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Minireview

Redox regulation of protein-tyrosine phosphatases

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Abstract

The protein-tyrosine phosphatases (PTPs) form a large family of signaling proteins with essential functions in embryonic development and adult physiology. The PTPs are characterized by an absolutely conserved catalytic site cysteine with a low pK_a due to its microenvironment, making it vulnerable to oxidation. PTPs are differentially oxidized and inactivated in vitro and in living cells. Many cellular stimuli induce a shift in the cellular redox state towards oxidation and evidence is accumulating that at least part of the cellular responses to these stimuli are due to specific, transient inactivation of PTPs, indicating that PTPs are important sensors of the cellular redox state.
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Phosphorylation of proteins on tyrosine residues is one of the most important regulatory cell signaling mechanisms, controlling cell proliferation, differentiation, and migration. Cellular phosphotyrosine levels are regulated by the antagonistic activities of two classes of enzymes, the protein-tyrosine kinases (PTKs)[1] and the protein-tyrosine phosphatases (PTPs). Until recently, little was known about regulation of PTPs, but now oxidation is emerging as an important regulator of PTPs.

The catalytic cysteine of PTPs is a target for oxidation

The human genome encodes approximately 100 genes that belong to the PTP superfamily with conserved catalytic sequences, including the absolutely conserved active site cysteine. Approximately 40 of these genes encode the classical PTPs that are highly specific for phosphotyrosine [1]. The other PTP superfamily members include the low molecular weight (LMW) PTPs, dual specificity phosphatases (DSPs), and lipid phosphatases, among which is the important tumor suppressor PTEN [2]. Roughly half of the classical PTPs contain a single transmembrane domain and are tentatively called receptor PTPs (RPTPs). Most RPTPs have two conserved cytoplasmic PTP domains of which the one closest to the cell membrane (D1) contains most—if not all—catalytic activity [3]. The membrane distal PTP domain (D2) has a regulatory role.

Due to their microenvironment, the catalytic cysteines have a low pK_a [4,5]. Under normal conditions, the active site cysteines are in the thiolate anion form and therefore, they are highly susceptible to oxidation. By now, members of each subfamily have been shown to be oxidized by treatment with oxidizing agents (e.g., H_2O_2), including classical PTPs [6], LMW PTPs [7], DSPs [8], and lipid phosphatases [9]. Oxidation of the catalytic cysteine blocks the capacity of these enzymes to dephosphorylate their targets, because catalysis is mediated by transfer of the phosphate moiety from the substrate to the catalytic cysteine, followed by rapid hydrolysis of the phosphate [10]. In general, oxidation of

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[1] *Abbreviations used:* PTK, protein-tyrosine kinase; PTP, protein-tyrosine phosphatase; LMW, low molecular weight; DSP, dual specificity phosphatase; RPTP, receptor PTP; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; DCF, dichlorofluorescein; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; FRET, fluorescence resonance energy transfer; GFP, green fluorescent protein.

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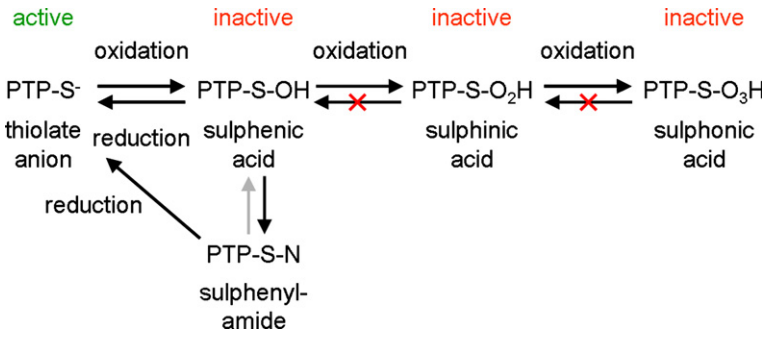

Fig. 1. Oxidation of PTPs. The catalytic cysteine is in the thiolate anion form under normal conditions due to its low pK_a. Oxidation leads to sulfenic acid formation and further oxidation leads to irreversible sulfinic and sulfonic acid formation. Sulfenic acid is rapidly converted to cyclic sulfenylamide. Sulfenylamide cannot be further oxidized to sulfinic or sulfonic acid, but can be reduced to the thiolate anion form in response to thiols. Only the reduced form is catalytically active.

cysteine residues to sulfenic acid is reversible, while highly oxidizing conditions will induce further oxidation to sulfinic and sulfonic acid, which is irreversible [8]. Recently, a novel bond was found to be formed upon oxidation of the classical cytoplasmic PTP1B, which was termed sulfenylamide or sulfenamide [11,12]. The crystal structure of oxidized PTP1B revealed that sulfenamide is characterized by a five-membered ring that forms by binding of the sulfur of the cysteine to the backbone nitrogen of the neighboring serine residue (Fig. 1). Conversion of sulfenic acid to sulfenamide is fast, because sulfenic acid was not observed in PTP1B crystals upon oxidation. Interestingly, sulfenamide—unlike sulfenic acid—is not easily further oxidized to sulfinic and sulfonic acid. Given the high conservation of the catalytic sites in the PTP family, cyclic sulfenamide formation may be a general mechanism of oxidation. Cyclic sulfenamide can be reduced by thiols, including glutathione. The sulfenic acid form and presumably also the cyclic sulfenamide form of PTP1B is readily converted in the presence of glutathione to the more stable S-glutathionylated PTP1B [13], which can be reduced by DTT or thioltransferase.

Cyclic sulfenamide formation protects classical PTPs against inadvertent irreversible further oxidation to sulfinic and sulfonic acid. S-glutathionylation also prevents irreversible oxidation of PTPs. Another protective mechanism that was discovered in non-classical PTP superfamily members is disulfide bond formation. In LMW-PTP, CDC25, and PTEN, intramolecular disulfide bonds involving the catalytic cysteine and an adjacent cysteine have been observed [7,9,14]. Intramolecular disulfide bond formation involving the catalytic cysteine of classical PTPs has not been reported to date.

Physiological stimuli that regulate PTPs by oxidation

Many stimuli, including growth factors, cytokines, and ultraviolet (UV) light, induce the production of reactive oxygen species (ROS). Evidence is accumulating that ROS production in response to growth factors is mediated by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase protein complex (for reviews, see [15,16]). Intracellular ROS levels in response to natural stimuli have been determined using fluorescent ROS indicators, such as derivatives of dichlorofluorescein (DCF). For instance, platelet-derived growth factor (PDGF) induces ROS levels in cells that are comparable to the levels in cells resulting from exogenously added H_2O_2 concentrations of 0.1–1.0 mM [17]. Given the sensitivity of PTP catalytic cysteines to oxidation in vitro, these PDGF-induced ROS levels are more than sufficient to oxidize active site cysteines in PTPs.

Growth factor signaling is actually dependent on ROS production, since ROS quenching abolishes growth factor signaling [17,18]. Epidermal growth factor (EGF)-induced ROS production coincides with inhibition of PTP1B activity [18]. Inactivation of PTPs by growth factor-induced oxidation would explain why ROS are essential for growth factor signaling. In fact, mathematical analysis of the minimal reaction network involving a growth factor receptor PTK on the one hand and PTPs that are inactivated by oxidation upon PTK activation on the other mimics experimental EGFR phosphorylation in cells [19], corroborating the PTK-induced ROS-mediated PTP inactivation model. Meng et al. [20] provided compelling evidence for the growth factor-induced PTP inactivation model using a modified in gel phosphatase assay that allows detection and identification of oxidized PTPs. This assay was validated using H_2O_2 that induces oxidation of multiple PTPs in Rat-1 cells in a concentration-dependent manner. The SH2-containing PTP, Shp-2, is specifically and transiently oxidized in response to PDGF in Rat-1 cells. PDGF-induced signaling is reduced in the presence of *N*-acetylcysteine, a ROS-quencher, indicating that ROS-mediated inhibition of PTPs is essential for PDGF signaling [20]. Association of Shp-2 with the PDGF

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