Is Leptin Involved in the Signaling Cascade After Myocardial Ischemia and Reperfusion?

To the Editor:

We read with great interest the elegant study by Chandrasekar et al1 about the upregulation of CCAAT/enhancer binding protein, interleukin-6, the interleukin-6 receptor, and the signal transducer gp130 during reperfusion after a brief period of myocardial ischemia. The rapid and sustained production of interleukin-6 and the concomitant expression of the interleukin-6 receptor and gp130 suggest that these factors may participate in a local inflammatory cascade after myocardial ischemia and reperfusion. We approach this finding from a complementary point of view and comment on the possible involvement of leptin in the signaling cascade of postischemic myocardium.

The ob gene product, also known as leptin, was discovered because of its very specific biological action: the ability to regulate body weight and appetite.2 Interestingly, leptin has a structure similar to that of the family of helical cytokines, which includes interleukins. Many cytokines, which were originally isolated on the basis of particular biological actions, have subsequently been shown to be capable of stimulating a variety of biological responses in a wide spectrum of cell types. Thus, leptin shares with other cytokines an extreme functional pleiotropy, and it is involved in quite diverse physiological functions, such as reproduction, hematopoiesis, immunity, and angiogenesis.2,3

The functional leptin receptors (OB-R), which have a widespread distribution, including the myocardium, belong to the class I cytokine receptor family.2 The extracellular and cytoplasmic regions of OB-R and gp130 possess conserved motifs and are closely related to each other. OB-R and gp130 seem to mediate overlapping but distinct cytoplasmic signals.4 Furthermore, recent reports have shown that OB-R stimulates transcription via interleukin-6 and hematopoietin receptor responsive elements.5

Inflammation and vascularization play an important role in tissue healing after injury. In this sense, the activation of the immune system by leptin, together with its angiogenic effect, may prove of extraordinary physiological relevance. Thus, leptin may participate in the development of an inflammatory reaction in the infarcted tissue and accelerate tissue repair. The involvement of leptin in the signaling cascade after myocardial infarction is feasible both from a molecular and functional point of view. Interestingly, a worse clinical outcome after acute myocardial infarction is observed in obese patients, in whom a state of leptin-resistance may exist.

In our opinion, a study of the potential participation of leptin may provide valuable information concerning cooperation among the different signaling systems and further our understanding of cytokine induction, which operates in a cascade fashion.

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Response

We are grateful for the opportunity to respond to the comments of Drs Frühbeck and Salvador regarding our recent publication in Circulation.

Myocardial reperfusion injury is a complex and redundant pathobiology. It is quite likely that we have only begun to unravel the key players of this most common disease of the heart. In prior studies, we showed that during reperfusion after a single episode of sublethal ischemia, interleukin (IL)-1β and tumor necrosis factor-α (TNF-α), cytokines with negative inotropic effects in the myocardium,1 and IL-6 were induced. The induction of IL-6 showed a pattern of expression that was distinct from that of IL-1β and TNF-α; in a subsequent study, we showed that its expression was associated with the concomitant overexpression of IL-6R and the signal transducer gp130.2 The precise functional role of this cytokine in the postischemic heart has not been defined, although there is speculation that it may participate in aspects of remodeling and that it may modulate apoptosis.

In both humans and rodents, the administration of lipopolysaccharide (endotoxemia) or proinflammatory cytokines increased serum levels of leptin.3,4 Leptin, the ob (obese) gene product, has a structure similar to that of the IL-6 family of cytokines. Furthermore, its receptor (Ob-R) is homologous to gp130. Both Janus kinases and signal transducers and activators of transcription are involved as downstream components of leptin and IL-6 signaling, which demonstrates several similarities between leptin and the IL-6 family.5

Mice with a leptin deficiency show an increased mortality when given endotoxin, which suggests that leptin may have a beneficial role. Moreover, the administration of leptin increases serum levels of the IL-1 receptor antagonist (IL-1Ra) and IL-10.6 IL-1Ra attenuates the effects of IL-1β by blocking receptor-ligand interactions, and IL-10 inhibits proinflammatory cytokine expression. Hence, it is fair to speculate that in addition to its effects on metabolism, immune function, and angiogenesis, leptin may serve the beneficial role of enhancing the production of anti-inflammatory proteins (IL-1Ra and IL-10) during myocardial reperfusion injury. It remains to be seen whether such positive effects will be important after periods of ischemia that are long enough to induce necrosis and apoptosis in the heart.

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