CMLS, Cell. Mol. Life Sci. 62 (2005) 931–936
1420-682X/05/090931-06
DOI 10.1007/s00018-004-4448-1

CMLS Cellular and Molecular Life Sciences

Visions & Reflections

Oxidation and tyrosine phosphorylation: synergistic or antagonistic cues in protein tyrosine phosphatase

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Received 11 October 2004; received after revision 26 January 2005; accepted 10 February 2005
Available online 29 March 2005

Abstract. Protein tyrosine phosphatases (PTPs) have been generally recognised as key modulators of cell proliferation, differentiation, adhesion and motility. During signalling, several PTPs undergo two posttranslational modifications that greatly affect their enzymatic activity: tyrosine phosphorylation and cysteine oxidation. Although these modifications share their reversibility depending on the intracellular environment, their effects on enzymatic activity are opposite, tyrosine phosphorylation being correlated to enzyme activation and thiol oxidation to complete inactivation. Several papers have suggested that both these modifications occur in response to the same stimuli i.e. cell proliferation induced by numerous growth factors and cytokines. Conversely, the possibility that these two regulation mechanisms act simultaneously on PTPs has not been established and very few reports investigated this dual regulation of PTPs. To underline the relevance of the question, we discuss several possibilities: (i) that tyrosine phosphorylation and cysteine oxidation of PTPs may share the same target molecules but with different kinetics; (ii) that PTP phosphorylation and oxidation may take place on different subcellular pools of the same protein and (iii) that these two modifications, although having divergent effects on enzyme activity, cooperate in the integrated and coordinated function of PTPs during receptor tyrosine kinase signalling. We believe that our perspective will open new perspectives on an ancient problem – the apparent contradiction of opposing enzymatic regulation of many PTPs – thus clarifying their role as positive or negative transducers (or both) of many extracellular stimuli.

Key words. tyrosine phosphatase; PTP phosphorylation; PTP redox regulation; tyrosine kinase receptors; reactive oxygen species.

The protein tyrosine phosphatase family

Reversible tyrosine phosphorylation of proteins is a key event in signal transduction implicated in the regulation of several processes such as cell growth, proliferation and differentiation. Protein tyrosine phosphatases (PTPs) catalyse the hydrolysis of phosphotyrosine residues in proteins and together with protein tyrosine kinase (PTK) regulate the level of tyrosine phosphorylation of cellular proteins. The superfamily of PTPs is encoded by approximately 100 genes, characterised by the presence of a conserved active site signature motif C(X)5R. Based on structure and substrate specificity, the PTP superfamily is divided into four distinct subfamilies: (i) pTyr-specific PTPs, (ii) dual-specificity phosphatases, (iii) Cdc25 phosphatases and (iv) low molecular weight (LMW) PTPs [1, 2].

Despite the differences in substrate specificity, PTPs employ a common chemical mechanism for phosphate hydrolysis involving a transient cysteinyl-phosphate intermediate. In vivo, PTPs undergo essentially two regulation mechanisms: they are inhibited through reversible oxidation of the active-site cysteine residue and are activated through tyrosine phosphorylation of specific tyrosine residues located near the catalytic cleft [3]. Interestingly, both these posttranslational modifications are elicited by the same input, i.e. receptor tyrosine kinase

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(RTK) signalling. The available data regarding the concomitant but opposing regulation of PTPs by tyrosine phosphorylation and oxidation are extraordinarily few and mainly related to Src homology 2 domain PTP (SHP2), PTP1B and LMW PTP. Nevertheless, the picture that emerges from the little experimental data can sustain a provocative perspective of dualistic PTP regulation.

The redox regulation of PTPs

During the past decade, evidence has accumulated that reactive oxygen species (ROS) play a key role during the signal transduction regulating the extent of protein phosphorylation on tyrosine residues [4]. Intracellular ROS, including H_2O_2, are produced in response to a variety of stimuli such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin, several other cytokines and integrin [5]. H_2O_2 is a mild oxidant and may oxidize cysteine residues in proteins to cysteine sulphenic acid or disulphide, both of which are readily reduced back to cysteine by various cellular reductants. The cysteine residue in the PTP signature motif, Cys-X-X-X-X-X-Arg exists as a thiolate anion at neutral pH, a condition favouring oxidation to the cysteine sulphenic derivative by various oxidants, including H_2O_2 [6]. Oxidation of PTPs leads to enzymatic inactivation, because the modified Cys can no longer function as a phosphate acceptor in the first step of the PTP-catalysed reaction. Remarkably, this modification can be reversed after incubation with thiol compounds [7–9]. These findings suggest that oxidation of the catalytic cysteine of PTPs may occur in vivo in response to ROS or to a boost in redox potential. In agreement with this idea, reversible oxidation was demonstrated for PTP1B during EGF [9] and insulin [10] signalling, and for LMW-PTP [11] and SHP2 [12] during PDGF stimulation. The phosphatase activity of these PTPS is fully restored by the re-reduction. In addition, confirming that redox regulation is a common feature of the whole PTP family, reversible oxidation has been reported for the lipid phosphatase PTEN [13], for Cdc25C phosphatase [14] and for the transmembrane PTP-α (RPTPα) [15]. Finally PTP1B and TC45, the 45-kDa spliced version of T cell PTP, have been found to be involved in insulin receptor regulation through reversible oxidation [16].

A general feature of PTP redox regulation is the formation of an S-S bridge or a sulphenyl-amide intermediate containing the catalytic-site cysteine, which is thus preserved from further and irreversible oxidation [8, 17]. Considering the differences in the pKa values of catalytic cysteines among PTPs, the availability as thiolate ions and the structural distance between the two cysteines involved in the disulphide may strongly influence the ability of a given phosphatase to be rapidly regulated by changing intracellular redox conditions, thereby representing a degree of specificity for PTP redox regulation [18]. Moreover, the oxidation of a given PTP may take advantage of other redox-sensitive enzymes like thiol peroxidases, that first sense ROS and form a mixed disulphide with the PTP. After the reduction of the peroxidase, the PTP stores the oxidation for slightly longer in an intramolecular disulfide [19]. In these circumstances, the peroxidase may behave as a redox sensor located upstream of the PTP and may add a further level of regulation to the whole process of PTP redox regulation.

We have previously proposed a model suggesting that signal transduction by ROS through reversible PTP inhibition represents a widespread and conserved component of the biochemical machinery that is triggered by RTKs. In particular, the transient negative regulation of PTPs, due to oxidants produced in response to RTK ligand stimulation, represents a strategy adopted by cells to promote RTK signalling by avoiding its prompt inactivation by PTPs. Afterwards, the increase in redox potential, due to a decrease in ROS, leads to PTP activity recovery and thus to termination of RTK signalling [18].

In addition, we speculate that the redox regulation of PTPs may depend on different oxidative stress conditions, being tissue or differentiation dependent. For example, the great burst of ROS production during phagocyte activation may lead to hyperoxidation of PTPs [20]. Conversely, during the commitment of cell differentiation, a decrease in ROS content has been proposed [21]. In fact, during muscle differentiation, ROS content is dramatically decreased and LMW-PTP shifts towards its reduced state, thus increasing its enzymatic activity [21, 22].

The regulation of PTPs by phosphorylation

The recent literature has indicated several phosphorylation sites, either on tyrosine or serine/threonine residues, as key regulators of PTP activity, although the functional significance of this modification is somewhat puzzling. To date tyrosine phosphorylation has been described for the SH2 domain-containing PTPs (SHP1 and 2), PTP1B and LMW-PTP, all sharing the same stimulus, i.e. cell proliferation induced by numerous growth factors. Although the phosphorylation on serine has been reported for both SHP2 [23] and PTP1B [24], only tyrosine phosphorylation of these phosphatases has been linked to a clear effect on their enzymatic activity.

SHP2 contains two SH2 domains at the N terminus, a PTP domain and a C-terminal tail [25]. Like several SH2 domain-containing enzymes that are catalytically inactive as a consequence of SH2 domain-mediated autoinhibition, SHP2 is essentially inactive under basal conditions [26]. In fact, during resting circumstances, the N-terminal SH2 domain of SHP2 is inserted into the catalytic cleft, resulting in autoinhibition of the PTP domain. The displace-

ment of the autoinhibiting SH2 domain of SHP2 by tyrosine phosphorylated ligands dramatically increases PTP activity, due to opening of the enzyme conformation. Recently, the tyrosine phosphorylation of the two C-tail tyrosines of SHP2, namely Tyr542 and Tyr580, has been proposed as an additional regulatory mechanism causing activation. The simultaneous replacement of SHP2 Tyr542 and Tyr580 with a non-hydrolysable phosphotyrosine analogue confirms that the phosphorylation at each position stimulates catalysis by about threefold, thus suggesting that the double phosphorylation should lead to about tenfold activation [27]. Both these phosphorylated tyrosines bind to autoinhibiting SH2 domains, leading to activation of the enzyme with consequent phosphatase activation. One should note that SHP2 undergoes phosphorylation at both C-terminal tyrosyl residues in response to some (fibroblast growth factor, PDGF and EGF) but not all (insulin and insulin-like growth factor) growth factors [28–31].

The cytosolic phosphatase PTP1B was one of the first PTPs shown to exist as a phosphoprotein in vivo. Similar to SHP2, PTP1B is able to bind to activated RTKs, thus causing a negative control of RTK signal transduction. Upon activation, several RTKs are able to directly phosphorylate PTP1B. Unfortunately, the role of this phosphorylation on phosphatase activity is much more controversial. EGF-r kinase is able to in vitro phosphorylate PTP1B on tyrosine 66, thereby causing a threefold increase in the catalytic activity of PTP1B [32]. In addition, Dadke et al. [33] reported that in vivo PTP1B is a direct substrate of the insulin receptor tyrosine kinase leading to an increase in its catalytic activity of 38-fold over the basal condition. This activation could facilitate the dephosphorylation of PTP1B substrates, namely the insulin receptor itself and insulin receptor substrate-1, thereby terminating insulin signalling. Contradicting these data, Tao et al. [34], observed in a mouse model an opposite effect of insulin-mediated PTP1B tyrosine phosphorylation, correlating with a decrease in PTP1B activity of about 60–70%, thus conferring on PTP1B tyrosine phosphorylation an ambiguous role.

Additional indications for the positive role of PTP tyrosine phosphorylation come from LMW PTP. A first indication of LMW PTP tyrosine phosphorylation was obtained in NIH-3T3 cells transformed with the v-src tyrosine kinase [35] that phosphorylates LMW PTP leading to its enzymatic activation. Furthermore, Tailor et al. [36] demonstrated phosphorylation of LMW PTP at Tyr131 and, to a lesser extent, at Tyr132 by Lck and Fyn tyrosine kinases in T lymphocytes. They also showed a twofold enzymatic activation upon phosphorylation. Later, Bucciantini et al. using Tyr131 to Ala and/or Tyr132 to Ala mutants showed that in vitro Src tyrosine kinase phosphorylates these two residues, although phosphorylation at either residue has a different effect on the enzyme behaviour. Tyr131 phosphorylation is followed by a strong (about 25-fold) increase in enzyme specific activity, while phosphorylation at Tyr132, in contrast, does not affect enzyme activity but creates a binding site for the adaptor protein Grb2 [37]. Finally, in response to PDGF, the cytoskeleton-associated pool of LMW PTP has been reported to be strongly phosphorylated by the c-Src tyrosine kinase. As a consequence of its phosphorylation, LMW PTP increases its catalytic activity about 20-fold and causes a feedback loop acting on the phosphorylated PDGF-r, thus determining the termination of the signal [38]. Interestingly, LMW PTP is not phosphorylated in response to insulin, thus suggesting a degree of specificity in growth factor (GF) signalling through this PTP [39].

To come to the point, the picture that emerges from the data concerning PTP tyrosine phosphorylation, although there are a few exceptions, identity this posttranslational modification as a positive modulator of phosphatase activity operating in response to RTK activation.

Integration and balance of the dual regulation

This outline of a concomitant but opposing regulation of PTPs by tyrosine phosphorylation and oxidation encourages a provocative perspective on dualistic PTP regulation.

A first issue to be addressed, is the temporal and spatial separation of the double regulation. Meng et al. [12] reported that in response to PDGF, the kinetics of SHP2 oxidation reaches a maximum between 2–5 min, in apparent concomitance with the peak of its tyrosine phosphorylation by PDGF-induced signalling [and M. L. Taddei, unpublished data]. Conversely, LMW PTP oxidation and tyrosine phosphorylation in response to PDGF display dissimilar kinetics, the former having a peak at 10 min and the latter at 20 min. A differential temporal distribution may suggest that the maximum of catalytic inactivation (due to oxidation) precedes the superactivation (due to tyrosine phosphorylation) of a given PTP. This may guarantee that during PTP oxidation, the signal elicited by a given substrate (i.e. PDGF-r) may be assured, while at the recovery of the phosphatase activity, via thiolreduction, the enzymatic activity of the PTP is further enhanced to assure the rapid termination of the signal.

Another intriguing possibility that can justify the coexistence of opposite regulations of a given PTP in response to the same hormonal signal may be a spatial separation of oxidised and tyrosine-phosphorylated PTP pools during signalling. Unfortunately, the only available data supporting this viewpoint are related to LMW PTP, which is split in response to PDGF into a cytoskeleton associated and tyrosine-phosphorylated pool and a cytosolic, membrane-recruited and oxidized pool [40].

A second point to be addressed is the possibility that each regulation may influence the other. Again the available data are very few, likely owing to experimental difficulties in separating the two phenomena. Remarkably, the oxidation of a given PTP may influence its tyrosine phosphorylation state. The first concept that we want to reinforce is that oxidized/inactive PTPs can be phosphorylated by their cognate PTKs even more rapidly than their reduced/active counterparts. This effect could be due to either a conformational change of the oxidized PTP and/or to a block of autophosphorylation. Meng et al. [12] reported that the oxidized SHP2 is hyperphosphorylated with respect to the reduced SHP2, likely due to redox-mediated inactivation of the autocatalytic activity. In agreement, the tyrosine phosphorylation of oxidized PTP1B in response to insulin receptor kinase (IRK) activation was greatly enhanced [17]. Again the redox-mediated inhibition of the autocatalytic activity of PTP1B was indicated as responsible for the hyperphosphorylation of the oxidized, phosphatase. These indications suggest that tyrosine phosphorylation of an oxidized i.e. transiently inactive, PTP may be preparatory for the consecutive phase, i.e. the reduction-mediated recovery of activity. In this way, the tyrosine phosphorylated, newly reduced PTP may recover an enhanced enzymatic activity, thus guaranteeing a more efficient termination of the RTK signal. The tyrosine phosphorylation of an oxidized PTP may eliminate the problem of continuous autodephosphorylation and warrants that at the recovery step, the highest enzymatic activity is reached. In this light, the twin function of PTPs during RTK signalling, i.e. the oxidation-mediated inactivation yielding RTK signal transduction and the following rescue of catalytic activity culminating in termination of the signal, may be improved by superimposing the oxidation/reduction and tyrosine phosphorylation of a given PTP (see fig. 1).

This viewpoint is further strengthened by data on the disruption of the complex between a given PTP and its substrate upon oxidation. Although the recruitment of SHP2 to PDGF-r is required for oxidation of the phosphatase

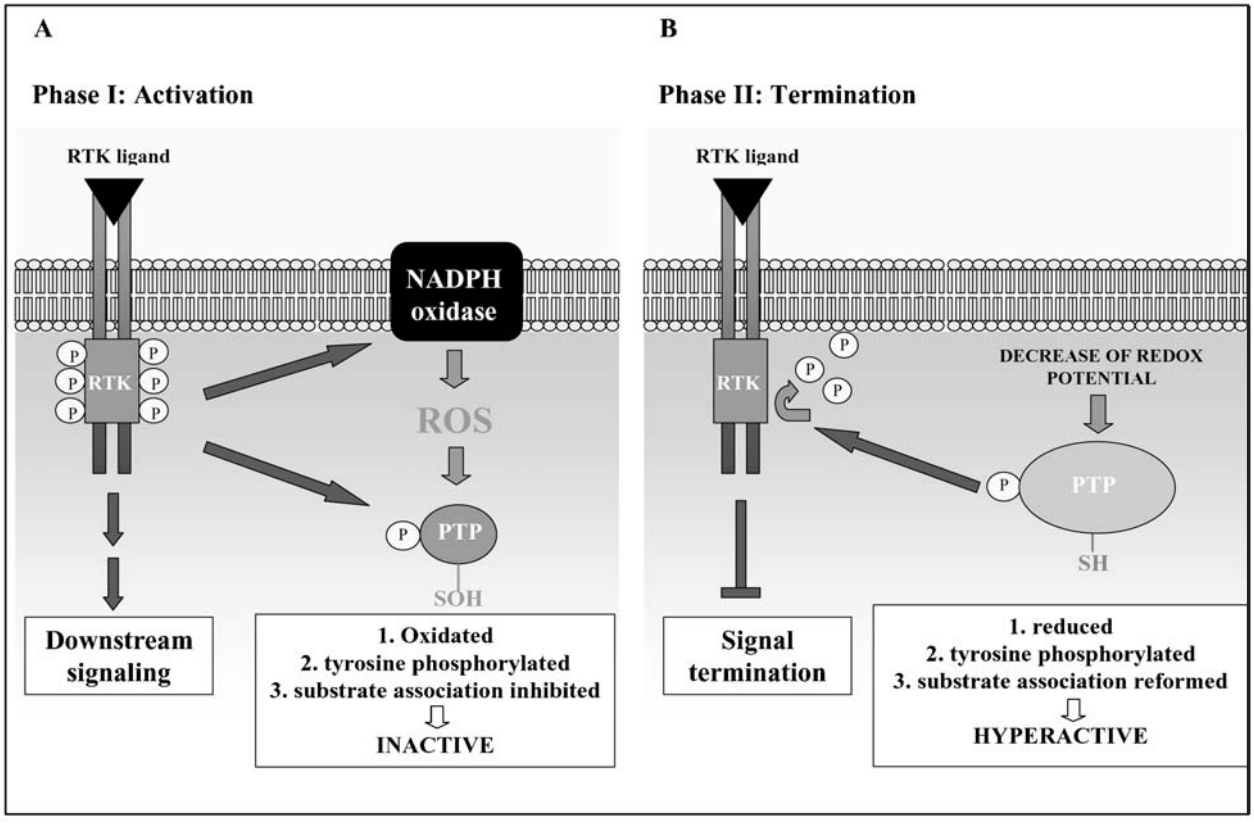

Figure 1. Proposed model of PTP regulation by oxidation and tyrosine phosphorylation during growth factor stimulation. (*A*), During the early phase of tyrosine kinase receptor activation, ROS production is able to oxidise and inhibit the RTK-recruited PTPs. During this phase, PTP are concomitantly phosphorylated following the receptor activation. These events result in a complete inactivation of PTP catalytic activity and in their hyperphosphorylation. The final effect is the propagation of signal transduction events downstream of receptor activation. (*B*), During the second phase of growth factor signalling, the decrease of intracellular oxidants allows recovery of the reduced state of PTPs. In this phase, PTPs are still phosphorylated, owing to their previous inactivation/oxidation. Hence, PTPs now become hyperactive, due to both the recovery of their reduced state and to the phosphorylation-mediated enhancement of their activity. In this condition, PTPs are able to efficiently dephosphorylate their substrates, i.e., RTKs, thus terminating the elicited signal.

[12], their association is disrupted by the oxidation of the catalytic thiol group of SHP2. In agreement with these data, the oxidation of PTP1B during insulin signalling is accompanied by large conformational changes in the catalytic site that inhibit substrate binding [17]. Finally, oxidation of the catalytic thiol of LMW PTP disrupts the association with PDGF-r or focal adhesion kinase (FAK), during mitogenic or integrin signalling, respectively [41 P. Chiarugi, unpublished data]. Thus, in addition to the redox-mediated inactivation upon RTK commitment, interference with substrate binding upon PTP oxidation may cooperate in the transmission of an active signal by a ligand-engaged RTK.

In light of these considerations on the double regulation of PTPs during RTK signalling, we propose the revision of a previous model [18]. After ligand engagement, RTKs need a first phase in which their tyrosine phosphorylation level must be high to guarantee signal propagation (fig. 1A). This high level is granted by transient oxidation of PTPs and by the disruption of association with their receptor substrates. The concomitant tyrosine phosphorylation of oxidized PTPs, performed in response to RTK activation, is ineffective on their abolished enzymatic activity and preparative for the second phase. Afterwards, RTK signalling needs termination to avoid cell transformation (fig. 1B). In this phase, PTPs recover enzymatic activity due to re-reduction of the catalytic thiol group, and immediately become hyperactive due to their previous tyrosine phosphorylation, thus granting the rapid and efficient termination of the signal. Therefore, the redox inhibition of PTPs likely has an important function in RTK signalling, and the rescue (via re-reduction) of the PTP catalytic activity after oxidation is probably followed by a dephosphorylation of activated receptors, consequently terminating the signal. Hence, the ROS produced after RTK engagement may be considered as intracellular second messengers, actually involved in the signal transduction machinery of many ligands. They lead to a feedback loop that, throughout the inhibition of PTPs, results in an up-regulation of RTK tyrosine phosphorylation and finally in their activation. Moreover, tyrosine phosphorylation of PTPs could also act as recruitment sites for either positive or negative regulators of signalling elicited by cytokines and growth factors [42]. In this condition, the oxidation/inactivation of a given PTP, may become particularly important in preserving the phosphotyrosine docking site of the PTP, and finally determines signalling outcome. Here, PTPs, while tyrosine phosphorylated, may act simply as adapter molecules, as recently reported for SHP1 during Grb2/Socs1 binding [42] and for LMW PTP during Grb2 recruitment [P. Chiarugi, unpublished data].

Finally, we speculate that such a complex and intricate interplay between RTKs and PTPs may cause specificity of different signals. We suspect that the kinetics and the relative intensities of redox- and phosphorylation-based regulation of PTPs may differ greatly among GFs. This may imply that upon differential hormonal stimuli, able to differentially elicit a burst of oxidants and a tyrosine phosphorylation response, the balance and the duration of both inactivation and superactivation of PTPs may vary, thus conferring specificity to different signals. To support this speculation, we have reported that both SHP2 and LMW PTP are tyrosine phosphorylated during PDGF but not during insulin signalling [43, 44], while both these GFs are able to elicit a ROS boost. During insulin signalling, the propagation of the signal is conceivably assured by the redox inactivation of SHP2 and LMW PTP, while the termination of the signal may be less efficient due to the lack of PTP superactivation.

We hope that our perspective, owing to its highly speculative nature, will open a new perception of role of dual PTP regulation during RTK signalling, and possibly encourage original and innovative approaches that bypass the experimental barriers that, at present, have impeded complete clarification.

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