Protein Tyrosine Phosphatases: Potential Roles in Disease

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The activation of protein tyrosine kinases (PTKs), followed by the reversible phosphorylation of tyrosyl residues in cellular proteins, accounts for the control of many fundamental cellular functions including proliferation, migration, morphogenesis, cytoskeletal changes and gene expression [1]. In recent years, protein tyrosine phosphatases (PTPs) have been recognized as a biochemical counterbalance to PTKs, and although much progress has been made in our understanding of the structure, function and regulation of PTKs, PTPs are less well characterized. PTPs are a large gene family of nearly 100 members and individual members exhibit substrate selectivity and control specific aspects of intracellular signaling [2]. Hence, cell function is regulated by the coordinated action of PTKs and PTPs.

PTPs can be divided into two structurally distinct subgroups: transmembrane (receptor-like) PTPs, referred to as RPTPs, and cytoplasmic PTPs. The cytoplasmic enzymes are further subdivided into tyrosine-specific PTPs and dual specificity PTPs (DSPs) which can dephosphorylate phosphoserine, phosphothreonine or phosphorylated lipids, in addition to phosphotyrosine (see Figure 1). Despite their marked diversity in overall structure, virtually all PTPs possess a core sequence (I/V)HCX_5R(S/T)G that contains conserved cysteine and arginine residues that are critical for enzymatic activity, although the final glycine is more variable in the DSPs. Recently, an excellent review has been published that summarizes the functional relevance and evolutionary conservation of these and other motifs [3]. Transmembrane PTPs often have two tandem catalytic domains in the cytoplasmic region with an extracellular domain containing variable numbers of fibronectin type III domains, immunoglobulin-like domains, or carbonic anhydrase (CAH)-related domains (see Figure 1). Non-receptor PTPs generally contain a single catalytic domain and are commonly associated with other regulatory regions such as Src homology 2 (SH2) domains, ER targeting sequences, FERM domains or PEST sequence [3].

Intracellular Functions of Protein Tyrosine Phosphatases

Although initial observations of the effects of overexpression of PTPs suggested that these enzymes might simply counteract the signaling events elicited by PTKs, more recent genetic and biochemical evidence indicates that PTPs play more complex roles in a wide range of cellular activities [4,5]. For example, SHP-1 and SHP-2, two SH2 domain-containing cytoplasmic PTPs, play negative and positive regulatory roles, respectively, in PTK signaling [6]. Members of the band 4.1/FERM family of cytoplasmic PTPs, including PTPH1 and PTPMEG, are thought to regulate cytoskeletal reorganization [7,8]. The transmembrane enyzme PTPα affects cell-substratum adhesion and cellular transformation by regulating the activity of the PTK *src* [9]. In the immune system, the transmembrane PTP CD45 is essential for the activation of lymphocyte-specific kinase (lck) and downstream signaling of the T cell receptor [10], and SHP-1 is a negative regulator of natural killer (NK) cell signaling [11]. Many receptor PTPs (RPTPs) are transmembrane molecules that possess both intracellular catalytic domains as well as defined extracellular motifs. RPTPs, such as leukocyte common antigen (LAR), PTPσ and PTPδ influence neural development and synaptic plasticity [12-14]. An understanding of RPTP function has been hampered by the orphan status of most RPTPs, and, where ligands have been identified, their effects on RPTP activity are unclear. Recent studies have led to the hypothesis that ligands induce dimerization and suppress RPTP activity [15-17]. Due to their critical role in cell regulation, PTPs are implicated in many diseases. This review, in addition to surveying the major topics, will also highlight some less documented aspects of the role of PTPs in human disease.

Protein Tyrosine Phosphatases and Malignancy

PTKs have long been acknowledged to be potential oncogenes. However, there is now growing evidence that some PTPs can either induce neoplastic transformation or act as tumor suppressors. PTPα has been shown to dephosphorylate and activate c-src in breast cancer cell lines [18-20], potentially leading to unregulated proliferation. Indeed, increased PTPα levels have been detected in late stage colon carcinomas and squamous cell carcinomas [21,22]. However, there may also be some cell type specificity as it has been reported that PTPα inhibits tumor cell growth and correlates with low grade tumor grade in breast carcinoma [23]. PTPε, another PTPα family member, has been reported to increase the risk of mammary hyperplasia in transgenic mice [24]. Several other PTPs, such as PTP1B and SHP-1, are thought to activate c-src by dephosphorylation of tyrosine 527 [25-28]. Although some progress has been made towards understanding the role of PTPs in c-src activation in neoplasia, there are still significant gaps in our knowledge of the basic cell biology of PTPα/src-induced oncogenesis, including its importance in epithelial cell neoplasia in breast, colon and prostate, the role of other PTPs in activating c-src, and the genetic changes induced by increases in PTP activity.

About the Author

Stuart Kellie received his Ph.D. in 1980 from the University of St. Andrews in Scotland. Following postdoctoral appointments at the University of Leicester and the Imperial Cancer Research Fund Laboratories in London, during which time he worked on the identification of cellular substrates for the v-src oncogene, he took up a lectureship in 1986 in the Department of Biochemistry at the Royal College of Surgeons of England. In 1990 he was appointed Group Leader at the Yamanouchi Research Institute in Oxford where he led a team investigating the potential of tyrosine kinases and phosphatases as molecular targets for several human diseases. He currently holds a joint appointment as Senior Lecturer in Immunology and Group Leader at the Institute for Molecular Biosciences, University of Queensland, Brisbane, Australia, and is a project leader in the Cooperative Research Centre for Chronic Inflammatory Diseases.

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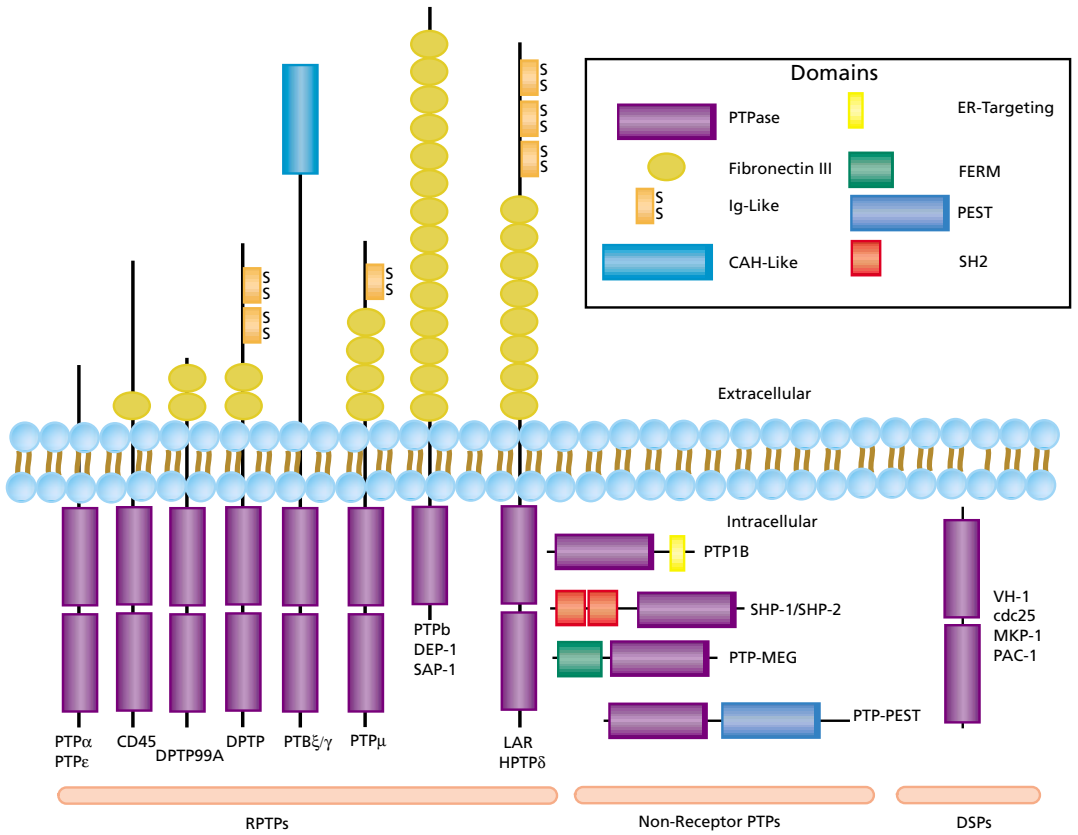

Figure 1. Diagramatic representation of the structures of representative members of the protein tyrosine phosphatase family. Receptor PTPs often have two intracellular catalytic domains, one of which is inactive, and extracellular regions comprising Ig-like domains (Ig-like), fibronectin type III motifs (Fibronectin III), or carbonic anhydrase-like domains (CAH-like). Intracellular regulatory domains include: ER-targetting, FERM (Four point one, Ezrin, Radixin, Moesin) domain, PEST (rich in proline (P), glutamic acid (E), serine (S) and threonine (T)).

The SH2 domain-containing PTPs, SHP-1 and SHP-2, have been implicated either in oncogenesis or tumor suppression depending on the cells investigated. SHP-1 expression is decreased in many leukemia and lymphoma cell lines, suggesting a suppressor role in the proliferation of these cells. However, in other tumors, positive or negative roles in oncogenesis have been proposed. For example, SHP-1 expression has been reported to be increased in human breast cancer samples [29], but has been shown to strongly suppress *ret* oncogene activity [30]. The expression of SHP-1 in solid tumors is also variable, and may be related to the tumor type, the differentiation state or the hormone receptor status of the tumor [31]. SHP-2 has been found to be upregulated in breast carcinoma in more than half of primary samples assayed [32], and has been shown to promote growth factor stimulation of ERK activity [33]. More recently, it has been shown that SHP-2 is an intracellular target for the CagA protein from *H. pylori* that can result in stomach cancer [34]. It has been suggested that PTPCAAX2 may be a potential oncogene [35], and in an exciting study, Saha et al. [36] have identified the tyrosine phosphatase PRL-3 as a gene associated with metastasis of colorectal carcinoma.

A subfamily of RPTPs that contain a single catalytic domain in the cytoplasmic region, a single transmembrane domain and eight fibronectin type III-like domains in the extracellular region have also been implicated in the regulation of neoplastic cell growth. DEP-1 (Density Enhanced Phosphatase-1; CD148) is induced in breast carcinoma cells as they reach confluency, and its rat homolog has been reported to suppress the transformed phenotype of retrovirally transformed thyroid cells [37,38]. Further weight to the concept that DEP-1 may function as a tumor suppressor comes from the report that DEP-1 is the underlying gene in the mouse scc1 (susceptibility to colon cancer 1) locus and is frequently deleted in human cancer [39]. In contrast, another member of this family, Sap-1, has been reported to be abundant in a subset of pancreatic and colorectal cancer cell lines and tissues, but not in their normal counterparts [40,41].

PTPbas (FAP-1) expression has also been shown to have a strong association with malignancy, however, this appears to occur by a mechanism distinct from that of other PTPases described previously. PTPbas is upregulated in hepatoblastomas and other carcinomas [42-44], and this leads to the induction of resistance to CD95-mediated apoptosis [45-47]. A dual specificity phosphatase, cyclin-dependent kinase-associated phosphatase (KAP), is overexpressed in breast and prostate cancer, and downregulation of this gene by antisense RNA leads to inhibition of the transformed phenotype [48]. PTPase domains have been identified by PCR amplification using degenerate primers. In mouse macrophages, for example, 10 PTPase family

members were identified. One member, DEP-1, was identified as a macrophage-enriched PTPase that is regulated by colony stimulating factor (CSF-1) and lypopolysaccharide (LPS) [49]. A similar approach has identified PTPκ and PTPπ as genes that are down regulated in melanoma cells [50].

Protein Tyrosine Phosphatases and Inflammatory Disease

Macrophages are possibly the most important inflammatory cell type to be aberrantly activated in chronic inflammatory diseases such as rheumatoid arthritis, but little is known about intracellular regulation of PTPs in these cells. The best characterized PTP in macrophage-like cells is SHP-1, which is a negative regulator of CSF-1 receptor signaling. The activity of this protein is dramatically reduced in the allelic motheaten viable (Me^v/Me^v) mouse and leads to constitutive activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway [51]. Although DEP-1 has been implicated in the control of epithelial cell proliferation (as discussed earlier), it also appears to regulate hematopoietic cell activation and proliferation. It is expressed throughout the hematopoietic system and in a wide variety of tissues including pancreas, thyroid, kidney, mammary gland and nervous system [52,53]. DEP-1 is expressed at low levels in resting T cells, but is upregulated in activated T cells. Ligation with anti-DEP-1 antibodies induced proliferation of anti-CD3 activated T cells, and gave a calcium flux response. Interestingly, in transient transfection experiments, DEP-1 has been reported to be a negative regulator of T cell activation, and also results in a reduction of both TCR-mediated extracellular signal-related kinase I (ERK-1) and ERK-2 activation and tyrosine phosphorylation [54-59]. Baker et al. [60] have shown that DEP-1 expression inhibits TCR-mediated activation of Ras and calcium release, with phospholipase C γ (PLCγ) and linker for activation of T cells (LAT) as potential targets.

Although the evidence is indirect, it is possible that PTPs may play a role in chronic inflammatory diseases and atherosclerosis. Midkine is a heparin-binding growth and differentiation factor that induces haptotaxis of macrophages, osteoclasts and smooth muscle cells [61]. One receptor for midkine is PTPζ, and antibodies against PTPζ enhance midkine-induced migration [62,63].

Protein Tyrosine Phosphatases and Type II Diabetes

Tyrosine phosphorylation is central to insulin-stimulated glucose uptake in adipose tissue and skeletal muscle. Several PTPs have been identified as negative regulators of the insulin signaling pathway, including PTPα and PTPε [64], PTP-LAR [65,66], PTP1B [67,68] and SHIP-2 [69]. Recently, a PTP1B knockout has been developed that has provided evidence that PTP1B is a key regulator of insulin signaling. Mice lacking PTP1B displayed both increased insulin sensitivity and obesity resistance [70]. Curiously, although PTP1B is expressed in many tissues, including adipose tissue and skeletal muscle, enhancement of glucose uptake in PTP1B knockout mice was restricted to skeletal muscle [71]. The reasons for this are unclear, but point to PTP1B having different functions in different cell types. The use of antisense oligonucleotides against PTP1B has confirmed its central role in insulin receptor signaling and glucose homeostasis [72], and highlighted the potential use of inhibitors of PTP1B activity as potential therapeutics for diabetes (see later).

Association of Protein Tyrosine Phosphatases with other Diseases

PTPs have been implicated in the etiology of a number of diseases, as summarized in Table 1. Recently, evidence has been published that suggests that mutations in the PTPN11 gene (SHP-2) leads to Noonan's syndrome, a developmental disease characterized by craniofacial disorders [73]. Furthermore, knockout mouse studies have implicated many PTPs in neuronal cell function. For example, PTPs such as LAR, PTPβ, PTPζ and PTPσ may play a role in neurite outgrowth and neuroregulation and are thus candidates for involvement in neurodegenerative diseases or possibly neuroprotection following trauma or stroke [74]. In addition, PTPβ regulates a voltage-gated sodium channel and may be central to long term potentiation in neurons [75].

The activation or suppression of PTP activity is also central to the etiology of a number of infectious diseases. As stated above, SHP-2 has been identified as a target of the CagA gene of *H. pylori*, potentially resulting in its deregulation and hyperproliferation [34]. Interestingly, both PTPβ and PTPα have been reported to be receptors for *H. pylori*, raising the possibility that several PTPs control *H. pylori*-mediated pathogenesis [76,77]. Other infectious agents also appear to regulate PTPs. For example, Vaccinia virus and other poxviruses can evade host defenses by a number of mechanisms. One of these is dependent on the expression of the VH1 gene, whose product is a dual specificity phosphatase essential for virus viability within cells [78,79]. More recent evidence indicates that the VH1 phosphatase may suppress host responses by inhibiting the activation of STAT-1 and therefore interferon γ signal transduction [80]. Another example of host suppression is the resistance to phagocytosis of *Yersinia spp*, occurs by the injection of a

Table 1. Summary of Protein Tyrosine Phosphatases and possible disease associations.

PTP	Disease	References
PTP1B, LAR, SHIP-2	Diabetes	65-69
PTPα, KAP, cdc25, FAP1, SHP-1, SHP-2, PTPCAAX, DEP-1, SAP-1, PTEN	Cancer	18-48, 118-121
PRL3	Metastasis	36
TC-PTP, DEP-1, CD45, SHP-1	Inflammation	54-60
RPTPγ, RPTPβ, RPTPζ	Neurodegeneration	12-14, 74,75
SHP-2	Noonan's syndrome	73
SHP-2, PTPα, PTPβ	*H. pylori* ulceration	34, 76-77
RPTPζ	Atherosclerosis	61-63

Protein Tyrosine Phosphatases...(continued)

PTP, the YopH gene, into the phagocyte, thereby suppressing phagocyte function [81]. Mycobacteria and *Salmonella spp*. may also subvert host cell signaling in a similar manner [82,83]. There is also some evidence that *Leishmania spp* activates SHP-1 in macrophages, resulting in a downregulation of macrophage responses and intracellular survival of the pathogen [84].

Pharmacological Regulation of Protein Tyrosine Phosphatases

Due to its role in type II diabetes, PTP1B has potential as a therapeutic target. Many biotech and pharmaceutical companies and academic groups have developed selective chemical inhibitors of PTP1B that have shown efficacy in animal models and derivatives of these may lead to better therapies for diabetes. Several different classes of chemical inhibitors have been developed. Burke and his colleagues have pioneered the use of difluoromethylene phosphonates as phosphate mimetics [85-87]. Modification of oxalylaminobenzoic acid, another phosphotyrosine mimetic, and the use of structure-based drug design have also generated a number of PTP1B inhibitors [88,89]. A number of other selective chemical inhibitors of PTP1B have been reported as potential leads for diabetes therapy [90-92]. Zhang and colleagues have also used structure-based design to develop selective inhibitors [93,94]. Further information on the therapeutic potential of PTP1B inhibitors is contained in three recent reviews [95-97]. Another possible approach to therapy in humans is the use of PTP1B antisense oligonucleotides which have been shown to normalize glucose levels in diabetic mice [72]. Derivatives of some of these compounds are now in clinical development and results are awaited with keen interest.

Few selective inhibitors for other PTPs have been published. However, the use of non-specific PTP inhibitors has indicated that more selective compounds may be useful for other diseases. The ability to express and purify PTPs in bacterial expression systems and subsequently perform structural studies has aided enormously the ability to both design potent and selective inhibitors and identify specific substrates. Active recombinant **PTP1B** (Prod. No. **P 7365**), **LAR** (Prod. No. **L 0907**), **TC-PTP** (Prod. No. **T 1196**) and **YOP PTP** (Prod. Nos. **Y 4127** and **Y 4252**) are now available for routine laboratory use. Inhibitors with relative selectivity for the PTP family, such as **sodium orthovanadate** (Prod. No. **S 6508**), have been used extensively as research tools, and other, more stable vanadate derivatives are now available. One caveat for the use of such compounds is that they have effects on other enzymes, and vanadate can inhibit kinases and ATPases due its phosphate transition state mimicry. However, the IC_{50} values for most PTPs are in the micromolar range whereas ATP inhibition occurs in the millimolar range. Indeed, vanadium compounds have been used for over 100 years in the treatment of diabetes [98,99], and it is likely that the molecular target for vanadate in these studies was PTP1B or another PTP regulating insulin signaling. Recently, the antibiotic **dephostatin** (Prod. No. **D 8065**) has been reported to be a PTP inhibitor [100,101] and so may be useful in PTP functional studies, although its relative selectivity with respect to other enzymes has yet to be fully investigated. The utility of compounds *in vitro* is underscored by the extensive list of publications. The vast majority of these have reported that treatment of cells with vanadate has a similar effect to cell stimulation. Thus, it can be reasonably hypothesized that under normal conditions there is a basal PTP activity that suppresses cell activation. The logical extension of this is that cells can be stimulated either by activation of PTKs or by inhibition of PTPs, a possibility often overlooked in cell signaling experiments. Vanadate-containing compounds are competitive inhibitors probably by PTP transition state mimicry. On the other hand, pervanadate is an irreversible inhibitor due to its ability to oxidize the catalytic cysteine residue. Nitric oxide (NO) and reactive oxygen species (ROS) can also inactivate PTPs by oxidizing the active site cysteine. Thus NO donors, such as nitrosothiols, can lead to activation of cells by inactivation of PTPs [102]. There is growing evidence that some compounds and drugs which have been used historically to treat certain diseases, but whose mechanism of action is unknown, may function through regulation of PTPs. An example of this is sodium stibogluconate, an antimony-containing compound that has been used for the past 30 years as a treatment for Leishmaniasis. This disease is characterized by the intracellular survival and proliferation of *Leishmania spp*. in macrophages. Stibogluconate appears to activate macrophages that subsequently destroy the intracellular organisms and there is growing evidence that this occurs via the inhibition of the PTP SHP-1. Cellular and *in vitro* assays have revealed that stibogluconate forms a stable complex with SHP-1, inhibiting its activity and resulting in augmentation of cytokine responses [103].

Protein Tyrosine Phosphatase Products Available from Sigma-RBI

P 8984 **Monoclonal Anti-Protein Tyrosine Phosphatase** μ, Clone SBK10 (mouse)
P 0857 **Monoclonal Anti-Protein Tyrosine Phosphatase 1B**, Clone FG6-1G (mouse)
P 9109 **Monoclonal Anti-Protein Tyrosine Phosphatase PEST**, Clone AG25 (mouse)
P 0732 **Monoclonal Anti-T-Cell Protein Tyrosine Phosphatase (TC PTPase)**, Clone CF4-1D (mouse)
P 9864 **Protein Tyrosine Phosphatase-β (PTP-β) Human**
PTP-101 **Protein Tyrosine Phosphatase (PTP) Assay Kit,** non-radioactive
P 6337 **Protein Tyrosine Phosphatase Substrate (Human insulin receptor fragment (1142-1153))**
P 6462 **Protein Tyrosine Phosphatase Substrate Monophosphate ([pTyr^{1146}]-Insulin receptor fragment (1142-1153))**
S 2938 **SC-ααδ9** (cdc25A protein phosphatase inhibitor)
P 5726 **Phosphatase Inhibitor Cocktail 2**

Protein Tyrosine Phosphatases...(continued)

Several compounds have also been shown to activate PTPs. These include **phosphatidic acid** (Prod. No. P 4013), **phosphatidylserine** (Prod. No. P 7769), **cardiolipin** (Prod. No. C 0563) and other acidic phospholipids such as phosphatidylinositol 3,4,5 trisphosphate (PIP_3) that activate SHP-1, possibly by binding to the carboxyl-terminal domain [104,105]. Lipoarabinomannan, a derivative of *M. tuberculosis*, can also activate SHP-1, probably leading to suppression of macrophage activity and evasion of the host immune responses by the pathogen [106]. Similarly, phosphopeptides based on the tyrosine phosphorylation site of IRS-1 or PDGF receptor have been shown to activate SHP-2 [107]. While there has been intense effort directed at generating specific PTK inhibitors, the potential to selectively activate PTPs has been relatively ignored, although in principle this should lead to a similar suppression of cell activation. The therapeutic potential of PTP activators has yet to be explored, but would seem to be a worthwhile alternative approach.

Dual specificity PTPs (DSPs) such as cdc25 have been implicated in a number of proliferative diseases, particularly in cancer. There are three Cdc25 homologs: A, B and C [108], which are expressed and activated at different times during the cell cycle acting on different cyclin-Cdk complexes. Cdc25B and Cdc25C function primarily at the G2/M transition, while Cdc25A promotes S-phase entry. Microinjection of neutralizing Cdc25A antibodies prevented entry into S phase, demonstrating that Cdc25A is required for cellular progression through the G1/S checkpoint [109-111]. Overexpression of Cdc25A also induces premature activation of both cyclin E- and cyclin A-Cdk2 complexes. These cell cycle checkpoint genes are attractive targets for therapeutic agents in hyperproliferative diseases, such as cancer. In support of this Cdc25B mRNA was found to be expressed at high levels in almost one third of human breast cancers [112], in addition to being oncogenic when expressed as a transgene [113]. Cdc25A overexpression has also been associated with breast cancer [114]. Another DSP, KAP, is overexpressed in breast and prostate cancer and down regulation of this gene results in the loss of the transformed phenotype both *in vitro* and *in vivo* [48].

Several small molecular weight inhibitors of DSPs have been developed which are proving useful in dissecting out the relative roles of DSPs and other phosphatases [115,116]. One example is **NSC 95397** (Prod. No. N 1786), a cdc25-selective inhibitor which has been shown to inhibit the proliferation of human and murine carcinoma cells by blocking the G2/M phase transition [117]. Another class of dual specificity phosphatase with relevance to human disease is PTEN, a phosphatase that possesses activity against both phosphotyrosine and inositol phospholipids [118]. Genetic studies have demonstrated that its absence leads to a number of human tumors and PTEN is now classed as a tumor suppressor [119,120]. Although originally described as a phosphotyrosine and phospholipid phosphatase, subsequent studies have demonstrated that it is the phospholipid phosphatase activity that is critical for its tumor suppression function [121]. While no small molecular weight molecules have been described which regulate the lipid phosphatase activity of PTEN, it remains an interesting target.

Perspectives

The success of the Abelson PTK inhibitor STI-157 (Glivec) as a therapy for chronic myeloid leukemia and other malignancies has provided 'proof of principle' that targeting molecules that regulate tyrosine phosphorylation can be clinically effective. Several phosphatase-selective inhibitors have now been developed that exhibit efficacy both *in vitro* and *in vivo*, and it seems likely that the number of such inhibitors entering clinical trials will increase in the next few years. The most likely therapeutic areas for the development of a clinically effective PTP inhibitor are non-insulin dependent (Type II) diabetes and/or obesity. However, we may also see inhibitors being used for the treatment of cancer in the near future. In the meantime, an increase in the availability of selective PTP inhibitors will undoubtedly generate a greater understanding of the role of these molecules in cell regulation.

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New Product Highlights

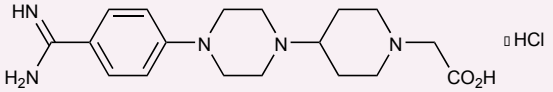
GR 144053: Non-peptide antagonist of the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) fibrinogen receptor

Following vascular injury, platelets become activated and adhere to damaged blood vessel walls and exposed sub-endothelial connective tissues thereby forming the initial platelet plug. Platelets play a central role in thrombus formation and are known to participate in many life-threatening thrombotic disorders such as acute myocardial infarction, stroke and pulmonary embolism. One platelet receptor involved in this activation is glycoprotein Ib/IX (GP Ib/IX) together with its ligand von Willebrand factor (vWF). Activation causes the exposure of phospholipids (PL) and the membrane glycoprotein IIb/IIIa (GP IIb/IIIa) on the platelet surface, providing a platform upon which the members of the coagulation cascade can assemble.

GR 144053 (Prod. No. **G 6418**) is a potent and selective, non-peptide antagonist at the glycoprotein IIb/IIIa (GP IIb/IIIa) fibrinogen receptor [1,2]. It acts as a mimetic of the peptide RGD-sequence, a potent inhibitor of GPIIb/IIIa. Binding of GR 144053 to GPIIb/IIIa competitively blocks the binding of its normal ligand, **fibrinogen** (Prod. No. **F 4883**), and alters the signaling properties of the GPIIb/IIIa heterodimer. It attenuates platelet aggregation, activation and degranulation both *in vivo* and *in vitro* and inhibits ADP-induced platelet aggregation with an IC_{50} value of 17.7 nM [2].

GR 144053 also suppresses the activation of platelets by **aurintricarboxylic acid** (ATA, Prod. No. **A 0885**) [2]. The molecular mechanism of ATA action has not been completely elucidated. One possible mechanism is through its binding to GP Ib, thereby blocking binding of vWF. This observation suggests additional activities for GR 144053 that are not mediated by the GP IIb-IIIa receptor [2].

GR 144053 is a useful tool for studying the of mechanisms of platelet activation and degranulation events. Currently, anti-thrombotic therapy includes anti-platelet, anti-coagulant, pro-thrombolytic or pro-fibrinolytic agents. GR 144053 may be potentially useful in achieving anti-thrombosis effects while maintaining the integrity of the vascular system.



GR 144053
(Prod. No. G 6418)

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