IL-6 and metabolism—new evidence and new questions

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Does the cytokine IL-6 play a role in the regulation of metabolism? From a rather unexciting existence as a lacklustre, but dependable player in the textbook version of the inflammatory response, IL-6 has recently taken centre stage in the search for culprits underlying the inflammatory component of the metabolic syndrome. Reduced insulin action following in vitro exposure of cultured adipose and hepatocyte cells to IL-6 has been submitted as evidence strongly implicating IL-6 in the direct induction of insulin resistance [1–4]. In contrast, data indicating that IL-6 deficiency in mice leads to obesity and insulin resistance provides evidence against a causative effect of IL-6 in insulin resistance [5]. Furthermore, contraction-stimulated release of IL-6 from skeletal muscle has been coupled to positive metabolic effects associated with exercise, such as the enhancement of insulin sensitivity [6]. Numerous explanations for these two divergent opinions have been put forward, including differences in model systems, chronic versus pulsatile exposure, and in vitro vs in vivo effects [7, 8]. In this issue of *Diabetologia*, Franckhauser and colleagues add another piece to the puzzle [9]. In an elegant

set of experiments, circulating IL-6 levels were increased by introducing a cytomegalovirus-driven *Il6* gene into several skeletal muscle groups in the mouse hindlimb by electro-transfer. This gene manipulation results in a rapid (within days) and sustained elevation of circulating IL-6 levels in an in vivo system.

What is the effect of the enhanced whole body delivery of IL-6? Certainly, it appears that adipose cells do not thrive in the presence of IL-6. Mice lost 20% of their body weight in just 1 week, with the actual fat pad weight dropping by a remarkable 75%, and the remaining adipose cells appearing significantly smaller. Leptin levels fell in parallel with the reduction in fat mass. More surprising was the paradoxical reduction in circulating adiponectin levels (see Fig. 1). Despite the expeditious reduction in fat mass, the *Il6*-expressing mice did not alter their food intake, suggesting that IL-6 is promoting increased energy expenditure and enhanced fat oxidation. The enhanced reliance on lipid as an energy source is confirmed by reduced circulating NEFA and triacylglycerol. Skeletal muscle glucose uptake in the basal state was reduced, again possibly pointing to a preferential utilisation of lipids. In response to a glucose challenge, *Il6*-expressing mice disposed of glucose more efficiently, suggesting that they are not insulin resistant per se. The latter issue is, however, complicated by the fact that the elevation in circulating IL-6 is accompanied by hypoglycaemia, which appears to stem from reduced hepatic glucose production, and an inappropriate fasting hyperinsulinaemia (postprandial insulin does not appear elevated above levels observed in control mice). The hyperinsulinaemia is accompanied by an unexpected increase in beta cell insulin content. *Il6* overexpression also leads to increased

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Fig. 1 Weighing up the evidence. Mice with elevated circulating IL-6 as described by Franckhauser et al. [9] display enhanced lipid utilisation and reduced body weight, and develop hypoglycaemia and inappropriate hyperinsulinaemia

circulating levels of serum amyloid A and hepatic infiltration of neutrophil-like cells, indicating that liver function is impaired in the face of increased IL-6 levels. However, liver fat content was reduced, again underscoring the enhanced reliance on lipid as a major energy source.

The dramatic shift in metabolism noted in mice following the increase in circulating IL-6 begs the question: which signalling pathways are being activated? There is recent evidence indicating that IL-6 activates AMP kinase [10–12]. Indeed, Franckhauser et al. [9] report increased AMP kinase phosphorylation in skeletal muscle from mice with increased *Il6* expression. IL-6-mediated activation of liver AMP kinase could also explain the reduced glucose production. Whether all the effects noted in the mice rely on AMP kinase-dependent signals is unlikely, but remains to be determined.

The use of electro-transfer to introduce and express a gene in an adult animal is elegant and useful, bypassing the developmental adaptation that may occur with germ-line genetic approaches. Since expression persists for several weeks, there is ample opportunity to probe the system further. Why, then, do the animals not defend their body weight by increasing food intake? How will they respond when challenged by a high-fat diet, or by an exercise training protocol? How is IL-6 affecting beta cell insulin content and function? What are the tissue-specific insulin responses following a euglycaemic–hyperinsulinaemic clamp, and how would a similar approach affect other mice models, such the *ob/ob* or *db/db* mice? The follow-up studies are eagerly awaited, and promise to give important insights.

Where does this leave the impasse regarding the role of IL-6 in either promoting, or indeed, protecting the body from the development of insulin resistance and metabolic disease? The jury may have to deliberate for a while longer. At issue again is the question of timing and dosage. During exercise, the contracting skeletal muscle produces and releases IL-6.

This increase may be up to 100-fold higher than resting levels, peaking just after cessation of exercise [13]. In this context, IL-6 may play a role in ensuring adequate substrate supply for the working muscle, via effects on liver and adipose cells. Mice that lack IL-6 show reduced exercise endurance and a progressive decrease in oxygen consumption as compared with control wild-type mice, supporting a role for IL-6 in maintaining skeletal muscle nutrient supply [14]. However, for a systemic effect to be notable, the exercise needs to be both prolonged and involve considerable skeletal muscle mass. The most pronounced effect of contraction-induced IL-6 is thus likely to be localised directly to the muscle and the immediately surrounding tissue. Again, the contribution of IL-6 in this context has not been fully elucidated, since the contraction per se will lead to activation of AMP kinase. Recent work from Muñoz-Cánoves' group highlights that IL-6 is an essential regulator of satellite cell-mediated hypertrophic muscle growth [15]. The satellite cells surrounding the working muscle may thus be (one of) the primary target(s), at least for muscle-derived IL-6.

So how does this relate to human physiology? In resting healthy humans, plasma IL-6 is normally about 1–2 pg/ml or less [16]. Although exercise itself leads to an acute increase in IL-6 production and release by the working muscle, exercise training leads to reduced circulating IL-6 levels and, at least according to changes in levels of molecules in the IL-6 signalling pathway, an increased IL-6 sensitivity in skeletal muscle [17]. The increased circulating levels of IL-6 noted in the absence of exercise and in the context of human type 2 diabetes and/or obesity are about two- to threefold higher than those measured in healthy individuals with normal glucose tolerance, with largely overlapping ranges [18]. In contrast to exercise, this represents a low but chronic IL-6 exposure. In this situation, macrophages are believed to be a major source of IL-6, and it is possible that local concentrations are higher than the circulating values. The IL-6 levels achieved following electro-transfer by Franckhauser and colleagues [9] is around 800 pg/ml, i.e. many hundredfold above both normal and diabetic values, and about fivefold higher than those seen following strenuous exercise. Concentrations are equivalent to those noted in the context of severe infections. Thus, caution should be used when extrapolating these very dramatic increases in circulating IL-6, to the low-grade inflammation noted in people with type 2 diabetes. At the same time, the evidence presented by Franckhauser reduces enthusiasm for the application of IL-6 to cure obesity or enhance physical performance.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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