Focus on “Skeletal muscle interleukin-6 regulation in hyperthermia”

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Traditionally, the drastic increase in circulating IL-6 and other cytokines seen during exercise was thought to originate from mononuclear cells associated with the general inflammatory response. Activation of the IKK/NF-κB pathway associated with inflammation would lead to the production of IL-6 and other cytokines (1). However, more recent data have shown that IL-6 expression remains unchanged or even decreases in monocytes during exercise (9). Furthermore, studies as early as the late 1990s have shown that many tissue types, including skeletal muscle, produce cytokines (6). The increase in IL-6 expression in skeletal muscle occurs fairly rapidly upon the start of exercise and can increase 100-fold during prolonged physical activity. Thus, the role of skeletal muscle is being considered more broadly to include its function as a pseudo-endocrine organ.

The mechanisms of increased IL-6 expression, however, have not yet been fully elucidated. There are drastic intra- and extracellular environmental changes that occur during contractions and exercise, and these alterations give rise to numerous potential pathways of IL-6 expression. Changes in calcium, reactive oxygen species (ROS), cellular energy levels, hormones, and temperature may initiate the expression of IL-6 (Fig. 1). Many studies have shown that increases in calcium and the Ca$$^{2+}$$ ionophore ionomycin result in increased IL-6 expression. However, the exact mechanism of calcium-induced IL-6 expression is unresolved. Early studies suggested that calcium-induced expression of IL-6 occurred via the calcineurin/NFAT pathway. More recent data have shown a fiber-type-specific expression of IL-6 in fast-twitch fibers, implying that calcium-induced expression of IL-6 most likely occurs through a different, but unknown, pathway (2). Thus, the specific pathways for calcium-induced IL-6 expression may be different in slow- and fast-twitch fibers. Exercise has also been shown to significantly increase the production of ROS in skeletal muscle as a result of oxidative stress during exercise. This increase in ROS may not just be toxic to cells, but may trigger intracellular pathways, including pathways that upregulate cytokine production. The ROS-induced expression of IL-6 most likely occurs by means of the JNK/p38(MAPK)/activator protein-1 (AP-1) pathway (4). Furthermore, low glycogen levels have been found to increase IL-6 expression, suggesting that a low energy status of muscle cells may trigger cytokine production (3).

In this issue of the American Journal of Physiology-Cell Physiology, Welc et al. (12) from Dr. Clanton’s laboratory have presented interesting data on the mechanisms of IL-6 expression in response to hyperthermic conditions. These researchers found that both heat shock factor-1 (HSF-1) and AP-1 play major roles in hyperthermic induction of IL-6 in C2C12 cells. An earlier study by these researchers showed that
IL-6 levels increases 1,000-fold two hours following heat shock in mice (11). In addition to molecular chaperones (heat shock proteins) that protect, fold, or unfold proteins, hyperthermia induces the expression of numerous genes associated with cellular repair (general review, 8). Many of these genes are associated with apoptosis and protein degradation, cell cycle, and cytokine production. The role that the transcription factor HSF-1 has in gene regulation in response to hyperthermia has been well documented, especially in reference to the expression of heat shock proteins. HSF-1 is rapidly activated during elevated temperatures by trimerization and that allows it to bind to the heat shock element (HSE) promoter sequence (7). In the previous study by Welc et al. (11), it was shown that the inhibition of HSF-1 with KNK437 during heat shock prevented IL-6 transcription in skeletal muscle cells. As a follow-up to that study, these researchers utilized a luciferase reporter plasmid under transcriptional control of the mouse IL-6 promoter in muscle myotubes that were then allowed to differentiate. Under hyperthermic conditions, IL-6 promoter activity increased over 150%. Additional studies were performed to show the vital role that HSF-1 and AP-1 have in regulating IL-6 transcription in response to hyperthermic environments.

Certain cellular responses to heat shock may not actually be due to increased temperature, but may be due to the endoplasmic reticulum stress signaling, also known as the unfolded protein response (UPR) (10). However, prior to the study profiled in this edition of American Journal of Physiology-Cell Physiology by Welc et al. (12), it has yet be determined whether the UPR regulates IL-6 expression in skeletal muscle. In this study they showed an increase in IL-6 secreted from C2C12 cells exposed to four different nonspecific pharmacological agents known to induce the UPR. Further research in this area is needed as a possible target for the treatment of muscle-related diseases and disorders.

The role that muscle-derived IL-6 plays in the body is somewhat controversial (5). IL-6 has both pro- and anti-inflammatory properties. IL-6 has been associated with muscle atrophy and cachexia and has been shown to inhibit the expression of other proinflammatory cytokines in skeletal muscle. The fact that HSF-1 and AP-1 are required for IL-6 expression in skeletal muscle suggests that the role of IL-6 associated with the heat shock and stress response may be undervalued. IL-6 plays an important part in the inhibition of protein synthesis, in increased protein degradation, and in the inhibition of apoptosis. Thus, increased IL-6 expression during hyperthermia may be a vital approach that cells employ to manage heat stress and support survival.

REFERENCES