The Double Face of IRF4 in Metabolic Reprogramming

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The prevalence of obesity has tripled over the past four decades, adding a further burden to our health care systems, patients, caregivers, and families. Of importance, obesity is associated with chronic low-grade inflammation, which is linked to an increased incidence of insulin resistance and type 2 diabetes. Indeed, inflammation in adipose tissue contributes to whole-body insulin resistance by secreting cytokines, known as adipokines, into the circulation that impair insulin sensitivity in various tissues, including skeletal muscle and liver. However, emerging evidence indicates that in the setting of obesity, inflammation can also occur in skeletal muscle itself, leading to impairment in whole-body insulin sensitivity (1). Toll-like receptors (TLRs) and their downstream signaling have been strongly connected with obesity-induced inflammation (2), and TLR activation, especially that of TLR4, leads to the induction of interferon regulatory factors (IRFs) (3). IRFs are a family of nine transcription factors that play pivotal roles in regulating a wide range of cellular functions, including adipogenesis and inflammatory responses (4,5). For example, several studies have shown that IRF4 is highly expressed in adipocytes and plays a critical role in regulating obesity-induced inflammation and adipocyte lipid handling (6,7). Intriguingly, in this issue of *Diabetes*, Yao et al. (8) demonstrate that IRF4 also plays an important role in the development of obesity and insulin resistance and regulates skeletal muscle amino acid metabolism (Fig. 1), particularly that of the branched-chain amino acids (BCAAs).

Yao et al. (8) performed RNA sequencing on human muscle biopsy specimens from lean and obese subjects and found that IRF4 is one of the most upregulated genes in obese individuals. They also observed that protein and gene expression of IRF4 is significantly increased in muscles of obese subjects as well as in gastrocnemius muscles from two different animal models of obesity (diet-induced obesity [DIO] and *db/db* mice). To determine whether these changes in muscle IRF4 expression are adaptive or maladaptive in obesity and insulin resistance, the authors produced mice with a skeletal muscle–specific overexpression of IRF4 ($Irf4^{SkM/OVE}$) and mice with a skeletal muscle–specific deficiency of IRF4 ($Irf4^{SkM-/-}$). Of interest, they demonstrate that $Irf4^{SkM/OVE}$ mice are more susceptible to DIO, glucose intolerance, and insulin resistance. On the contrary, $Irf4^{SkM-/-}$ mice were resistant to DIO and exhibited improved glucose tolerance and insulin sensitivity. Furthermore, what appears responsible for these metabolic adaptations in $Irf4^{SkM-/-}$ obese mice is decreased expression of mitochondrial branched-chain aminotransferase (BCATm), the first enzyme of BCAA catabolism that converts BCAAs to branched-chain α-ketoacids (BCKAs). To validate this, the authors used a luciferase reporter assay in 293T cells to show that IRF4 directly regulates BCATm activity in the 2041/+103 region of the BCATm promoter.

To complement their in vitro studies, Yao et al. (8) overexpressed BCATm in the gastrocnemius of $Irf4^{SkM-/-}$ obese mice using adenovirus-mediated gene delivery and showed that these mice were no longer protected against DIO, glucose intolerance, and insulin resistance. Accordingly, the authors concluded that IRF4 regulates skeletal muscle metabolic adaptations in a BCATm-dependent manner (Fig. 1). Intriguingly, the Rosen laboratory observed that mice lacking IRF4 in adipose tissue are more vulnerable to DIO while being glucose intolerant and insulin resistant (6). Another study from the same group also revealed that mice with a brown adipose tissue–specific deficiency of IRF4 are obese and insulin resistant and exhibit reduced thermogenic gene expression and energy expenditure (9). The observations of Yao et al. (8) and the latter studies from the Rosen laboratory clearly indicate that IRF4 regulates metabolic reprogramming in a tissue-specific manner.

Yao et al. (8) also reported that circulating and muscle BCAA levels are decreased in $Irf4^{SkM/OVE}$ obese mice and increased in $Irf4^{SkM-/-}$ obese mice. Based on these findings, they proposed that $Irf4^{SkM-/-}$ mice are protected

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COMMENTARY

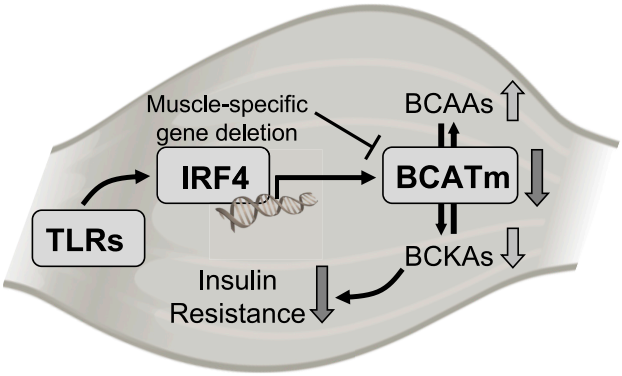

Figure 1—IRF4 regulates skeletal muscle BCAA catabolism. The study by Yao et al. (8) demonstrates that IRF4 plays an important role in the development of obesity and insulin resistance and regulates skeletal muscle metabolic adaptations in a BCATm-dependent manner.

against the development of insulin resistance in part by elevated BCAA levels in both skeletal muscle and plasma (Fig. 1). In contrast, several studies have reported that obesity-induced insulin resistance is associated with increased BCAA levels (10,11), and BCAA accumulation shows an inverse association with insulin sensitivity (12). Therefore, the augmentation of intramuscular BCAA accumulation in *Irf4*$^{\mathrm{SkM}-/-}$ obese mice is unlikely to be responsible for alleviating insulin resistance and improving insulin sensitivity. Indeed, the global deletion of BCATm raises plasma BCAA levels in mice and yields remarkable improvements in glucose and insulin tolerance (13); however, BCKA levels were completely abolished in these mice. Deleting BCATm in the heart also decreases cardiac BCKA levels and increases BCAA levels, which are associated with improved cardiac insulin sensitivity (14). Mice with an adipose tissue–specific deficiency of BCATm are also resistant to DIO, whereas BCKA supplementation in mouse drinking water revokes the phenotype (15). These studies suggest that the accumulation of BCKAs, rather than BCAAs, is a critical factor for mediating insulin resistance. Thus, this specific study by Yao et al. (8) would have greatly benefited from measurements of muscle BCKA levels. In addition, it was previously reported that mouse expressing Cre recombinase in the skeletal muscle are protected against obesity-induced glucose intolerance (16). Thus, another aspect missing from this study is the appropriate use of an inducible Cre mouse model, such as the human α-skeletal actin Cre mouse (HSA-MerCreMer mice; strain number 025750 from The Jackson Laboratory), as their control littermates for comparison.

Taken together, the observations of Yao et al. (8) are important, as they add provocative new information surrounding the pathological role of muscle IRF4 in obesity. They also revealed, for the first time, that IRF4 transcriptionally regulates muscle BCATm. Finally, because the authors documented an increase in muscle BCATm protein expression in obese subjects, future studies are required to determine whether the lack of BCATm specifically in mouse skeletal muscle confers protection against obesity-induced insulin resistance.

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