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Review Article

The Genetics of *PTPN1* and Obesity: Insights from Mouse Models of Tissue-Specific PTP1B Deficiency

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The protein tyrosine phosphatase PTP1B is a negative regulator of both insulin and leptin signaling and is involved in the control of glucose homeostasis and energy expenditure. Due to its prominent role in regulating metabolism, PTP1B is a promising therapeutic target for the treatment of human obesity and type 2 diabetes. The PTP1B protein is encoded by the *PTPN1* gene on human chromosome 20q13, a region that shows linkage with insulin resistance, type 2 diabetes, and obesity in human populations. In this paper, we summarize the genetics of the *PTPN1* locus and associations with metabolic disease. In addition, we discuss the tissue-specific functions of PTP1B as gleaned from genetic mouse models.

1. Introduction

Obesity is the chronic condition of having excess adiposity, and its prevalence is increasing in the United States and worldwide [1]. In 2009-2010, the prevalence of obesity (BMI $\geq$ 30) was 35.9%, and the prevalence estimate for obese and overweight individuals combined (BMI $\geq$ 25) was near 70% [2]. In addition to increased body weight and fat mass, obesity is a risk factor for a variety of associated disorders including diabetes, cardiovascular disease, and even certain cancers. Today, calorie-dense food options are widely available, and people live increasingly sedentary lifestyles. However, certain individuals are more susceptible to weight gain than others; thus, the causes of obesity include both environmental (external) and biological (genetic) influences. Research into the biological causes of weight gain has revealed numerous hormonal signals and cellular signaling pathways acting in concert, influencing the regulation of energy homeostasis. One protein implicated in the biological basis of obesity is the protein tyrosine phosphatase PTP1B.

2. Genetics of *PTPN1* and Human Obesity

PTP1B is a ubiquitously expressed protein tyrosine phosphatase (PTP) encoded in humans by the *PTPN1* gene. PTP1B is a known negative regulator of leptin and insulin signaling *in vivo*, two pathways important in energy homeostasis [3–6]. The human *PTPN1* gene is located on chromosome 20q13 [7], a region which has been identified as a quantitative trait locus associated with obesity and type 2 diabetes in a number of studies [8–10]. More recently, association studies have found single nucleotide polymorphisms (SNPs) within the *PTPN1* gene associated with obesity and associated metabolic disorders (Table 1). In 2004, a novel SNP located in an intronic region of the *PTPN1* gene was discovered to be frequently associated with morbid obesity in a cohort of obese French subjects compared to nonobese controls [11]. Furthermore, a single *PTPN1* SNP was found to be significantly associated with both type 2 diabetes and moderate obesity in two separate case-control studies of French subjects [12]. In the HERITAGE Family

Study examining body fat distribution in white and black subjects, white subjects homozygous for G82G at the *PTPN1* IVS6 + G82A polymorphism displayed elevated BMI, percent body fat, plasma leptin, and amount of subcutaneous fat [13]. In a study of Chinese children examining the effect of *PTPN1* variants on the pathogenesis of childhood obesity, the Pro303Pro polymorphism was found to associate with BMI and waist circumference [14]. The SNP 1484insG in the 3′ UTR of *PTPN1* showed significant association with higher values in insulin-resistance index and serum triglycerides in a group of Italian males [15] and was also shown to be associated with insulin resistance and cardiovascular risk factors in an Iranian population [16]. Importantly, PTP1B mRNA was overexpressed in skeletal muscle of subjects carrying the variant, demonstrating a functional link between a SNP in the *PTPN1* locus and altered protein expression [15]. In a population of Hispanic Americans, 20 *PTPN1* SNPs were found linked to insulin sensitivity and fasting blood glucose, including the 1484insG variant [17]. Another variant of the PTP1B gene (P387L) has been shown to be associated with increased risk with type 2 diabetes in a Danish population; this variant also results in impaired serine phosphorylation of PTP1B [18].

In addition to associations with obesity and type 2 diabetes, several *PTPN1* polymorphisms have recently been linked to lipid abnormalities and cardiovascular disease risk. For example, three *PTPN1* SNPs have been found to be associated with total cholesterol and LDL in a population of Dutch men [19]. Two *PTPN1* SNPs were found to correlate with serum cholesterol and triglyceride levels in a normoglycaemic, nonobese French population [12]. In a type 2 diabetes patient population, several *PTPN1* SNPs were associated with coronary calcified plaque, a proxy measure of atherosclerosis and cardiovascular disease [20]. In a study analyzing a cohort of Japanese and Chinese subjects, six SNPs in the *PTPN1* gene were found to be in linkage disequilibrium, and haplotypes including all six SNPs were associated with hypertension; additionally, a number of the individual SNPs were found to be associated not only with BMI but also with cholesterol levels [21, 22]. In examining the effect of *PTPN1* variants on the pathogenesis of childhood obesity, the Pro303Pro polymorphism was found to associate with serum triglycerides and low density lipoprotein cholesterol (LDL) [14].

Although numerous studies to date have found *PTPN1* variants to be associated with obesity, diabetes, and insulin resistance [16, 18, 23–26], two studies in healthy European populations did not find any significant associations between *PTPN1* SNPs or haplotypes and metabolic measures including body weight, BMI, and leptin levels [27, 28]. Additionally, no *PTPN1* SNPs were found to be significantly associated with type 2 diabetes or obesity in a population of Pima Indians [29]. Eight different *PTPN1* SNPs showed no association with type 2 diabetes in an Asian Indian population from south India [30]. The 1484insG 3′ UTR polymorphism has also been the source of debate since Dahlman et al. did not find significant correlation of this polymorphism with features of the metabolic syndrome in a Swedish population [31, 32]. Taken together, however, the majority of published studies indicate that human *PTPN1* variants are linked to obesity and other metabolic disorders (summarized in Table 1). Differences in subject populations, sample size, and the particular SNPs examined may explain the heterogeneity of the findings across studies.

3. Biochemical and Cellular Role of PTP1B in the Regulation of Energy Balance

PTP1B belongs to a superfamily of PTPs which, in the human, comprises approximately 100 genes; every PTP contains the $HC(X)_5R$ active-site motif where the conserved cysteine residue is required for catalytic activity [33]. PTP1B's substrates have been discovered largely through *in vitro* studies and the generation of substrate-trapping mutants. Early studies established PTP1B as a negative regulator of insulin signaling through microinjection into *Xenopus* oocytes, whereby injection of purified PTP1B enzyme led to decreased insulin-stimulated tyrosine phosphorylation [34]. PTP1B's regulation of insulin signaling was further confirmed by a number of groups (reviewed in [35, 36]). In addition to insulin signaling, PTP1B has been found to regulate a variety of intracellular signaling pathways and downstream effectors; other known/suspected substrates of PTP1B include receptor tyrosine kinases (e.g., epidermal growth factor receptor, insulin-like growth factor 1 receptor) and intracellular protein tyrosine kinases (e.g., c-Src, JAK2, TYK2) as well as a number of transcription factors and adapter proteins (reviewed in [37]).

The first indication that PTP1B may be a regulator of energy balance was discovered through the generation of PTP1B-deficient mice. Elchelby et al. generated PTP1B−/− mice by targeting exons 5 and 6 of the *Ptpn1* gene [3]. PTP1B−/− mice were shown to be insulin hypersensitive via glucose and insulin tolerance tests, and fed serum glucose and insulin levels were decreased in PTP1B−/− mice compared to wild type controls. Consistent with a role for PTP1B as a negative regulator of the insulin receptor (IR), insulin-stimulated phosphorylation of IR in peripheral tissues of PTP1B−/− mice was increased compared to PTP1B+/+ mice. In addition to improved insulin sensitivity, PTP1B−/− mice were resistant to high-fat diet- (HFD-) induced obesity compared to wild type controls. While PTP1B+/+ mice rapidly gained weight during 10 weeks of HFD exposure, PTP1B−/− and PTP1B+/− mice showed significant protection against diet-induced weight gain; food intake was unchanged between genotypes [3]. Whole body PTP1B knockouts were also generated by another group and further characterized in 2000. Klaman et al. generated PTP1B−/− mice by disrupting the ATG-coding exon 1 [4]. These PTP1B knockouts recapitulated the improved insulin sensitivity and decreased body weight phenotypes. The mice were also found to display significantly decreased adiposity as measured by fat pad weight and body composition analysis due primarily to significant increases in basal metabolic rate and total energy expenditure. Consistent with decreased adiposity, PTP1B−/− mice also displayed decreased circulating

Table 1: Summary of human *PTPN1* SNP studies and the associated metabolic disorder/parameter investigated. n.s.: not significant.

SNP/polymorphism	Sample size	Associated phenotype	P value	References
IVS5 + 3666delT, intronic downstream of exon 5	Obese patients $n = 711$ Nonobese patients $n = 427$	Morbid obesity (BMI ≥ 40)	$P = .02$	[11]
rs9144858 C/G, 10 kb downstream of *PTPN1*	Diabetic patients $n = 1227$ Normoglycaemic patients $n = 1047$	Type 2 diabetes	$P = .02$	[12]
rs9144858 C/G, 10 kb downstream of *PTPN1*	Moderate obese patients $n = 616$ Nonobese patients $n = 736$	Moderate obesity $30 < \text{BMI} < 40$	$P = .04$	[12]
IVS6 + G82A, (G82G homozygotes)	From HERITAGE study White patients $n = 502$	Increased percent fat Increased plasma leptin Increased subcutaneous fat	$P = .031$ $P = .028$ $P = .003$	[13]
rs2230604, (Pro303Pro) silent mutation	Chinese children Obese $n = 147$ Nonobese $n = 118$	Increased BMI Increased waist circumference Increased serum triglycerides Higher LDL levels	$P = .033$ $P = .046$ $P = .020$ $P = .009$	[14]
1484insG, in the 3' UTR	Italian males $n = 335$	Increased plasma insulin Higher HOMA insulin resistance Increased serum triglycerides	$P < .01$ $P < .01$ $P < .001$	[15]
1484insG, in the 3' UTR	Iranian males $n = 412$	Increased plasma insulin Higher total cholesterol Higher LDL levels Higher ApoB levels Higher HOMA insulin resistance	$P = .003$ $P = .012$ $P = .037$ $P = .015$ $P = .011$	[16]
20 unique SNPs within *PTPN1*, including 1484insG	Hispanic population $n = 811$	Insulin sensitivity index Fasting glucose	$P = .003$–$.044$ $P \leq .001$–$.029$	[17]
P387L, missense mutation	Danish Caucasian population Type 2 diabetic patients $n = 527$ Glucose tolerant controls $n = 542$	Type 2 diabetes	$P = .037$	[18]
rs6067484, rs6020611, rs1060402	Dutch Caucasian males $n = 382$	Higher total cholesterol Higher LDL levels	$P < .05$ $P < .05$	[19]

Table 1: Continued.

SNP/polymorphism	Sample size	Associated phenotype	P value	References
12 SNPs within *PTPN1* coding sequence	American Caucasian population $n = 590$	Increased coronary calcified plaques	$P \leq .0001$–$.043$	[20]
g.54281T>A and g.58585T>C, g.−7077G>C	Two Asian populations, Japanese and Chinese $n = 1553$	Increased BMI Higher cholesterol	$P < .05$ $P = .0124$	[21]
981C>T	Oji-Cree population $n = 728$	Lower risk for impaired glucose tolerance or type 2 Diabetes	$P = .04$	[24]
rs2206656, rs1570179, rs3787345, rs754118, rs3215684, rs2282147, rs718049, and 1484insG	Caucasian type 2 diabetic patients with end-stage renal disease $n = 300$ Control nondiabetic patients $n = 310$	Type 2 Diabetes	$P = .015$–$.048$	[26]
rs718049	Caucasian female twin population $n = 2777$	Higher waist circumference Lower insulin sensitivity Higher fasting insulin Higher serum triglycerides Higher systolic blood pressure	$P = .008$ $P = .002$ $P = .028$ $P = .023$ $P = .025$	[27]
rs1885177	Caucasian female twin population $n = 2777$	Lower insulin sensitivity	$P = .039$	[27]
rs6067484, rs1885177, rs2282146, rs718049, rs3787348, and 1484insG	Caucasian female twin population $n = 2777$	Leptin levels Body weight BMI Total fat	n.s.	[27]
rs6067484, rs6020611, rs3787348, rs1060402	Dutch Caucasian males $n = 382$	BMI Total fat Waist-to-hip ratio	n.s.	[28]
25 SNPs	Pima Indian population Type 2 diabetic patients $n = 573$ Nondiabetic patients $n = 464$	Type 2 diabetes obesity	n.s.	[29]
rs941798, rs3787345, rs2230604 (Pro303Pro), rs2282147, rs718049, rs718050, rs16995309 (Pro387Leu), and rs16989673 (1484insG)	Asian Indian population Type 2 diabetic patients $n = 262$ Nondiabetic patients $n = 249$	Type 2 diabetes	n.s.	[30]
1484insG	Swedish population $n = 2309$	HOMA insulin resistance Serum triglyceride levels BMI Percent body fat	n.s.	[31]

leptin levels and decreased leptin mRNA expression in white adipose tissue (WAT) [4].

A molecular explanation for why PTP1B−/− mice exhibit a lean metabolic phenotype was later discovered when PTP1B was found to regulate leptin signaling. Leptin is a hormone released by adipose into the circulation which plays a major regulatory role in feeding and energy expenditure via action in the central nervous system (CNS) [38]. Leptin decreases food intake and increases energy expenditure by affecting neuron activity and altering neuropeptide expression. The essential role for leptin signaling in regulating energy balance was confirmed by the obese and hyperphagic phenotypes of mice with a mutation in the gene encoding leptin (*ob/ob*) mice or its receptor (*db/db* mice) [39–41]. Leptin signals via the canonical JAK-STAT signaling pathway, and leptin resistance facilitates the obese state [42, 43]. PTP1B was shown to be a negative regulator of leptin signaling by acting to directly dephosphorylate the active site of the leptin receptor-associated tyrosine kinase, JAK2 [5, 6, 44]. *In vivo* analysis demonstrated that PTP1B−/− mice are indeed hypersensitive to the effects of leptin, further confirming that PTP1B's metabolic effects are likely a result of its role as a negative regulator of leptin signaling [5, 6]. Interestingly, when a PTP1B−/− mouse model was generated on a leptin-deficient *ob/ob* background, PTP1B−/−: *ob/ob* double mutants exhibited attenuated weight gain compared to *ob/ob* single mutant mice, suggesting that the metabolic effects of PTP1B deficiency may be mediated by both leptin-dependent and -independent pathways [6].

4. Neuron-Specific PTP1B-Deficient Models Reveal CNS-Specific Effects on Body Weight and Adiposity

Targeted deletion of PTP1B using the Cre-loxP system in mice reveals PTP1B's regulation of body weight and adiposity to be tissue specific (Table 2). Brain-specific PTP1B−/− mice recapitulate the decreased body weight and adiposity phenotype of whole body PTP1B−/− mice on HFD [45]. Like whole body PTP1B knockouts, brain-specific PTP1B−/− mice display increased energy expenditure, increased leptin sensitivity, and increased insulin sensitivity. Brain-specific PTP1B−/− mice also have slightly decreased food intake [45]. Additional CNS-targeted deletions of PTP1B also display metabolic improvements. POMC neuron-specific deletion of PTP1B (POMC-PTP1B−/−) results in mice with decreased body weight and adiposity on high-fat diet. Food intake is similar to wild type control mice while energy expenditure and core temperature are increased in POMC-PTP1B−/− mice. Like brain-specific and whole body PTP1B knockouts, POMC-PTP1B−/− mice show improved leptin sensitivity. Interestingly, insulin sensitivity is also improved in POMC-PTP1B−/− mice even when controlled for body weight and adiposity, suggesting that central PTP1B cannot only regulate energy balance, but peripheral glucose homeostasis as well [46]. Recently, our lab has generated a leptin receptor-expressing cell-specific PTP1B-deficient mouse model through the use of a leptin receptor-driven Cre line [47]. Like brain-specific PTP1B−/− mice, leptin receptor-specific PTP1B−/− (LepRb-PTP1B−/−) mice are leaner than their wild type littermate controls on both chow and HFD and have enhanced leptin sensitivity (unpublished data Tsou and Bence).

In contrast to neuron-specific PTP1B knockout models, muscle-, adipocyte-, or liver-specific deletion of PTP1B results in no differences in body weight or adiposity on either chow or HFD (Table 2) [45, 48–50]. Despite no differences in body weight or adiposity, muscle-specific PTP1B−/− mice demonstrate improved glucose tolerance and insulin sensitivity on HFD [48]. Similar to muscle-specific PTP1B deficient mice, liver-specific PTP1B−/− mice show improved glucose tolerance, decreased fed blood glucose levels, and improved insulin-to-glucose ratios on HFD [49]. Notably, liver-specific PTP1B−/− mice also exhibit decreased markers of endoplasmic reticulum (ER) stress on an HFD [51]. These studies are consistent with the role of PTP1B as a negative regulator of insulin signaling in insulin-responsive tissues such as muscle and liver. The role of PTP1B in adipose is less clear; the generation of a PTP1B-deficient mouse model using the aP2-driven Cre line results in mice with *increased* body weight on HFD [45]. However, whether adipocyte-specific PTP1B deletion explains the increased body weight phenotype of aP2-PTP1B−/− mice is unclear, as these mice only display ∼50% reduction in PTP1B expression in adipocytes isolated from WAT. Additionally, and of greater concern, aP2-Cre-mediated recombination has been shown to occur in other cell types including macrophages, osteoblasts, and cardiomyocytes [52, 53]. More recently, adipocyte-specific PTP1B−/− mice were generated using the adiponectin-Cre line [54] in order to achieve a more efficient, adipocyte-specific deletion. These mice (adip-PTP1B−/−) have normal body weight, adiposity, and glucose tolerance/insulin sensitivity, although adipocyte size is increased [50]. Despite normal body weight, adip-PTP1B−/− mice display elevated serum leptin levels and reduced leptin sensitivity when fed HFD. Interestingly, insulin signaling is comparable in adipocytes isolated from adip-PTP1B−/− and wild type controls, suggesting that PTP1B is not a major regulator of the insulin receptor in adipocytes [50]. Taken together, these findings indicate that central PTP1B deficiency decreases body weight/adiposity and improves peripheral glucose homeostasis, while PTP1B-deficiency in muscle or liver does not alter body weight but does significantly improve insulin sensitivity and glucose tolerance.

5. Obesity and PTP1B: More Than Genetics

Many factors likely contribute to the current obesity epidemic, including genetic and epigenetic influences. The "heritability" of obesity is currently a topic of active investigation, with epigenetic variation and its effects on gene expression taking center stage [55]. It is unknown whether variations in the human *PTPN1* locus persist across generations or are acquired spontaneously. While the genetics behind PTP1B expression and function may influence one's susceptibility to

Table 2: Summary of PTP1B-deficient genetic mouse models and their associated metabolic phenotypes. ND: not determined.

PTP1B-deficient mouse model	Body weight/adiposity phenotype	Leptin sensitivity	Glucose homeostasis	References
Global (whole body)	Decreased	Increased	Improved GTT Improved ITT	[3, 4]
Brain specific (Nestin-Cre)	Decreased	Increased	Improved GTT Improved ITT	[45]
POMC-neuron specific (POMC-Cre)	Decreased	Increased	Improved GTT Improved ITT	[46]
Adipose/macrophage specific (aP2-Cre)	Increased	ND	ND	[45]
Muscle specific (MCK-Cre)	No change	ND	Improved GTT Improved ITT	[48]
Liver specific (Albumin-Cre)	No change	ND	Improved GTT	[49]
Adipocyte specific (adiponectin-Cre)	No change in body weight Increased adipocyte size	Decreased	Mild glucose intolerance	[50]
LepRb specific (LepRb-Cre)	Decreased	Increased	Improved GTT	Unpublished (Tsou and Bence)

obesity as demonstrated by a variety of human and animal studies, external, nongenetic factors can also regulate PTP1B and its role in the development of obesity. The rapid rise of obesity in only the last few decades suggests that broad changes in the environment have influenced the increasing ease for weight gain. The abundance and availability of palatable foods coupled with a decreased need for physical activity have created an environment that promotes energy storage and weight gain. The effect of diet on PTP1B expression and the development of leptin resistance has been explored using mouse models of diet-induced obesity. HFD feeding in mice induces expression of PTP1B in a variety of leptin/insulin-target tissues including the arcuate nucleus of the hypothalamus, muscle, and liver [56]. Moreover, leptin-deficient *ob/ob* mice fed a HFD also show increases in hypothalamic PTP1B, suggesting there are additional leptin-independent mechanisms mediating diet-induced alterations in PTP1B expression [57].

Obesity-associated inflammation may also play a role in the regulation of PTP1B expression. High-fat feeding of mice not only increases hypothalamic PTP1B but also coincides with increased adipocyte expression of the proinflammatory marker tumor necrosis factor α (TNFα) [56]. Furthermore, TNFα delivered intracerebroventricularly (i.c.v) in rats leads to increases in both PTP1B expression and activity in whole hypothalamus [58]. Similarly, in mice, TNFα delivered intravenously to maintain high circulating TNFα levels increases PTP1B expression in the arcuate nucleus after four hours [56]. Additionally, isolated rat hypothalamic cultures incubated with TNFα show increases in PTP1B protein expression and activity in a dose-dependent manner, confirming the relationship between TNFα and PTP1B within the hypothalamus [59]. Interleukin-6 (IL-6), a proinflammatory cytokine associated with the obese state, has also been shown to increase PTP1B mRNA expression in cultured muscle cells [60]. These results suggest that PTP1B interacts with a variety of cytokine signals and may modulate body weight and/or leptin sensitivity via mechanisms involving hypothalamic inflammation. ER stress can be induced in response to inflammation, and hypothalamic ER stress has recently been connected to the development of cellular leptin resistance [61]. A specific role for PTP1B in obesity-associated inflammation and hypothalamic ER stress remains to be explored.

6. Conclusion

Human genetic association studies and the development of tissue-specific PTP1B knockout mouse models have identified PTP1B as a key player in the regulation of body weight and glucose homeostasis. Thus, PTP1B is an attractive therapeutic target for the treatment of human obesity and type 2 diabetes. It is currently unclear whether most of the identified *PTPN1* SNPs alter PTP1B expression, enzymatic activity, or protein function. Furthermore, it is not clear whether *PTPN1* SNPs directly result in the associated metabolic phenotypes seen in patient populations. Future research is warranted in connecting the genetics of the *PTPN1* locus with functional alterations in the PTP1B protein and ultimately to features of the metabolic syndrome.

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