Inhibiting PTEN

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Abstract

PTEN (phosphatase and tensin homologue deleted on chromosome 10) is well known as a tumour suppressor. In dephosphorylating the 3-position of the inositol ring of phosphoinositides such as PtdIns(3,4,5)P3, PTEN’s lipid phosphatase activity is an important counteracting mechanism in PI3K (phosphoinositide 3-kinase) signalling. This is essential for cell motility and migration due to the achievement of a PtdIns(3,4,5)P3/PtdIns(4,5)P2 gradient that is also involved in metastasis. Furthermore, PTEN’s tumour suppressor role is linked to the control of cell-cycle progression and cell proliferation by counteracting Akt (also called protein kinase B) signalling which is PtdIns(3,4,5)P3-dependent. Akt is upstream of several kinases involved in proliferation and apoptotic signalling which are often found to be deregulated or mutated in tumours. However, Akt is also the key enzyme in insulin signalling regulating glucose uptake and cell growth. Therefore PTEN has recently moved into the spotlight as a drug target in diabetes. This review summarizes studies undertaken on PTEN’s role in glucose uptake, insulin resistance, diabetes and its controversial role in GLUT (glucose transporter)-mediated glucose uptake. Currently available techniques for inhibiting PTEN and the suitability of PTEN as a drug target will be discussed.

Role of PTEN (phosphatase and tensin homologue deleted on chromosome 10) in insulin signalling and glucose uptake

The key event in glucose signalling is the activation of GS (glycogen synthase) and increased glucose uptake, causing the conversion of blood glucose into muscle glycogen (Figure 1). This is initiated by insulin, which interacts with the insulin receptor on the outer surface of the plasma membrane, leading to a series of phosphorylation events and the activation of PI3K (phosphoinositide 3-kinase). Consequently, PI3K translocates to the plasma membrane where it converts PtdIns(4,5)P2 into PtdIns(3,4,5)P3, causing the recruitment of PDK1 (phosphoinositide-dependent kinase 1) and Akt (also called protein kinase B) to the plasma membrane via their PH domains (pleckstrin homology domains). Akt gets activated by two phosphorylation events (on Ser-473 and Thr-308) and phosphorylates several downstream targets, such as GSK3 (GS kinase-3). This reduces GSK3 activity and promotes activation of GS, leading to enhanced production of glycogen. This together with the PtdIns(3,4,5)P3-dependent stimulation of glucose uptake via GLUT4 (glucose transporter type 4) enhances the conversion of blood glucose into muscle glycogen.

PTEN in insulin resistance and diabetes

Type 2 diabetes is characterized by insulin resistance whereby insulin-regulated processes in muscle, liver, and fat cells become resistant to insulin. This can be due to a mutation or loss of expression of an enzyme involved in the insulin signalling pathway (Figure 1) such as the insulin receptor, at the very beginning of the cascade, or GLUTs at the end. Defects observed in adipose tissue from Type 2 diabetic patients include defective stimulation of PI3K activity, decreased association of PI3K with IRS-1 (insulin receptor substrate-1), reduced IRS-1 tyrosine phosphorylation during insulin stimulation [1] and loss of GLUT4 expression [2].

PTEN is a potential drug target as it metabolizes mainly PtdIns(3,4,5)P3 and the inhibition of this enzyme would increase the amounts of PtdIns(3,4,5)P3 and might therefore mimic insulin signalling (Figure 1). PTEN inhibition has been shown to increase Akt phosphorylation on both sites [3] and more specifically, Nakashima et al. [4] report that microinjection of an anti-PTEN antibody increased basal and insulin-stimulated PtdIns(3,4,5)P3 levels leading to the translocation of GLUT4 to the plasma membrane where its exocytosis participates to increase glucose uptake [5].

However, the role of PTEN in insulin-stimulated glucose uptake is controversial in the literature. Tang et al. [6] show that knock-down of PTEN by siRNA (small interfering RNA) enhances insulin-dependent glucose uptake into adipocytes, whereas Mosser et al. [7] suggest that PTEN does not modulate GLUT4 translocation and metabolic functions of insulin under normal physiological conditions based on their experiments with cells overexpressing a dominant inhibitory PTEN mutant. Nevertheless, they find that overexpression of wild-type PTEN antagonizes the metabolic actions of insulin dependent on PI3K.

Key words: diabetes, insulin signalling, phosphatase and tensin homologue deleted on chromosome 10 (PTEN), phosphatidylinositol 3,4,5-trisphosphate, phosphoinositide 3-kinase (PI3K), vanadate.

Abbreviations used: GLUT, glucose transporter; GS, glycogen synthase; GS3K, GS kinase-3; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; PTP, protein tyrosine phosphatase; SHIP, SH2 (Src homology 2)-containing inositol phosphatase; siRNA, small interfering RNA.

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PTEN’s role in insulin signalling and glucose metabolism

Insulin interacts with the insulin receptor (IR) on the outer surface of the plasma membrane, leading to its autophosphorylation. Consequently, the receptor phosphorylates IRS-1, which then binds to PI3K. PI3K translocates to the plasma membrane where it converts PtdIns(4,5)P₂ [P(4,5)P₂] into PtdIns(3,4,5)P₃ [P(3,4,5)P₃], causing activation of Akt by two phosphorylation events (on Ser-473 and Thr-308). PTEN counteracts PI3K action and Akt signalling by dephosphorylating the inositol headgroup of PtdIns(3,4,5)P₃ on the 5-position. One of Akt’s downstream targets is GSK3. Upon its phosphorylation, GSK3 activity is reduced, which promotes the activation of GS, leading to enhanced production of glycogen. This, together with the PtdIns(3,4,5)P₃-dependent stimulation of glucose uptake via GLUT4, enhances the conversion of blood glucose into muscle glycogen. Whether Akt triggers the rate of GLUT4 translocation directly is not known. However, upon inhibition of PTEN, steady-state levels of PtdIns(3,4,5)P₃ will be increased, enhancing GLUT4 translocation and Akt downstream events such as glycogen synthesis. P(3,4)P₂, PtdIns(3,4)P₂.

Another lipid phosphatase breaking down PtdIns(3,4,5)P₃ is SHIP2 [SH2 (Src homology 2)-containing inositol phosphatase-2]. SHIP2 dephosphorylates the 5-position of the inositol ring of PtdIns(3,4,5)P₃ [8]. Besides PtdIns(3,4,5)P₃, also PtdIns(3,4)P₂ is essential for activating Akt [9] and therefore SHIP is no necessarily countering the PI3K downstream signalling on Akt providing there are basal levels of PtdIns(3,4,5)P₃ present. SHIP’s role in insulin resistance is not very well explored and controversial. Tang et al. [6] report that SHIP does not play a role in insulin signalling in L1 adipocytes, whereas others found an increased Akt activity in SHIP2-deficient cells upon serum stimulation [10]. Moreover, SHIP2 inhibitors would need to be highly selective because the related SHIP1 isofrom is crucial for immune function.

In summary, it is widely accepted that glucose uptake is PtdIns(3,4,5)P₃-dependent and inhibition of PTEN seems to increase the rates of glucose uptake, but whether GLUT4 translocation can be stimulated by PTEN inhibition remains to be resolved. Therefore, depending on where the defect in the insulin signalling cascade occurs, PTEN targeting might help to overcome insulin resistance.

PTEN inhibitors

The above-mentioned findings on PTEN’s role in insulin resistance result from experiments that were carried out with rather invasive methods, such as knock-down with siRNA, which can have severe side effects or are not always efficient in abolishing endogenous activity. Genetic knockout studies are a time-consuming and expensive approach and the result might not reflect physiological conditions due to compensation by other proteins. PTEN has a PDZ domain-binding motif in the C-terminal region, which has been shown to interact with other proteins, such as MAGI-2 (membrane-associated guanylate kinase with inverted domain structure-2), forming a stable signalling complex [11]. In knock-down or dominant-negative mutant overexpression studies this interaction is likely to be disturbed due to a change in molar ratios of the interacting proteins. Therefore a chemical PTEN inhibitor would be useful in order to facilitate the investigation of its controversial role in Type 2 diabetes and other unresolved pathways. Pharmacological inhibitors have the advantage that the target retains its scaffolding function and ability to interact with other proteins, while solely its enzyme activity can be reduced in a dose-dependent manner. In addition, based on the current understanding of PTEN’s role in diabetes, the idea has recently gained credibility that the inhibition of its lipid phosphatase activity might have the potential of enhancing insulin-sensitivity and overcoming insulin resistance, which would be beneficial for the development of diabetes therapeutics.

It has been shown that compounds of the element vanadium are able to mimic a variety of insulin-like effects in in vitro and in vivo systems [12] and that they can enhance glucose uptake [13]. These effects are partly explainable by...
the well-characterized broad inhibitory function of vanadates on PTPs (protein tyrosine phosphatases) [14]. Owing to the high homology of PTEN’s catalytic subunit to other PTPs, vanadates also inhibit PTEN. Indeed, bisperoxovanadium compounds have been shown to be potent PTEN inhibitors in the nanomolar range [15]. Based on these compounds and exploiting unique structural properties of PTEN [16], a very specific small molecule inhibitor has recently been developed [17].

**Concluding remarks**

While a specific chemical PTEN inhibitor is doubtlessly very useful for research purposes it is questionable if a PTEN inhibitor should be considered as a potential drug in antidiabetic treatment considering its well-known effect as a tumour suppressor and its loss causing migratory and invasive properties of cells [18]. However, it has been reported that PTEN loss in pancreatic β-cells [19] is not tumorigenic and that selective PTEN deletion in skeletal muscle protects against the development of insulin resistance without the development of cancer [20]. A targeted tissue-specific drug could therefore be considered for the treatment of diabetes without causing malignant cell growth.

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**References**


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