exercise is not clear. Despite regulation by hypoxia inducible factor (HIF), increased HIF on exercise, and Po₂ falling to single digit values during exercise, muscle-specific HIF knockout does not impair performance or capillarity, leaving many unanswered questions.