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Protein Tyrosine Phosphatase 1B (PTP1B): A Critical Molecular Target for Treatment and Management of Related Complications in Type-II Diabetes and Obesity

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KEYWORDS

PTP1B, Diabetes mellitus, Obesity, Insulin, insulin-to-insulin receptor

ABSTRACT:

One of our society's biggest health challenges is type 2 diabetes mellitus. In order to control this chronic condition and its associated problems, novel therapies are being developed despite the wide range of alternatives available for existing medication treatments. Since protein tyrosine phosphatase 1B (PTP1B) is an essential component of a negative regulator in the insulin and leptin signaling pathways, it is a promising therapeutic target for a number of human disorders, including type 2 diabetes (T2DM) and obesity. PTP1B inhibitors improve insulin receptor sensitivity and can treat illnesses linked to insulin resistance. Type 2 diabetes mellitus and the group of cardiovascular risk factors known as the "metabolic" syndrome are strongly linked to resistance to the cellular action of insulin, a fundamental pathophysiological defect that accompanies the global obesity epidemic. The creation of new pharmaceuticals that lessen insulin resistance may be crucial for treating and preventing diabetes as well as lowering the cardiovascular risk profile that goes along with it. Research on the function of protein-tyrosine phosphatase PTP1B in the cell has now demonstrated unequivocally that it is a crucial negative regulator of the tyrosine phosphorylation cascade, which is essential to the insulin signaling pathway. In over nourished situations, PTP1B inhibition also decreases the amount of triglycerides stored in adipose tissue and is not linked to any apparent harm. In general, these investigations have cleared the path for the commercialization of PTP1B inhibitors, which could potentially function as an innovative kind of "insulin sensitizer" for the treatment of type 2 diabetes and the metabolic syndrome.

Introduction

Globally, the prevalence of diabetes mellitus (DM), a chronic multifactorial illness, is rising [1]. According to the American Diabetes Association's classification published in 2021, diabetes mellitus (DM) can be broadly classified into four categories: type 1 DM, type 2 DM, gestational DM, and specialized kinds of DM resulting from various causes. Of those, type 2 diabetes accounts for 90–95% of all instances of the disease [2]. It is the most common kind of diabetes. This kind of diabetes usually has a history of insulin resistance and gradually decreased pancreatic β cell insulin production. Hyperglycemia, or persistent blood glucose levels, is the result of these anomalies [3, 4].Biguanides, sulfonylureas, thiazolidinediones (TZD), meglitinides, dipeptidyl peptidase 4 (DPP-4) inhibitors, α-glucosidase inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are among the various medication groups now licensed for the treatment of type 2 diabetes [5]. In spite of the large number of type 2 DM medications that are already licensed, over 7,000 clinical trials are filed to explore novel formulations [6]. Even if the number of therapeutic choices has increased over the past few decades, the therapies that are currently available have shown limitations and downsides. Even though metformin is the medication most frequently administered to people with type 2 diabetes, little is known about how it works. Additionally, using it is linked to adverse gastrointestinal consequences [7]. Other now licensed medications for the treatment of type 2 diabetes also have a number of drawbacks, such as hypoglycemia, changes in body weight, an increased risk of cardiovascular disease, and urinary tract infections [5]. Furthermore, 4.2 million deaths

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worldwide were attributed to diabetes in 2019, according to the International Diabetes Federation [8]. Therefore, in order to treat type 2 diabetes and the related micro- and macrovascular problems, new therapeutic strategies are required. In comparison to the treatments that are now in use, the innovative emerging therapies are anticipated to show added value, such as the possibility of weight loss, the absence of hypoglycemia risk, better drug delivery techniques, and a reduction in the frequency of usage [6].

The translation of the metabolic insulin signal is a multifaceted process (Figure 1). To put it briefly, when insulin binds to the insulin receptor (IR), tyrosine residues are autophosphorylated, which activates and recruits insulin receptor substrate (IRS) proteins. As a result, the intracellular signaling molecules protein kinase B (PKB; also called Akt) and phosphatidylinositol 3-kinase (PI3K) are activated, which encourages the translocation of the glucose transporter vesicles to the membrane and glucose uptake [9] (**Figure 1**).

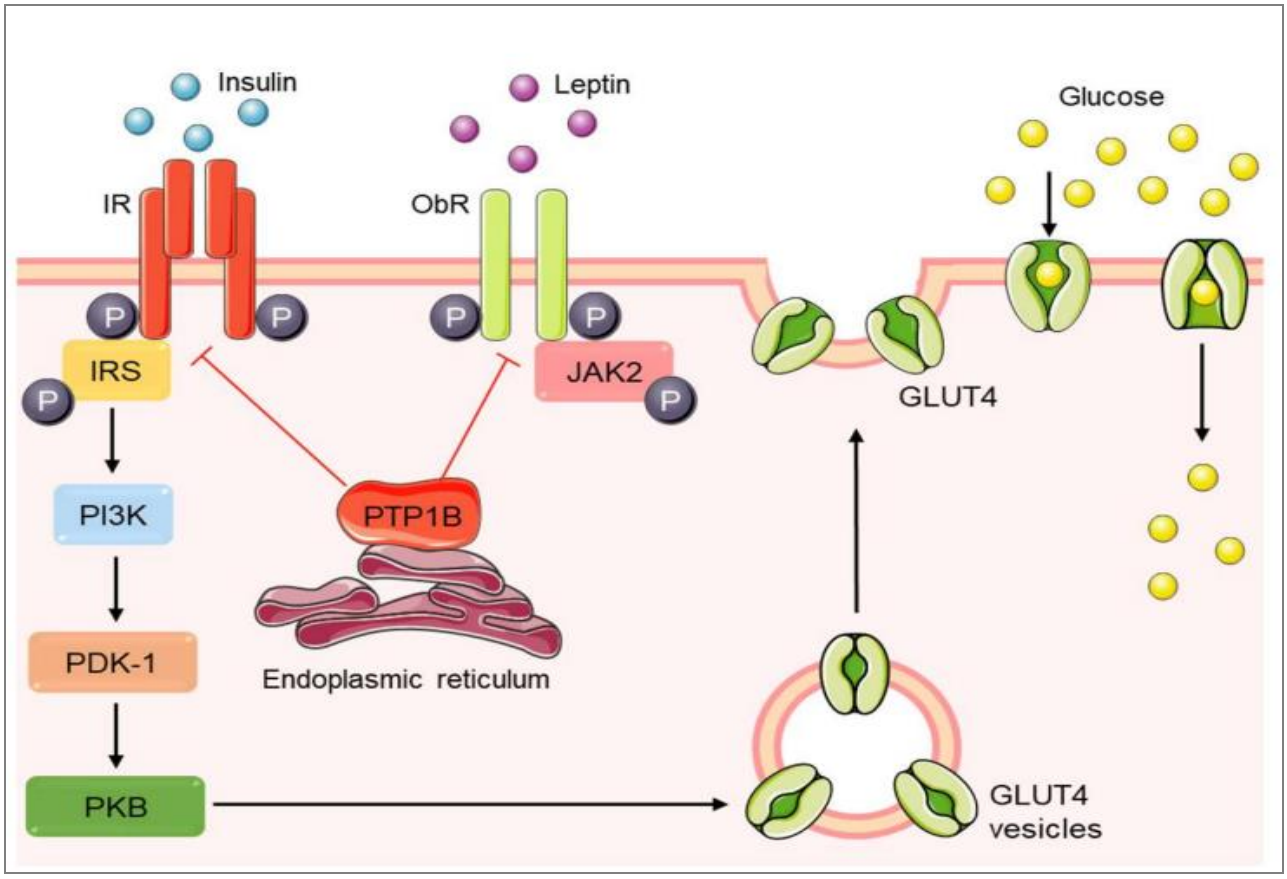

Figure 1: Diagram showing how protein tyrosine phosphatase 1B (PTP1B) negatively regulates the insulin and leptin signaling pathways. Reproduced from Image bank [27]. GLUT4: glucose transporter 4; IR: Insulin Receptor; IRS: Insulin Receptor Substrate; JAK2: Janus Kinase 2; ObR: Leptin Receptor; PDK-1: 3-phosphoinositide Dependent protein Kinase-1; PI3K: Phosphatidylinositol 3-kinase; PKB: Protein Kinase B; PTP1B: Protein Tyrosine Phosphatase 1B.

One potential treatment target for type 2 diabetes is the enzyme protein tyrosine phosphatase 1B (PTP1B), which is a negative regulator of the insulin signaling pathway. [10]. As a negative regulator of insulin signaling, PTP1B dephosphorylates IRS and IR, which reduces insulin signaling as a result. As a result, PTP1B inhibition will raise insulin sensitivity and phosphorylate IRS and IR [11]. Furthermore, PTP1B is a leptin signaling negative regulator and is thought to be a possible target for obesity (Figure 1). Insulin resistance and obesity are associated with physical inactivity. Over time, obesity and a genetic

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susceptibility lead to insulin resistance and β cell failure, which reduce insulin secretion and eventually result in type 2 diabetes [9].

PTP1B is an intriguing therapeutic target since it can function both positively and negatively in several signaling pathways. As a result, researchers have focused on finding and using PTP1B modulators to treat diabetes, obesity, and even cancer [12].Elchebly and Comeau et al.'s studies have demonstrated that mice lacking PTP1B are protected from diet-induced obesity, as shown in **Figure 2**. In contrast, PTP1B-knockout mice show insulin sensitivity and glycemic control, are resistant to obesity, and have significantly lower triglyceride levels [13–15]. Thus, PTP1B inhibitors could be new medications used to treat obesity and type 2 diabetes. In clinical studies, no effective and selective PTP1B inhibitor has yet been discovered.

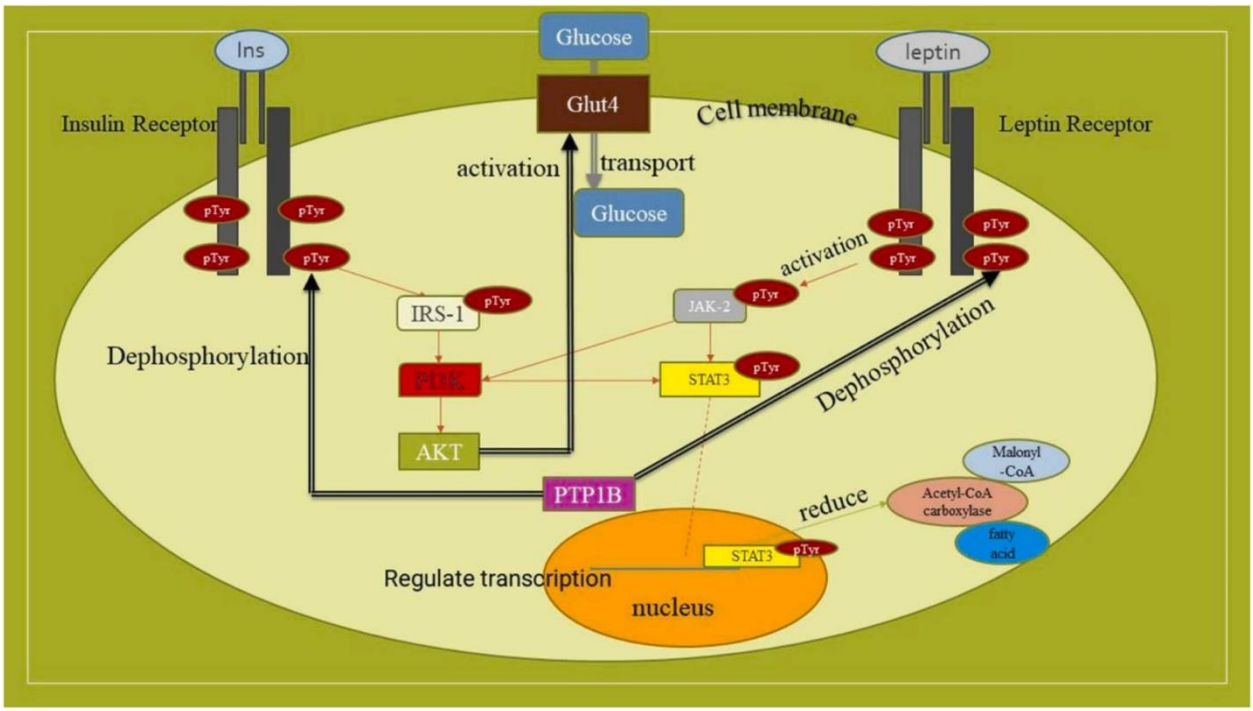

Figure 2. PTP1B metabolism mechanisms and implications for insulin and leptin signaling pathways. Reproduced with the permission from [16].

Protein Tyrosine Phosphatase 1B

The primary role of the numerous enzymes known as PTPs, which are made up of over 100 distinct proteins, is to inhibit the activities of protein tyrosine kinases (PTKs) [17]. Since the first PTP was purified in 1988, a total of 125 PTPs have been identified in the human genome [18]. The highly conserved catalytic domain of this superfamily, which consists of about 240 amino acids and bears the active site characteristic motif C(X)5R [19], also known as Cys-X5-Arg [20] and (I/V)HCXAGXXR(S/T)G, is what distinguishes it. A catalytic cysteine found in the signature motif is essential to the phosphatases' ability to catalyze the removal of the phosphate moiety from the phosphotyrosine substrate. Based on the specificities of its protein tyrosine, the superfamily is divided into three classes: class I, class II, and class III. The enzymes of class II, which includes the dual specificity PTPs, may also remove phosphate groups from phosphotyrosine residues and phosphoserine and phosphothreonine residues. Class I is made up of the traditional PTPs. Low molecular weight PTPs are included in class III, to sum up (**Figure 3**).

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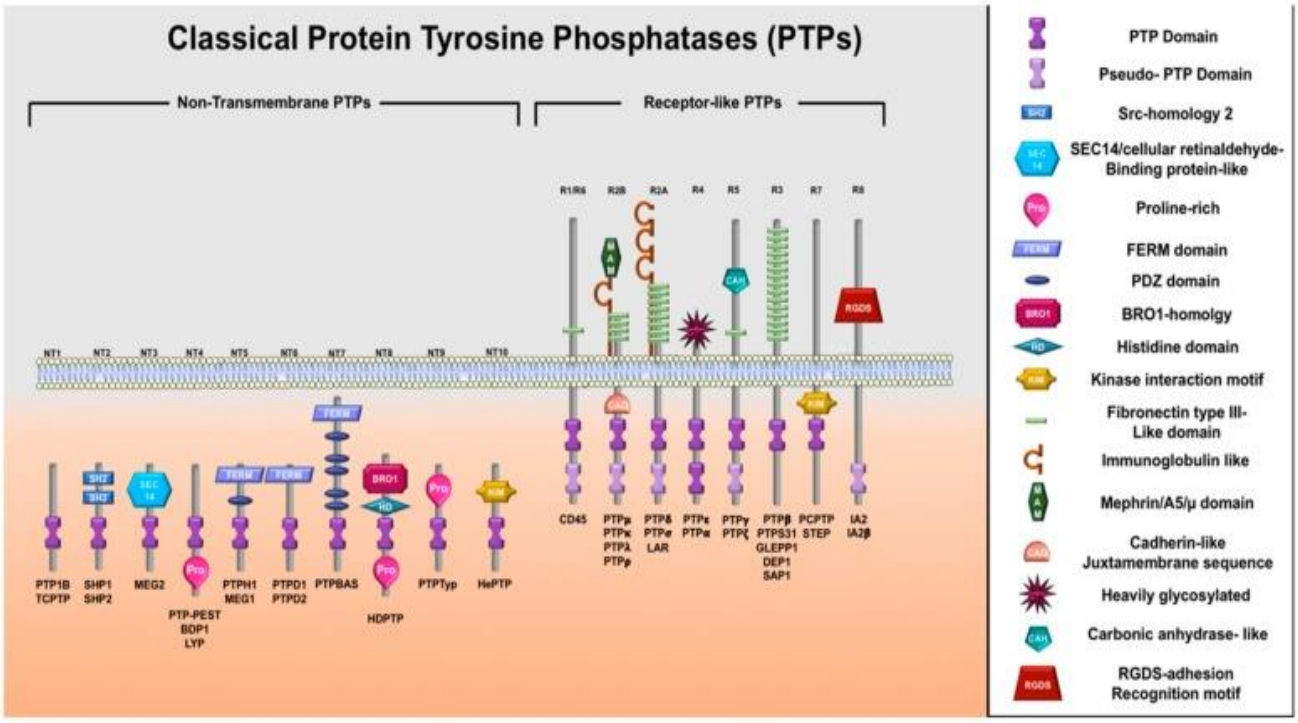

Figure 3. Traditional PTPs. The 37 members of the vast family of tyrosine phosphatases known as the classical PTPs are further classified into 16 non-transmembrane (cytosolic) PTPs and 21 transmembrane receptor-like PTPs based on where they are found in the cell. While receptor-like PTPs contain one or two catalytic domains and an intrinsic catalytic cysteine residue, non-transmembrane phosphatases only have one. Reproduced with the permission from [21].

PTP1B as a Potential Therapeutic Target

PTP1B has gained attention as a potential therapeutic target due to its involvement in a number of clinical diseases, including cancer and metabolic disorders [22]. But there are obstacles in the path of every achievement. Numerous obstacles have to be overcome in the course of creating selective PTP1B inhibitors, notwithstanding the enormous efforts made in this regard. The original plan was to use tiny compounds that mimicked phosphotyrosine to target the catalytic region, but this approach presented two significant difficulties. The members of the PTP family share a highly conserved catalytic domain, making them a very closely linked family. Targeting the catalytic domain of PTP1B caused suppression of other members of the family, which could have serious unintended off-target adverse effects. For example, PTP1B and T cell protein tyrosine phosphatase (TC-PTP), the most closely related classical PTP, are 72% identical overall. Moreover, the catalytic sites of PTP1B and TC-PTP are 94% identical [23, 24]. While TC-PTP-deficient pups died in infancy from severe anemia and elevated general inflammation, PTP1B-deficient mice demonstrated better insulin sensitivity and resistance to HFD-induced obesity [25]. This suggests that PTP1B inhibitors with extreme selectivity are required. Cell permeability and bioavailability presented the second difficulty. Small compounds that mimicked phosphotyrosine were employed to target the catalytic site, but their cellular permeability was limited due to their high charge density and positive charge [26].

Protein tyrosine phosphatase 1B (PTP1B): Clinical Significance

Protein tyrosine phosphates are categorized based on mechanism or locations as Class I (Classical PTPs), Class II (LMW-PTP), Class III(CDC25B), Asp-Based Phosphatases (EYA1, EYA2, EYA3, and EYA4), His-Based Phosphatases (UBASH3)[27,28,29]. Non-receptor PTPs with its location are PTP-1B, PTP-SL, SHP-1, SHP-2, STEP [30, 31]. Protein tyrosine phosphatase 1B (PTP1B) is negative modulator of insulin and leptin signaling pathways and have major impact on maintaining various metabolic disorders [32]. Insulin receptor (IR) signal transduction pathway is

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expressed in various cells and tissues [33]. Protein tyrosine phosphatase (PTP1B) inhibitors mediated dephosphorylation of the intracellular part of the receptor leads to desensitization. Desensitization of receptors leads to prolonging insulin effect thus has opened new targets for treatment of diabetes Mellitus [34]. By modifying, it improves the sensitivity of the insulin receptor. Experimental investigations have disclosed the role of MFGE8 in regulating insulin signaling [35]. PTP1B is attractive target over existing therapies as it improves glucose homeostasis and insulin signaling without lipid buildup in the liver. Having an impact on endothelial dysfunction helps to treatment and management of cardiovascular complications [36]. Recent studies have disclosed Phosphoeleganin a dual inhibitor of protein tyrosine phosphatase 1B (PTP1B) and aldose reductase (AR) enzymes as novel approach for treatment of dibetes millutus[37].PTP1B inhibitors including diaminopyrroloquinazoline, triazines, piperazinylpropanols, phenylsulphonamides, thiazoles, isothiozolidiones and thiazolodinone have promising potential [38].PTP-1B inhibitors could thus be promising drugs for treatment of diabetes Mellitus, obesity, resistance and cardiovascular complications [39, 40, and 41].

Protein tyrosine phosphatase 1B (PTP1B) inhibitors:

Phase II clinical trial of Ertiprotafib has disclosed PTP1B and IkappaB kinase beta (IKK-beta) inhibitor potential dual PPARalpha/PPARgamma agonism. [42,43]. MSI-1436 a PTP1B selective inhibitors have shown promising effects against Equine metabolic syndrome (EMS)[44].Microbial origin-based compound Trivaric acid is a potential PTP1b inhibitor and show its effect by stimulating IR/IRS/Akt/GLUT2 pathway and enhanced glucose consumption in HepG2 cells [45]. Experimental investigations have discloed Fumosorinone (FU) isolated from Isaria fumosorosea as potent PTP1b inhibitor [46]. Fucosterol downregulates expression of PTP1B and activation the insulin signaling pathway thus showing potential as antidibetic agent [47]. Investigations results disclosed that α-methyl artoflavanocoumarin (MAFC), a natural flavanocoumarin as mixed type PTP1B inhibitor [48]. Didymin (isosakuranetin 7-O-rutinoside) strongly inhibits α-glucosidase and protein tyrosine phosphatase 1B (PTP1B) [49]. Poncirin, an orally active flavonoid activates PI3K/Akt signaling pathway and shows potential in management of relaed complications in diabetes mellitus [50]. Ursonic acid from Artemisia Montana inhibits PTP1B and activates the PI3K/Akt signaling pathway. Ursonic acid is non-competitive inhibitor of PTP1B and α-glucosidase[51] studies suggested fungal metabolites such as fumosorinone A, nordivaricatic acid with some modifications may be developed as novel PTP1B inhibitors[52]. Thiazolidinedione derivatives (lobeglitazone) as PTP1B inhibitors [53]. coumarins, isolated from Angelica decursiva showed potent PTP1B and α-glucosidase inhibitory activities [54]. Sudies provide a novel scaffold mixed 3,3'-bisindoles, di-indolinone, 1H-2,3-dihydroperimidine derivatives as novel PTP1B inhibitors [55]. Studies disclosed that Safranal potently inhibits PTP1B and improved glucose tolerance in type 2 diabetic KK-A(y) mice [56].

Further Challenges and Perspectives of PTP1B Inhibitors

Approximately 500 PTP1B inhibitors have been discovered or produced during the last few decades, including 248 phenolics, 159 terpenoids, 40 alkaloids, 24 fatty acids, and 17 steroids. They mostly obstruct PTP1B's catalytic active site [57]. For instance, PTP1B inhibitors with oxidizing characteristics or the capacity to produce oxidative chemicals, which result in PTP1B inactivation, were given careful consideration since tyrosine phosphatases' catalytic cysteine is frequently oxidized, which causes their inhibition [58]. Furthermore, PTP1B is a metal-modulated enzyme; PTP1B phosphatase activity is lost in response to PTP1B inhibitors that contain metal ions, such as Zn^{2+}, Fe^{2+}, Cu^{2+}, Cd^{2+}, and Mg^{2+}. However, as both PTP1B inhibitor types work against all PTPs, it is to be expected that they have minimal specificity. Unprecedented growth of molecular target based USFDA approved have forecasted the promising future.

Conclusions

Diabetes and cardiovascular disease are two pathological processes in which PTP1B is implicated. In contrast to current insulin sensitizing tactics, it has been observed that blocking PTP1B function improves glucose metabolism and boosts insulin responsiveness without raising lipid metabolism or accumulating lipids in the liver. This is better than current pharmacological methods for treating diabetes since it would avoid

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adverse effects including weight gain and hepatic steatosis. PTP1B is a very desirable single therapeutic target for cardiovascular diseases due to its involvement in the development of cardiovascular disturbances such as endothelial dysfunction, impaired cardiac function, and aberrant angiogenesis. But because PTP1B is widely expressed and involved in many physiological systems, systemically targeting it could have unfavorable off-target side effects that could restrict its application in the future. Therefore, to maximize the therapeutic benefits of inhibiting PTP1B while lowering the risk of potential off target side effects, it is essential to develop novel strategies to specifically target tissues of interest, such as the cardiovascular system or insulin-sensitive tissues, in addition to overcoming the difficulties inherent in synthesizing potent and selective small molecule inhibitors for PTP1B. In near future Molecular targets based drugs have paved the way towards the permanent treatment and related complications in type 2 diabetes mellitus.

References

1. Bakhti, M., Böttcher, A., Lickert, H. Modelling the endocrine pancreas in health and disease. Nature Reviews Endocrinology. 2019 Mar;15(3):155-71. 2. American Diabetes Association.
2. Nuha, A., ElSayed, Grazia Aleppo, Vanita, R., Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Jason L. Gaglia, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane JeffrieSeley, Robert C. Stanton, Robert A. Gabbay, American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S19–S40.
3. DeFronzo, R.A., Ferrannini, E., Groop, L., Henry, R.R., Herman, W.H., Holst, J.J., Hu, F.B., et al. Type 2 diabetes mellitus. Nature Reviews Disease Primers. 2015 Jul 23;1(1):1-22.
4. Rocha, S., Lucas, M., Ribeiro, D., Corvo, M.L., Fernandes, E., Freitas, M. Nano-based drug delivery systems used as vehicles to enhance polyphenols therapeutic effect for diabetes mellitus treatment. Pharmacological Research. 2021 Jul 1;169:105604.
5. Chaudhury, A., Duvoor, C., Reddy, Dendi, V.S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Frontiers in Endocrinology. 2017 Jan 24;8:6.
6. Perreault, L., Skyler, J.S., Rosenstock, J. Novel therapies with precision mechanisms for type 2 diabetes mellitus. Nature Reviews Endocrinology. 2021 Jun;17(6):364-77.
7. Rines, A.K., Sharabi, K., Tavares, C.D., Puigserver, P. Targeting hepatic glucose metabolism in the treatment of type 2 diabetes. Nature Reviews Drug Discovery. 2016 Nov;15(11):786-804.
8. International Diabetes Federation. IDF Diabetes Atlas - Ninth Edition, 2019. [Available from: www.diabetesatlas.org]. (Accessed on January 21, 2024)
9. Johnson, T.O., Ermolieff, J., Jirousek, M.R. Protein tyrosine phosphatase 1B inhibitors for diabetes. Nature Reviews Drug Discovery. 2002 Sep;1(9):696-709.
10. Hussain, H., Green, I.R., Abbas, G., Adekenov, S.M., Hussain, W., Ali, I. Protein tyrosine phosphatase 1B (PTP1B) inhibitors as potential anti-diabetes agents: patent review (2015-2018). Expert Opinion on Therapeutic Patents. 2019 Sep 2;29(9):689-702.
11. Proença, C., Ribeiro, D., Freitas, M., Carvalho, F., Fernandes, E. A comprehensive review on the antidiabetic activity of flavonoids targeting PTP1B and DPP-4: a structure-activity relationship analysis. Critical Reviews in Food Science and Nutrition. 2021 Jan 16:1-57.
12. Pike, K.A., Tremblay, M.L., TC-PTP and PTP1B: Regulating JAK-STAT signaling, controlling lymphoid malignancies. Cytokine 2016, 82, 52–57.
13. K.K. Bence, M. Delibegovic, B. Xue, C.Z. Gorgun, G.S. Hotamisligil, B.G. Neel, B.B. Kahn. Neuronal PTP1B regulates body weight, adiposity and leptin action. Nat. Med., 12 (8) (2006), pp. 917-924
14. A.B. Comeau., D.A. Critton., R. Page., C.T. Seto. A focused library of protein tyrosine phosphatase inhibitors. J. Med Chem., 53 (18) (2010), pp. 6768-6772
15. M. Elchebly, P. Payette, E. Michaliszyn, W. Cromlish, S. Collins, A.L. Loy, D. Normandin, A. Cheng, J. Himms-Hagen, C.C. Chan, C.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1334-1342 | ISSN:2251-6727

Ramachandran, M.J. Gresser, M.L. Tremblay, B.P. Kennedy. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Sci. (N. Y., N. Y.), 283 (5407) (1999), pp. 1544-1548

16. Liu, Z., Gao, H., Zhao, Z., Huang, M., Wang, S., & Zhan, J. (2023). Status of research on natural protein tyrosine phosphatase 1B inhibitors as potential antidiabetic agents: Update. Biomedicine & pharmacotherapy = Biomedecine&pharmacotherapie, 157, 113990. https://doi.org/10.1016/j.biopha.2022.113990.
17. Thiebaut P.-A., Besnier M., Gomez E., Richard V. Role of protein tyrosine phosphatase 1B in cardiovascular diseases. J. Mol. Cell. Cardiol. 2016;101:50–57. doi: 10.1016/j.yjmcc.2016.09.002.
18. Hale A.J., terSteege E., den Hertog J. Recent advances in understanding the role of protein-tyrosine phosphatases in development and disease. Dev. Biol. 2017;428:283–292. doi: 10.1016/j.ydbio.2017.03.023.
19. Li L., Dixon J.E. Form, function, and regulation of protein tyrosine phosphatases and their involvement in human diseases. Semin. Immunol. 2000;12:75–84. doi: 10.1006/smim.2000.0209.
20. Stauffacher C.V., Charbonneau H. Protein tyrosine phosphatases. In: Conn P.M., Means A.R., editors. Principles of Molecular Regulation. Humana Press; Totowa, NJ, USA: 2000. pp. 323–347.
21. Abdelsalam, S. S., Korashy, H. M., Zeidan, A., &Agouni, A. (2019). The Role of Protein Tyrosine Phosphatase (PTP)-1B in Cardiovascular Disease and Its Interplay with Insulin Resistance. Biomolecules, 9(7), 286. https://doi.org/10.3390/biom9070286
22. Chio C.M., Yu X., Bishop A.C. Rational design of allosteric-inhibition sites in classical protein tyrosine phosphatases. Bioorg. Med. Chem. 2015;23:2828–2838. doi: 10.1016/j.bmc.2015.03.027.
23. Barr A.J. Protein tyrosine phosphatases as drug targets: Strategies and challenges of inhibitor development. Future Med. Chem. 2010;2:1563–1576. doi: 10.4155/fmc.10.241.
24. Li S., Zhang J., Lu S., Huang W., Geng L., Shen Q., Zhang J. The mechanism of allosteric inhibition of protein tyrosine phosphatase 1B. PLoS ONE. 2014;9:e97668. doi: 10.1371/journal.pone.0097668.
25. Tiganis T. PTP1B and TCPTP—Nonredundant phosphatases in insulin signaling and glucose homeostasis. FEBS J. 2013;280:445–458. doi: 10.1111/j.1742-4658.2012.08563.x.
26. Vieira M.N.N., Lyra e Silva N.M., Ferreira S.T., De Felice F.G. Protein tyrosine phosphatase 1B (PTP1B): A potential target for Alzheimer's therapy? Front. Aging Neurosci. 2017;9:7. doi: 10.3389/fnagi.2017.00007.
27. Julien, S. G., Dubé, N., Hardy, S., & Tremblay, M. L. (2011). Inside the human cancer tyrosine phosphatome. Nature Reviews Cancer, 11(1), 35-49.
28. Gurzov, E. N., Stanley, W. J., Brodnicki, T. C., & Thomas, H. E. (2015). Protein tyrosine phosphatases: molecular switches in metabolism and diabetes. Trends in Endocrinology & Metabolism, 26(1), 30-39.
29. Garg, M., & Wahid, M. (2020). Regulation of peripheral and central immunity: Understanding the role of Src homology 2 domain-containing tyrosine phosphatases, SHP-1 & SHP-2. Immunobiology, 225(1), 151847.
30. 31. Bollu, L. R., Mazumdar, A., Savage, M. I., & Brown, P. H. (2017). Molecular pathways: targeting protein tyrosine phosphatases in cancer. Clinical Cancer Research, 23(9), 2136-2142.
31. Kim, M., Morales, L. D., Jang, I. S., Cho, Y. Y., & Kim, D. J. (2018). Protein tyrosine phosphatases as potential regulators of STAT3 signaling. International journal of molecular sciences, 19(9), 2708.
32. Hussain, H., Green, I. R., Abbas, G., Adekenov, S. M., Hussain, W., & Ali, I. (2019). Protein tyrosine phosphatase 1B (PTP1B) inhibitors as potential anti-diabetes agents: patent review (2015-2018). Expert opinion on therapeutic patents, 29(9), 689-702.Servier Medical Art SMAS. [Available from: https://smart.servier.com/]
33. Teimouri, M., Hosseini, H., ArabSadeghabadi, Z., Babaei-Khorzoughi, R., Gorgani-Firuzjaee, S., & Meshkani, R. (2022). The role of protein tyrosine phosphatase 1B (PTP1B) in the pathogenesis of type 2 diabetes mellitus and its complications. Journal of physiology and biochemistry, 78(2), 307–322. https://doi.org/10.1007/s13105-021-00860-7
34. Nandi, S., & Saxena, M. (2020). Potential Inhibitors of Protein Tyrosine Phosphatase (PTP1B) Enzyme:

Promising Target for Type-II Diabetes Mellitus. Current topics in medicinal chemistry, 20(29), 2692–2707. https://doi.org/10.2174/1568026620999200904121432

35. Datta, R., Podolsky, M. J., Yang, C. D., Alba, D. L., Singh, S., Koliwad, S., Lizama, C. O., & Atabai, K. (2023). MFGE8 inhibits insulin signaling through PTP1B. bioRxiv : the preprint server for biology, 2023.05.30.542928. https://doi.org/10.1101/2023.05.30.542928
36. Abdelsalam, S. S., Korashy, H. M., Zeidan, A., & Agouni, A. (2019). The Role of Protein Tyrosine Phosphatase (PTP)-1B in Cardiovascular Disease and Its Interplay with Insulin Resistance. *Biomolecules*, *9*(7), 286. https://doi.org/10.3390/biom9070286
37. Genovese, M., Imperatore, C., Casertano, M., Aiello, A., Balestri, F., Piazza, L., Menna, M., Del Corso, A., & Paoli, P. (2021). Dual Targeting of PTP1B and Aldose Reductase with Marine Drug Phosphoeleganin: A Promising Strategy for Treatment of Type 2 Diabetes. Marine drugs, 19(10), 535. https://doi.org/10.3390/md19100535
38. Eleftheriou, P., Geronikaki, A., & Petrou, A. (2019). PTP1b Inhibition, A Promising Approach for the Treatment of Diabetes Type II. Current topics in medicinal chemistry, 19(4), 246–263. https://doi.org/10.2174/1568026619666190201152153
39. Kennedy B. P. (1999). Role of protein tyrosine phosphatase-1B in diabetes and obesity. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 53(10), 466–470. https://doi.org/10.1016/s0753-3322(00)88105-6.
40. Kennedy, B. P., & Ramachandran, C. (2000). Protein tyrosine phosphatase-1B in diabetes. Biochemical pharmacology, 60(7), 877–883. https://doi.org/10.1016/s0006-2952(00)00305-1
41. Boduła, A., Wdowczyk, M., & Adamiec, R. (2005). Rola białkowej fosfatazy tyrozynowej 1B (PTP-1B) w rozwoju insulinooporności [The role of protein tyrosine phosphatase (PTP-1B) in insulin resistance]. Postepy higieny i medycyny doswiadczalnej (Online), 59, 203–207.
42. Shrestha, S., Bhattarai, B. R., Cho, H., Choi, J. K., & Cho, H. (2007). PTP1B inhibitor Ertiprotafib is also a potent inhibitor of IkappaB kinase beta (IKK-beta). Bioorganic & medicinal chemistry letters, 17(10), 2728–2730. https://doi.org/10.1016/j.bmcl.2007.03.001
43. Erbe, D. V., Wang, S., Zhang, Y. L., Harding, K., Kung, L., Tam, M., Stolz, L., Xing, Y., Furey, S., Qadri, A., Klaman, L. D., & Tobin, J. F. (2005). Ertiprotafib improves glycemic control and lowers lipids via multiple mechanisms. Molecular pharmacology, 67(1), 69–77. https://doi.org/10.1124/mol.104.005553
44. Bourebaba, L., Serwotka-Suszczak, A., Pielok, A., Sikora, M., Mularczyk, M., & Marycz, K. (2023). The PTP1B inhibitor MSI-1436 ameliorates liver insulin sensitivity by modulating autophagy, ER stress and systemic inflammation in Equine metabolic syndrome affected horses. Frontiers in endocrinology, 14, 1149610. https://doi.org/10.3389/fendo.2023.1149610
45. Kostrzewa, T., Styszko, J., Gorska-Ponikowska, M., Sledzinski, T., Kuban-Jankowska, A. Inhibitors of Protein Tyrosine Phosphatase PTP1B With Anticancer Potential. Anticancer Res. 2019, 39, 3379–3384.
46. Liu, Z. Q., Liu, T., Chen, C., Li, M. Y., Wang, Z. Y., Chen, R. S., Wei, G. X., Wang, X. Y., & Luo, D. Q. (2015). Fumosorinone, a novel PTP1B inhibitor, activates insulin signaling in insulin-resistance HepG2 cells and shows anti-diabetic effect in diabetic KKAy mice. Toxicology and applied pharmacology, 285(1), 61–70. https://doi.org/10.1016/j.taap.2015.03.011
47. Jung, H. A., Bhakta, H. K., Min, B. S., & Choi, J. S. (2016). Fucosterol activates the insulin signaling pathway in insulin resistant HepG2 cells via inhibiting PTP1B. Archives of pharmacal research, 39(10), 1454–1464. https://doi.org/10.1007/s12272-016-0819-4
48. Jung, H. J., Seong, S. H., Ali, M. Y., Min, B. S., Jung, H. A., & Choi, J. S. (2017). α-Methyl artoflavanocoumarin from Juniperus chinensis exerts anti-diabetic effects by inhibiting PTP1B and activating the PI3K/Akt signaling pathway in insulin-resistant HepG2 cells. Archives of pharmacal research, 40(12), 1403–1413. https://doi.org/10.1007/s12272-017-0992-0

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JCHR (2024) 14(1), 1334-1342 | ISSN:2251-6727

49. Ali, M. Y., Zaib, S., Rahman, M. M., Jannat, S., Iqbal, J., Park, S. K., & Chang, M. S. (2019). Didymin, a dietary citrus flavonoid exhibits anti-diabetic complications and promotes glucose uptake through the activation of PI3K/Akt signaling pathway in insulin-resistant HepG2 cells. Chemico-biological interactions, 305, 180–194. https://doi.org/10.1016/j.cbi.2019.03.018
50. Yousof Ali, M., Zaib, S., Mizanur Rahman, M., Jannat, S., Iqbal, J., Kyu Park, S., & Seog Chang, M. (2020). Poncirin, an orally active flavonoid exerts antidiabetic complications and improves glucose uptake activating PI3K/Akt signaling pathway in insulin resistant C2C12 cells with anti-glycation capacities. Bioorganic chemistry, 102, 104061. https://doi.org/10.1016/j.bioorg.2020.104061
51. Ali, M. Y., Park, S. E., Seong, S. H., Zamponi, G. W., Jung, H. A., & Choi, J. S. (2023). Ursonic acid from Artemisia montana exerts anti-diabetic effects through anti-glycating properties, and by inhibiting PTP1B and activating the PI3K/Akt signaling pathway in insulin-resistant C2C12 cells. Chemico-biological interactions, 376, 110452. https://doi.org/10.1016/j.cbi.2023.110452
52. Deshmukh, S. K., Agrawal, S., & Gupta, M. K. (2023). Fungal Metabolites: A Potential Source of Antidiabetic Agents with Particular Reference to PTP1B Inhibitors. Current pharmaceutical biotechnology, 24(8), 927–945. https://doi.org/10.2174/1389201023666220506104219
53. Rocha, R. F., Rodrigues, T., Menegatti, A. C. O., Bernardes, G. J. L., & Terenzi, H. (2020). The antidiabetic drug lobeglitazone has the potential to inhibit PTP1B activity. Bioorganic chemistry, 100, 103927. https://doi.org/10.1016/j.bioorg.2020.103927
Bellomo, E., Singh, K.B., Massarotti, A., Hogstrand, C., Maret, W. The metal face of protein tyrosine phosphatase 1B. Coord. Chem. Rev. 2016, 327, 70–83.
54. Ali, M. Y., Jannat, S., Jung, H. A., Jeong, H. O., Chung, H. Y., & Choi, J. S. (2016). Coumarins from Angelica decursiva inhibit α-glucosidase activity and protein tyrosine phosphatase 1B. Chemico-biological interactions, 252, 93–101. https://doi.org/10.1016/j.cbi.2016.04.020
55. Wang, W. L., Yang, D. L., Gao, L. X., Tang, C. L., Ma, W. P., Ye, H. H., Zhang, S. Q., Zhao, Y. N., Xu, H. J., Hu, Z., Chen, X., Fan, W. H., Chen, H. J., Li, J. Y., Nan, F. J., Li, J., & Feng, B. (2013). 1H-2,3-dihydroperimidine derivatives: a new class of potent protein tyrosine phosphatase 1B inhibitors. Molecules (Basel, Switzerland), 19(1), 102–121. https://doi.org/10.3390/molecules19010102
56. Maeda, A., Kai, K., Ishii, M., Ishii, T., & Akagawa, M. (2014). Safranal, a novel protein tyrosine phosphatase 1B inhibitor, activates insulin signaling in C2C12 myotubes and improves glucose tolerance in diabetic KK-Ay mice. Molecular nutrition & food research, 58(6), 1177–1189. https://doi.org/10.1002/mnfr.201300675
57. Bellomo, E., Abro, A., Hogstrand, C.; Maret, W., Domene, C. Role of Zinc and Magnesium Ions in the Modulation of Phosphoryl Transfer in Protein Tyrosine Phosphatase 1B. J. Am. Chem. Soc. 2018, 140, 4446–4454.
58. Gorgulla, C., Boeszoermenyi, A., Wang, Z.-F., Fischer, P.D., Coote, P.W., Das, K.M.P., Malets, Y.S., Radchenko, D.S., Moroz, Y.S., Scott, D.A., et al. An open-source drug discovery platform enables ultra-large virtual screens. Nature 2020, 580, 663–668.