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REVIEW PAPER

PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) IN OBESITY AND TYPE 2 DIABETES

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ABSTRACT

Increased incidence in obesity is reaching epidemic proportions and is placing a major burden on the healthcare systems in developed countries. Obesity is a major risk factor for the development of type 2 diabetes, metabolic syndrome, cardiovascular disease and cancer. Thus, the search for molecules that regulate the development of obesity and its associated pathologies is ongoing. Protein tyrosine phosphatase 1B (PTP1B) has been found to be a major regulator of body fat stores, energy balance, and insulin sensitivity in vivo. Increased expression of PTP1B is associated with insulin resistance in rodents and humans and deletion of PTP1B leads to leanness and insulin sensitivity in rodents, suggesting that PTP1B may be a very attractive molecular target for anti-obesity, anti-diabetic agents.

Keywords: *type 2 diabetes; obesity; metabolic disease; protein tyrosine phosphatase 1B (PTP1B); insulin resistance; glucose homeostasis; leptin sensitivity*

INTRODUCTION

Diabetes mellitus is a condition where the amount of glucose in the blood is too high (hyperglycemia) due to defects in either insulin secretion or insulin action. Type 2 diabetes mellitus is a complex disease in which target tissues of insulin become resistant to its effects, a condition called "insulin resistance". Although there are numerous overlapping causes such as obesity and inflammation contributing to this defect, impaired insulin signalling has been identified as a major molecular basis for the development of type 2 diabetes. In this review we will discuss the role of protein tyrosine phosphatase 1B (PTP1B) as a major regulator of insulin signalling and how it maybe the perfect target for the prevention of both obesity and type 2 diabetes.

Mechanism of Insulin Action (Activation of Insulin Receptor Signalling)

Insulin is the major hormone that regulates glucose homeostasis. It controls the function of numerous proteins involved in cell metabolism at the level of gene transcription, protein translation and enzyme activity. Following secretion from pancreatic β-cells, insulin stimulates the uptake of glucose, fatty acids and

amino acids into skeletal muscle and adipose tissue[1], and stimulates their conversion into storage forms, triglycerides, glycogen and protein. In skeletal muscle, insulin increases the rate of glucose and amino acid uptake, and glycogen and protein synthesis, while inhibiting the degradation of glycogen and proteins. In adipocytes, it stimulates the uptake of glucose and fatty acids, and synthesis of triglycerides, while inhibiting lipolysis. In the liver, insulin stimulates conversion of glucose into glycogen, and inhibits glycogenolysis and gluconeogenesis. In addition, insulin has effects on many other tissues and promotes cell survival. Insulin achieves these effects by regulating key molecular targets, through activation of intracellular signalling pathways that alter the activity of proteins by reversible protein phosphorylation and the amount of other proteins by controlling gene transcription.

All of the actions of insulin are mediated by its binding to the insulin receptor (IR), a receptor tyrosine kinase, in the plasma membrane of cells of target tissues.[2,3] Binding of insulin to IR leads to transphosphorylation of tyrosine residues in the IR activation loop, which in turn leads to enhanced ability of the IR to phosphorylate tyrosine residues on target proteins, such as the IR substrate (IRS) proteins. Phosphotyrosyl residues on IRS proteins act as docking sites for many SH2 domain-containing proteins, including the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K). Binding of PI3K to IRS leads to its activation followed by activation of downstream targets such as Akt, and translocation of the glucose transporter GLUT4 from intracellular stores to the cell surface.[3] Further downstream, activation of insulin signalling pathway leads to the stimulation of anabolic processes such as glycogen synthesis and protein synthesis.

Impaired Insulin Signalling ("Insulin Resistance")

Insulin resistance is associated with obesity, aging, and a sedentary lifestyle. Moreover, insulin resistance and obesity are major risk factors for development of type 2 diabetes and cardiovascular disease, including myocardial infarction, stroke and peripheral vascular disease. In insulin resistant states, there are defects in multiple actions of insulin, including impaired stimulation of glucose uptake in skeletal muscle and adipocytes; impaired inhibition of glucose production from the liver; and alterations in lipid metabolism causing dyslipidemia.[4]

The detailed mechanisms underlying insulin resistance remain incompletely understood, although they are thought to result from impaired post-IR signalling. The balance between IR-IRS tyrosine phosphorylation and dephosphorylation is critical for the regulation of insulin action. Thus, increased activity of one or more protein-tyrosine phosphatases (PTPs) that regulate IR-IRS phosphotyrosine levels could lead to the development of insulin resistance. Indeed, there are several reports on obese humans and rodents in which the expression and/or activity of specific PTPs are increased in muscle and/or adipose tissue.[5-12] Examples include the transmembrane PTP leukocyte antigen-related phosphatase (LAR) and the intracellular PTPs protein-tyrosine phosphatase 1B (PTP1B) and/or src-homology 2 domain-containing phosphatase-2 (SHP2). Furthermore, transgenic overexpression of LAR and PTP1B in muscle leads to insulin resistance in mice.[13] Elucidating the signalling pathways involved in the pathogenesis of obesity and diabetes is vital for understanding of these diseases and developing novel targeted therapies.

Protein Tyrosine Phosphatase 1B (PTP1B) as a Key IR Phosphatase

PTP1B is an abundant, widely expressed enzyme, localized on the endoplasmic reticulum (ER) via its hydrophobic C-terminal targeting sequence.[14] Importantly, IR endocytosis is required for dephosphorylation by an ER-localised phosphatase. Over-expression of PTP1B in cultured cells inhibits insulin-stimulated phosphorylation of IR as well as IRS-1,[15-17] although it is not clear if inhibition of IRS-1 phosphorylation is a direct effect of PTP1B on IRS-1 or a consequence of decreased IR signalling. Conversely, osmotic loading of anti-PTP1B antibodies into cells enhances IR signalling .[18] Moreover, studies integrating crystallographic, kinetic, and PTP1B peptide binding data, reveal highly specific interactions between PTP1B and IR activation loop tyrosines, encompassing the tandem phosphotyrosine residues at 1162 and 1163.[19] PTP1B also can dephosphorylate phosphotyrosine residues on IRS1 with high specificity *in vitro*.[12] However, until recently, the physiological function of PTP1B was unclear.

Knockout of PTP1B Causes Insulin Sensitivity and Leanness

Two groups generated PTP1B knockout (KO) mice.[20,21] These mice exhibited increased insulin sensitivity and enhanced glucose tolerance. Hyperinsulinemic-euglycemic clamp analyses revealed that the elevated whole-body insulin sensitivity in PTP1B KO mice resulted mainly from increased glucose utilization in skeletal muscle and suppression of hepatic glucose output in liver. Notably, glucose uptake in adipose tissue was unchanged.[21] PTP1B KO mice also exhibited enhanced muscle and hepatic, but not adipose, IR

phosphorylation. Taken together, these data identified PTP1B as a key IR phosphatase *in vivo*.

These knockout mouse studies showed that PTP1B is not only a major regulator of insulin sensitivity, but also of energy balance and body fat stores *in vivo*. Unexpectedly, PTP1B KO mice failed to gain weight when maintained on a high fat diet. Body composition analysis revealed that the low body weight in PTP1B KO mice was due largely to a dramatic reduction in body fat content, despite a slightly increased food intake. This resistance to diet-induced obesity was characterized by a marked decrease in adipocyte mass without alteration in adipocyte number. Furthermore, PTP1B KO mice were hypermetabolic, with increases in both basal metabolic rate and total energy expenditure. Therefore, PTP1B was identified as a critical regulator of energy expenditure and body fat stores, as well as a tissue-specific regulator of insulin sensitivity.[20,21] However, it was not clear where in the body PTP1B acted to exert its effects on body mass regulation and insulin sensitivity.

Generation of tissue-specific PTP1B KO mice answered some of these questions. Studies on these mice revealed the brain to be the primary site mediating the effects of PTP1B on body mass.[22] Brain-specific PTP1B KO mice were leaner than controls on either, chow or high-fat diet, with improvements in insulin sensitivity. Interestingly however, muscle-specific deletion of PTP1B generated mice that weighed the same as their littermate controls, but exhibited dramatically improved insulin sensitivity and glucose homeostasis,[23] suggesting that muscle PTP1B plays an important role in regulating whole-body glucose homeostasis. In addition, liver-specific deletion of PTP1B also resulted in mice that weigh the same as their littermate controls, but these mice exhibited improved whole-body glucose homeostasis, increased hepatic insulin signalling, increased insulin-induced suppression of hepatic glucose production, as well as decreased triglyceride and cholesterol levels and diminished lipogenic genes.[44]

Leptin and Body Mass Control

Regulation of body mass is complex and involves pathways in the central nervous system and the periphery. However, the hormone leptin has been shown to be a major regulator of body mass and energy expenditure. Leptin is produced by adipocytes in proportion to body fat, and acts on the leptin receptor (LR), which is expressed on specific hypothalamic nuclei in the brain. In hypothalamic neurons, leptin controls the production of neuropeptides that regulate food intake (FI) and energy expenditure (EE). Leptin also affects several peripheral tissues, including liver, fat and muscle via both direct and indirect actions.[24,25] The LR is a typical cytokine receptor that, upon binding of leptin, leads to phosphorylation and activation of JAK2, and activation of the JAK/signal transducer and activator of transcription (STAT) pathway. Molecules that regulate the activity of LR-associated JAK2 were postulated to be potentially important regulators of body mass.[24,25]

Work performed on the global PTP1B KO mice revealed PTP1B as an *in vivo* regulator of LR signalling.[26,27] Upon administration of leptin, PTP1B KO mice showed increased leptin sensitivity, and this correlated with enhanced hypothalamic LR signalling.[26] STAT3 activation was higher in the hypothalami of PTP1B KO mice and reflected action of PTP1B on STAT3 directly, or on an upstream component(s) of the LR pathway such as JAK2. *In vitro* studies using wildtype or glutamate-181 to alanine, substrate-trapping mutant of PTP1B suggested that JAK2 is a direct target for PTP1B in the LR pathway.[27]

Pharmaco-therapeutic treatment with antisense oligonucleotides directed against PTP1B in obese hyperglycemic ob/ob mice lowered PTP1B protein and mRNA levels in liver and fat, but not in muscle or brain. Moreover, lowering of PTP1B levels in these peripheral tissues was associated with normalisation of hyperglycemia, improved insulin sensitivity and attenuated obesity in these mice.[28-30] These studies suggested that PTP1B plays a major role in the regulation of body mass in one or more peripheral tissues independently of effects in the brain.[29] Since these studies, a tissue-specific genetic analysis of the functional role of PTP1B has resolved this controversy. Brain-specific PTP1B KO mice were leaner than their littermate controls on both, chow and high-fat diet.[22] Muscle, liver or adipose tissue-specific PTP1B KO mice did not exhibit this resistance to obesity, suggesting that PTP1B acts primarily in the brain to control body weight.[22]

Obesity and Inflammation

One of the molecular links between Western feeding habits, increased adiposity and insulin resistance is thought to be cellular inflammation, where activated inflammatory pathways lead to increased production of cytokines that affect whole body insulin sensitivity. More recently the endoplasmic reticulum (ER) has been identified as an organelle that is stressed in obesity and could be a molecular link between obesity and impaired insulin action.[31]

ER serves as a site of protein synthesis and modification prior to directing proteins to other organelles. This is a highly regulated process consisting of chaperones, signalling molecules and a network of degradation machinery that maintain homeostasis.[32]

Upon disruption in either protein folding or modification within the ER, a state of stress ensues. Prolonged

ER stress leads to apoptosis, inflammation, and lipid accumulation[33] and functions via signalling through stress-sensing proteins found on the ER membrane such as the inositol-requiring kinase-1a (IRE-1a),[31,34] and is linked to major inflammatory, stress-signalling networks via several distinct mechanisms, including the activation of c-Jun N-terminal kinase (JNK). Interestingly, these pathways have been demonstrated to play an important role in obesity-induced inflammation and metabolic abnormalities.[31] For example, prolonged high-fat diet-feeding (longer than 12 weeks) or genetic obesity (ob/ob) in mice has been shown to lead to inflammation and insulin resistance associated with increased ER stress response in liver and adipose tissue.[35] Moreover, hyperactivation of JNK and IRE-1a-dependent pathways causes serine phosphorylation of IRS-1 which is a known molecular mechanism of impaired insulin signalling.[35]

Interestingly, PTP1B-/- primary and immortalized cells show impaired IRE1a signalling and decreased JNK activation,[36] suggesting that PTP1B may play a role in modulation of ER stress signalling. Indeed, liver-specific deletion of PTP1B protects against high-fat diet induced ER stress response *in vivo*.[44] In addition, PTP1B expression has been shown to be increased with high-fat feeding and obesity and associated with an increase in pro-inflammatory cytokine TNFα,[38] and PTP1B KO mice and myocytes obtained from PTP1B KO mice have been shown to be protected against TNFα induced insulin resistance.[39]

Thus, PTP1B may be a target of anti-inflammatory therapies and pharmacological agents targeted at various components of ER stress have been shown to be potential novel therapies in managing obesity and diabetes.[37]

Other Actions of PTP1B

PTP1B has been implicated as an oncogene in the case of breast cancer.[40] However, a couple of recent publications have revealed an important role for PTP1B as a positive regulator of the Erb2 (HER2/neu) protein tyrosine kinase. This PTK is over-expressed in about 25% of human breast cancers, where it is associated with a poor prognosis. Crossing transgenic mice expressing activated forms of ErbB2 with PTP1B KO mice caused delayed tumour development and decreased the incidence of lung metastases.[41,42] Thus, PTP1B inhibitors may not only be useful in treatment of diabetes, obesity and metabolic syndrome, but ultimately offer a new treatment for breast cancer.[40]

Reversible oxidation and inactivation of PTPs

The protein tyrosine phosphatases (PTPs) are critical regulators of signal transduction. Thus, it is important to understand how these enzymes are regulated *in vivo*. The signature motif [I/V]HCXXGXXR[S/T], which defines the PTP family of enzymes, contains an invariant Cys residue, which functions as a nucleophile in catalysis. Due to the unique chemical environment of the PTP active site, this Cys residue displays an unusually low pKα, which enhances its nucleophilic properties but renders it susceptible to oxidation. It has been demonstrated that PTPs are an important target of reactive oxygen species (ROS) in the induction of an optimal tyrosine phosphorylation response to a variety of physiological stimuli. Oxidation of the active site Cys abrogates its nucleophilic properties, thereby inhibiting PTP activity.[45]

For oxidation to represent a mechanism for reversible regulation of PTP function, it is essential that the active site Cys residue is not oxidized further than sulphenic acid (S-OH); higher oxidation to sulphinic S-O2H or sulphonic S-O3H acid is an irreversible modification. In PTP1B, following oxidation of the active site Cys to sulphenic acid, oxygen is rapidly eliminated to produce a more stabile derivative, a cyclic sulphenamide, which is a 5-atom ring structure in which a covalent bond is formed between the Cys sulphur atom and the main chain nitrogen of the adjacent Ser residue.[45]

CONCLUSION

Increased PTP activity in tissues of obese humans is potentially a treatable factor in insulin resistance, as improved sensitivity to insulin is observed in obese subjects following weight loss, and is accompanied by reduced PTPs in adipose tissue.[9] Moreover, deletion of PTP1B in mice results in resistance to diet-induced obesity and insulin sensitivity.[20-23]

In view of the salutary effects of PTP1B deficiency on body mass and glucose homeostasis, several pharmaceutical companies are attempting to develop PTP1B inhibitors for the treatment of diabetes and/or obesity. The design of such agents has proved challenging, with the most active compounds tending to be highly charged and unlikely to gain access to the central nervous system.[43] Data from tissue-specific PTP1B knockout mice reveals that even targeting PTP1B in peripheral tissues alone would have a dramatic effect on improvement of insulin sensitivity and lipid metabolism without the need for body mass or fat loss. In addition, data from muscle-specific PTP1B KO mice[23] suggest that addition of a PPARγ agonist, such as Rosiglitazone (anti-diabetic drug currently used

in clinics for diabetes treatment), to PTP1B deletion would have an additive effect on improvement of insulin sensitivity and glucose homeostasis.

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REFERENCES

1. Denton RM: Early events in insulin actions. Adv Cyclic Nucleotide Protein Phosphorylation Res. 20:293-341, 1986
2. Lizcano JM, Alessi DR: The insulin signalling pathway. Curr Biol. 12:R236-8, 2002
3. Taniguchi CM, Emanuelli B, Kahn CR: Critical nodes in signalling pathways: Insights into insulin action. Nat Rev Mol Cell Biol. 7:85-96, 2006
4. DeFronzo RA: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. Neth J Med. 50:191-197, 1997
5. Ahmad F, Considine RV, Goldstein BJ: Increased abundance of the receptor-type protein-tyrosine phosphatase LAR accounts for the elevated insulin receptor dephosphorylating activity in adipose tissue of obese human subjects. J Clin Invest. 95:2806-2812, 1995
6. Ahmad F, Goldstein BJ: Increased abundance of specific skeletal muscle protein-tyrosine phosphatases in a genetic model of insulin-resistant obesity and diabetes mellitus. Metabolism. 44:1175-1184, 1995
7. Ahmad F, Goldstein BJ: Alterations in specific protein-tyrosine phosphatases accompany insulin resistance of streptozotocin diabetes. Am J Physiol. 268:E932-40, 1995
8. Ahmad F, Azevedo JL, Cortright R, Dohm GL, Goldstein BJ: Alterations in skeletal muscle protein-tyrosine phosphatase activity and expression in insulin-resistant human obesity and diabetes. J Clin Invest. 100:449-458, 1997
9. Ahmad F, Considine RV, Bauer TL, Ohannesian JP, Marco CC, Goldstein BJ: Improved sensitivity to insulin in obese subjects following weight loss is accompanied by reduced protein-tyrosine phosphatases in adipose tissue. Metabolism. 46:1140-1145, 1997
10. McGuire MC, Fields RM, Nyomba BL, Raz I, Bogardus C, Tonks NK, Sommercorn J: Abnormal regulation of protein tyrosine phosphatase activities in skeletal muscle of insulin-resistant humans. Diabetes. 40:939-942, 1991
11. Cheung A, Kusari J, Jansen D, Bandyopadhyay D, Kusari A, Bryer-Ash M: Marked impairment of protein tyrosine phosphatase 1B activity in adipose tissue of obese subjects with and without type 2 diabetes mellitus. J Lab Clin Med. 134:115-123, 1999
12. Kusari J, Kenner KA, Suh KI, Hill DE, Henry RR: Skeletal muscle protein tyrosine phosphatase activity and tyrosine phosphatase 1B protein content are associated with insulin action and resistance. J Clin Invest. 93:1156-1162, 1994
13. Zabolotny JM, Haj FG, Kim YB, Kim HJ, Shulman GI, Kim JK, Neel BG, Kahn BB: Transgenic overexpression of protein-tyrosine phosphatase 1B in muscle causes insulin resistance, but overexpression with leukocyte antigen-related phosphatase does not additively impair insulin action. J Biol Chem. 279:24844-24851, 2004
14. Tonks NK: PTP1B: From the sidelines to the front lines! FEBS Lett. 546:140-148, 2003
15. Kenner KA, Anyanwu E, Olefsky JM, Kusari J: Protein-tyrosine phosphatase 1B is a negative regulator of insulin- and insulin-like growth factor-I-stimulated signalling. J Biol Chem. 271:19810-19816, 1996
16. Byon JC, Kusari AB, Kusari J: Protein-tyrosine phosphatase-1B acts as a negative regulator of insulin signal transduction. Mol Cell Biochem. 182:101-108, 1998
17. Byon JC, Kenner KA, Kusari AB, Kusari J: Regulation of growth factor-induced signalling by protein-tyrosine-phosphatases. Proc Soc Exp Biol Med. 216:1-20, 1997
18. Ahmad F, Li PM, Meyerovitch J, Goldstein BJ: Osmotic loading of neutralizing antibodies demonstrates a role for protein-tyrosine phosphatase 1B in negative regulation of the insulin action pathway. J Biol Chem. 270:20503-20508, 1995
19. Salmeen A, Andersen JN, Myers MP, Tonks NK, Barford D: Molecular basis for the dephosphorylation of the activation segment of the insulin receptor by protein tyrosine phosphatase 1B. Mol Cell. 6:1401-1412, 2000
20. Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Himms-Hagen J, Chan CC, Ramachandran C, Gresser MJ, Tremblay ML, Kennedy BP: Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science. 283:1544-1548, 1999
21. Klaman LD, Boss O, Peroni OD, Kim JK, Martino JL, Zabolotny JM, Moghal N, Lubkin M, Kim YB, Sharpe AH, Stricker-Krongrad A, Shulman GI, Neel BG, Kahn BB: Increased energy expenditure, decreased adiposity, and tissue-specific insulin sensitivity in protein-tyrosine phosphatase 1B-deficient mice. Mol Cell Biol. 20:5479-5489, 2000
22. Bence KK, Delibegovic M, Xue B, Gorgun CZ, Hotamisligil GS, Neel BG, Kahn BB: Neuronal PTP1B regulates body weight, adiposity and leptin action. Nat Med. 12:917-924, 2006
23. Delibegovic M, Bence KK, Mody N, Hong EG, Ko HJ, Kim JK, Kahn BB, Neel BG: Improved glucose homeostasis in mice with muscle-specific deletion of protein-tyrosine phosphatase 1B. Mol Cell Biol. 27:7727-7734, 2007
24. Moran O, Phillip M: Leptin: Obesity, diabetes and other peripheral effects--a review. Pediatr Diabetes. 4:101-109, 2003
25. Zabeau L, Lavens D, Peelman F, Eyckerman S, Vandekerckhove J, Tavernier J: The ins and outs of leptin receptor activation. FEBS Lett. 546:45-50, 2003
26. Zabolotny JM, Bence-Hanulec KK, Stricker-Krongrad A, Haj F, Wang Y, Minokoshi Y, Kim YB, Elmquist JK, Tartaglia LA, Kahn BB, Neel BG: PTP1B regulates leptin signal transduction in vivo. Dev Cell. 2:489-495, 2002
27. Cheng A, Uetani N, Simoncic PD, Chaubey VP, Lee-Loy A, McGlade CJ, Kennedy BP, Tremblay ML: Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. Dev Cell. 2:497-503, 2002

28. Rondinone CM, Trevillyan JM, Clampit J, Gum RJ, Berg C, Kroeger P, Frost L, Zinker BA, Reilly R, Ulrich R, Butler M, Monia BP, Jirousek MR, Waring JF: Protein tyrosine phosphatase 1B reduction regulates adiposity and expression of genes involved in lipogenesis. Diabetes. 51:2405-2411, 2002
29. Waring JF, Ciurlionis R, Clampit JE, Morgan S, Gum RJ, Jolly RA, Kroeger P, Frost L, Trevillyan J, Zinker BA, Jirousek M, Ulrich RG, Rondinone CM: PTP1B antisense-treated mice show regulation of genes involved in lipogenesis in liver and fat. Mol Cell Endocrinol. 203:155-168, 2003
30. Zinker BA, Rondinone CM, Trevillyan JM, Gum RJ, Clampit JE, Waring JF, Xie N, Wilcox D, Jacobson P, Frost L, Kroeger PE, Reilly RM, Koterski S, Opgenorth TJ, Ulrich RG, Crosby S, Butler M, Murray SF, McKay RA, Bhanot S, Monia BP, Jirousek MR: PTP1B antisense oligonucleotide lowers PTP1B protein, normalizes blood glucose, and improves insulin sensitivity in diabetic mice. Proc Natl Acad Sci U S A. 99:11357-11362, 2002
31. Gregor MG, Hotamisligil GS: Adipocyte stress: The endoplasmic reticulum and metabolic disease. J Lipid Res. , 2007
32. Schroder M, Kaufman RJ: ER stress and the unfolded protein response. Mutat Res. 569:29-63, 2005
33. Ji C, Kaplowitz N: ER stress: Can the liver cope? J Hepatol. 45:321-333, 2006
34. Ron D, Walter P: Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol. 8:519-529, 2007
35. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH, Hotamisligil GS: Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science. 306:457-461, 2004
36. Gu F, Nguyen DT, Stuible M, Dube N, Tremblay ML, Chevet E: Protein-tyrosine phosphatase 1B potentiates IRE1 signalling during endoplasmic reticulum stress. J Biol Chem. 279:49689-49693, 2004
37. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Gorgun CZ, Hotamisligil GS: Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science. 313:1137-1140, 2006
38. Zabolotny JM, Kim YB, Welsh LA, Kershaw EE, Neel BG, Kahn BB: Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. J Biol Chem. 283:14230-14241, 2008
39. Nieto-Vazquez I, Fernandez-Veledo S, Kramer DK, Vila-Bedmar R, Garcia-Guerra L, Lorenzo M: Insulin resistance associated to obesity: The link TNF-alpha. Arch Physiol Biochem. 114:183-194, 2008
40. Koren S, Fantus IG: Inhibition of the protein tyrosine phosphatase PTP1B: Potential therapy for obesity, insulin resistance and type-2 diabetes mellitus. Best Pract Res Clin Endocrinol Metab. 21:621-640, 2007
41. Julien SG, Dube N, Read M, Penney J, Paquet M, Han Y, Kennedy BP, Muller WJ, Tremblay ML: Protein tyrosine phosphatase 1B deficiency or inhibition delays ErbB2-induced mammary tumorigenesis and protects from lung metastasis. Nat Genet. 39:338-346, 2007
42. Bentires-Alj M, Neel BG: Protein-tyrosine phosphatase 1B is required for HER2/Neu-induced breast cancer. Cancer Res. 67:2420-2424, 2007
43. Pei Z, Liu G, Lubben TH, Szczepankiewicz BG: Inhibition of protein tyrosine phosphatase 1B as a potential treatment of diabetes and obesity. Curr Pharm Des. 10:3481-3504, 2004
44. Delibegovic M, Zimmer D, Kauffman C, Rak K, Hong EG, Cho YR, Kim JK, Kahn BB, Neel BG, Bence KK: Liver-Specific Deletion of Protein Tyrosine Phosphatase 1B (PTP1B) Leads to Improved Glucose and Lipid Metabolism and Decreased High-Fat Diet Induced ER Stress Response. Diabetes (accepted) Online Ahead of Print 15th December 2008
45. Tonks NK: Redox redux: revisiting PTPs and the control of cell signalling. Cell 121(5):667-70, 2005