HIGHLIGHT

New insights into leptin resistance by modifying cytokine receptor signal transduction

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It has been widely accepted that leptin treatment of obese humans is restricted to those few subjects that suffer from congenital leptin deficiency (1). The peripheral administration of leptin to overweight patients with fat mass-adjusted normal serum leptin concentrations does not reduce body weight substantially (2). These observations suggest that leptin resistance in obese human beings is similar to insulin resistance in patients with type 2 diabetes mellitus.

Several mechanisms contributing to leptin resistance have been identified so far. First, a saturable transporter allowing leptin to pass the blood–brain barrier was discovered. This mechanism impedes the hormone's transfer to the hypothalamus once certain plasma concentrations are exceeded (3, 4). Secondly, negative regulators of leptin signalling such as the tyrosine phosphatases protein tyrosine phosphatase 1B and SH-containing protein tyrosine phosphatase (5–8) as well as the suppressors of cytokine signalling (Socs) (9) have been shown to contribute to leptin resistance. Since leptin indeed acts via a cytokine receptor, the latter group is of particular interest. Socs molecules inhibit the function of cytokines and of other proteins such as leptin by interfering with receptor-dependent JAKs or STATs (Fig. 1). In fact, peripheral leptin administration in mice has previously been shown to increase the hypothalamic concentration of *Socs3* (10). This would suggest that increased serum concentrations of leptin in obese subjects might impede leptin function by interfering with receptor signalling through Socs proteins. At first glance it appears to be simple to test this hypothesis by watching the effect of leptin in a *Socs3*-deficient knock-out mouse model. However, homozygous *Socs3* knock-out mice are stillborn due to placental defects (11).

Therefore, it is of great interest that two recent articles eventually shed light on the role of *Socs3*, the suppressor of leptin function, using two different approaches. In the first report J S Flier's group used a heterozygous *Socs3* + / – mouse model to demonstrate in this non-lethal animal model reduced *Socs3* mRNA expression in the hypothalamus (12). The second report used a Cre-loxP system to allow neural cell-specific specific *Socs3* knock-out not interfering with

the non-neuronal functions of the protein (13). They were able to demonstrate complete absence of *Socs3* in the brain of their animals.

Using these two different approaches the two papers achieve amazingly consistent findings: (i) *Socs3* + / – animals as well as neural cell-specific knock-out mice do not gain significantly more weight or increase food intake compared with their normally fed littermates even when offered a high-fat diet. In contrast, wild-type mice developed a significant increase in food intake and body weight. This suggests that leptin-induced suppression of appetite is enhanced in the *Socs3*-deficient animals and that *Socs3* is a mediator of leptin resistance. (ii) While wild-type mice develop insulin resistance when exposed to high-fat diet this is not the case in the two different knock-out animals with reduction or absence of *Socs3* in the brain. This could be demonstrated by normalisation of insulin secretion as well as a normalised response to glucose tolerance tests. (iii) With regard to the mechanism of action, in both studies the hypothalamic response to peripheral leptin administration was increased in the knock-out animals, suggesting a lesser degree of impairment of leptin receptor function. Specifically, STAT3 phosphorylation, being the most important mode of signal transduction of leptin, was increased in both the heterozygous *Socs3* and the neural cell-specific *Socs3* knock-out following leptin application.

However, while the principal messages of both communications on *Socs3* suppression are in line, some of the findings are distinct: Howard *et al.* (12) do not report alterations in the hypothalamic gene expression of the leptin receptor downstream peptides neuropeptide Y (NPY), proopiomelanocortin (POMC) and agouti-related peptide (AgRP) with their heterozygous *Socs3* knock-out between wild-type and knock-out mice after leptin infusion. This leads them to suggest that other downstream peptides might be of relevance for leptin action. In contrast, the complete *Socs3* knock-out in brain tissue that is reached in experiments by Mori *et al.* (13) leads to an increase in hypothalamic POMC mRNA in contrast to wild-type animals 6 h after leptin infusion. This shows how important different approaches may be to elucidate the exact mechanisms of leptin action.

Figure 1 Mechanisms of hypothalamic leptin action, leptin signal transduction and key players in leptin resistance with regard to obesity control.

In summary, the papers of Howard *et al.* (12) and Mori *et al.* (13) add important new information on the physiology and pathophysiology of leptin resistance in animals and potentially in man. Further examination of the role of Socs3 in humans with leptin resistance and the development of strategies to inhibit the action of hypothalamic Socs3 might provide a possible new target in the fight against obesity.

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