Commentary

MOLECULAR METABOLISM

Relationship status update for PTP1B and LepR: It's complicated*

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The adipocyte-derived hormone leptin is an important regulator of systemic energy metabolism. Transported via the circulation to the brain in proportion to fat mass, leptin promotes its biological action through activation of the long form of the leptin receptor (LepRb). Accordingly, binding of leptin to the extracellular domain of LepRb promotes transphosphorylation of the LepRb-associated Janus kinase 2 (JAK2), which in turn phosphorylates other tyrosine residues (Tyr_{985}, Tyr_{1077}, Tyr_{1138}) along the intracellular tail of LepRb in order to facilitate downstream signaling [1]. The protein tyrosine phosphatase 1B (PTP1B) is an important negative regulator of leptin action due to its ability to directly inhibit LepRb-Jak2 signaling (Figure 1). The relevance of PTP1B to regulate energy metabolism was first shown in mice with global PTP1B deletion [2] and was later confirmed in a series of other studies. These whole body PTP1B deficient mice show decreased body weight, food intake and adiposity, leading to resistance to diet-induced obesity (DIO) and improved leptin sensitivity and glucose metabolism when exposed to a high-fat diet (HFD) [2]. Of appreciable note, mice with specific deletion of PTP1B in muscle, liver or adipose tissue show no overt changes in body weight, adiposity or glucose tolerance [3–5]. However, deletion of PTP1B specifically in the central nervous system (CNS) [6], in LepRb-expressing cells [7] and POMC neurons [8,9] mimics the results observed in the global PTP1B deficient mice. These studies strongly support the relevance of central PTP1B signaling in regulating energy metabolism. It remains unclear, however, whether and to what

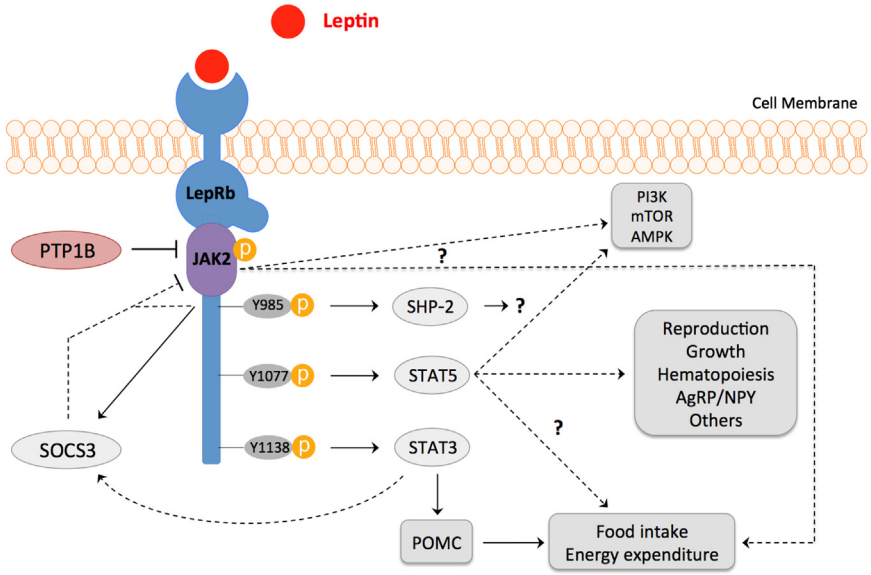

Figure 1: Schematic of how PTP1B affects intracellular leptin receptor signaling. Binding of leptin to the extracellular domain of LepRb leads to autophosphorylation of the Janus kinase 2 (JAK2). JAK2 in turn phosphorylates three LepRb tyrosine residues (Tyr_{985}, Tyr_{1077}, Tyr_{1138}), which facilitate activation of specific downstream targets, such as the tyrosine phosphatase SHP-2, and the signal transducer and activator of transcription 3 and 5 (STAT3 and STAT5). Homodimerization of STAT3 then initiates a cascade of signaling events that finally entail activation of POMC neurons but also induces activation of the suppressor of cytokine signaling 3 (SOCS3).
Adapted from Myers et al., Annual Review of Physiology 70:537–556.

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This commentary refers to "Improved metabolic phenotype of hypothalamic PTP1B-deficiency is dependent upon the leptin receptor by Tsou et al." (10.1016/j.molmet.2014.01.008).

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extent the metabolic benefits arising from central PTP1B deficiency depend on PTP1B's action within the hypothalamus and whether the observed effects on metabolism are mediated via hypothalamic leptin receptor signaling. An elegant step in solving these questions has now been taken by the group of Kendra Bence from the University of Pennsylvania [10]. In the current issue of Molecular Metabolism, Tsou and colleagues used mice with hypothalamus-specific expression of Cre recombinase (Nkx2.1 cre) to specifically delete PTP1B in the hypothalamus. Compared to wildtype control mice, these hypothalamus-specific PTP1B deficient mice (Nkx2.1 PTP1B$^{-/-}$) show decreased body weight, adiposity and food intake under chronic HFD exposure. These data corroborate previous reports about the relevance of central PTP1B signaling in the regulation of systems metabolism. Moreover, they show for the first time that the hypothalamus plays a key role in mediating PTP1B's action on metabolism and that hypothalamic selective PTP1B deletion mimics the phenotype of the whole body, whole brain, LepRb-expressing cell and POMC neuronal PTP1B knockout mice [6–9]. To further assess whether the metabolic benefits observed in the hypothalamus-specific PTP1B$^{-/-}$ mice depend on hypothalamic leptin receptor signaling, the authors generated mice with concomitant deletion of PTP1B and the leptin receptor in the hypothalamus (Nkx2.1 PTP1B$^{-/-}$: LepRb$^{-/-}$). Interestingly, when comparing these double mutant mice with hypothalamus-specific LepRb deficient mice, the metabolic benefits of PTP1B deletion vanished. No difference in body weight, food intake, adiposity or glucose tolerance was observed when double mutant mice were compared to mice that lack only the leptin receptor, but not PTP1B, in the hypothalamus. Together, the data indicate that the improved body weight and adiposity that is observed upon hypothalamic PTP1B deletion is mediated via interaction of PTP1B and the leptin receptor in the hypothalamus and that the metabolic benefits arising from PTP1B deficiency thus depend on a functional leptin receptor in the hypothalamus. These results underscore the importance of hypothalamic leptin receptor signaling for the regulation of energy and glucose metabolism and highlight the role of PTP1B in systems metabolism. In summary, the recent data by Tsou et al., combined with a series of previous studies, make PTP1B an interesting target for studies aiming to improve leptin sensitivity in states of pathologically increased body weight.

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