letters to the editor

The following is the abstract of the article discussed in the subsequent letter:

Gustafsson, Thomas, Adrian Puntschart, Lennart Kajiser, Eva Jansson, and Carl Johan Sundberg. Exercise-induced expression of angiogenesis-related transcription and growth factors in human skeletal muscle. Am J Physiol 276 (Heart Circ. Physiol. 45): H679–H685, 1999.—mRNA expression of vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and hypoxia-inducible factor (HIF) subunits HIF-1α and HIF-1β in human skeletal muscle was studied during endurance exercise at different degrees of oxygen delivery. Muscle biopsies were taken before and after 45 min of one-legged knee-extension exercise performed under conditions of nonrestricted or restricted blood flow (~15–20% lower) at the same absolute workload. Exercise increased VEGF mRNA expression by 178% and HIF-1β by 340%, but not HIF-1α and FGF-2. No significant differences between the restricted and nonrestricted groups were observed. The exercise-induced increase in VEGF mRNA was correlated to the exercise changes in HIF-1α and HIF-1β mRNAs. The changes in VEGF, HIF-1α, and HIF-1β mRNAs were correlated to the exercise-induced increase in femoral venous plasma lactate concentration. It is concluded that 1) VEGF but not FGF-2 gene expression is upregulated in human skeletal muscle by a single bout of dynamic exercise and that there is a graded response in VEGF mRNA expression related to the metabolic stress and 2) the increase in VEGF mRNA expression correlates to the changes in both HIF-1α and HIF-1β mRNAs.

Complementary studies of exercised-induced angiogenic growth factors in human skeletal muscle

To the Editor: From the outset of this communication, let me recognize that the work of Gustafsson et al. (1) published in February of 1999 was the first paper to demonstrate that vascular endothelial growth factor (VEGF) at the mRNA level increases in human skeletal muscle after an exercise bout (submitted 7/22/98). However, as should become apparent with this short history of events, possibly concurrently with this investigation, we were performing similar studies of the human angiogenic response to exercise. Our initial findings were submitted to the Journal of Applied Physiology on 7/7/98 as a Rapid Communication, but the paper was rejected with the suggestion of a conversion to a more comprehensive full manuscript. This was performed (submitted 11/9/98) and subsequently rejected in this format (2/24/99). The manuscript was revised and submitted (5/10/99) to the American Journal of Physiology-Heart and Circulatory Physiology and accepted (6) (submitted 7/16/99). Unfortunately, during the rewrite and submission of this work to the American Journal of Physiology-Heart and Circulatory Physiology, the paper was not updated to include the now published work of Gustafsson et al. (1).

With regard to the science contained within the two papers, it is clear that there are many similarities but also some differences. Both studies focus on the angiogenic response of human skeletal muscle to exercise in terms of VEGF and basic fibroblast growth factor (bFGF), with the Gustafsson paper (1) including hypoxia-inducible factor (HIF) subunits. Both studies utilized the single leg knee-extensor exercise model but with apparently different motives. Gustafsson et al. (1) chose this model for its easy combination with femoral venous blood samples (PO₂ and lactate) directly from the exercising muscle, whereas we wanted an isolated small muscle mass to allow myoglobin saturation measurements, rest and exercised samples to be taken on the same subject on the same day, and allow a repeated measures experimental design. Both studies collected muscle samples following the exercise bout: Gustafsson et al. (1) at 30 min and our study at an average of 60 min. Although both studies were interested in the effect of varying oxygen availability, the two studies achieved this in two very different fashions: Gustafsson et al. utilized external pressure that resulted in ischemia, whereas we used alterations in inspired oxygen concentration and no restriction to blood flow, thus making the two studies complementary. The assessment of this treatment at the tissue level was also very different between the two studies, with Gustafsson et al. using indirect measures of cellular oxygenation state (venous oxygen saturation, PO₂, venous lactate), whereas we directly measured intracellular myoglobin saturation to determine intracellular PO₂. At this point it should be recognized that there may be significant differences in the physiology associated with ischemia and hypoxia (3, 4), but oxygen delivery may play a fundamental role in both treatments (2).

The scientific conclusions of both these studies is that VEGF mRNA is upregulated in human muscle in response to exercise, whereas bFGF appears not to be affected. This VEGF upregulation is closely correlated to the change in both HIF subunits. However, the level of VEGF mRNA is not obviously related to alterations in oxygen availability during exercise, but measurements of intracellular PO₂ suggest a possible “threshold” of intracellular PO₂ (easily achieved in normoxia or with no flow restriction), beyond which no greater angiogenic stimulus is produced. Even the correlation found between femoral venous lactate production, as reported by Gustafsson et al. (1), should be interpreted with caution as a link to increasing intracellular hypoxia because we have previously documented that these two variables are unrelated (5).
In conclusion, the failure to cite Gustafsson et al. (1) in our paper (6) is regretted but was the consequence of the complicated review history of our paper, which was originally submitted before Gustafsson and colleagues’ work was published. We would like to suggest that since the two papers arrived at similar conclusions using quite different protocols, they should be viewed as providing complementary information on angiogenic growth factor gene regulation as the result of exercise.

REFERENCES


R. S. Richardson
Department of Medicine
University of California, San Diego
La Jolla, California 92093