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STUDIES OF SELECTIVE TISSUES DEVELOPMENT OF PROTEIN TYROSINE PHOSPHATASES AND EFFECT OF OXIDATIVE STRESS IN *ARACHIS HYPOGAEA L*

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ABSTRACT

Phosphorylation of tyrosine residues in protein has been envisaged to play a crucial role in the regulation of a variety of cellular processes, including the signal transduction and development in higher plants. The protein phosphorylation is around regulated by both protein kinases and specific protein phosphatases. The activity of Kinases and phosphatases can be modulated by the oxidation or reduction. The oxidative stress-mediated oxidation of PTP by hydrogen peroxide, superoxide or by hydroxyl radical could regulate the transduction of signals from the membrane to the nucleus via the modulation of cellular enzymatic activity. The present studies carried out that the peanut (*Arachis hypogaea L.*) seedling grown in dark on moistened whatman filter paper at 28±2˚C, localized tissue specific multi-cellular forms of protein tyrosine phosphatases (PTPases). The level of PTPases was increased by several-fold during the 6 to 10 days of germination period. The oxidative stress is carried out by treating seedlings with 1% H_2O_2 for 2-3 hours, resulted in 2.0 fold increases in the level of PTPase activity, which was followed by slowly decline in the PTPase activity and 4 hours treatment, the level of PTPase activity was decreased as compared to the untreated seedlings. The specific activity (unit/mg-protein) of PTPase was increased in the order Cotyledon, Epicotyls, Roots and highest in Hypocotyls when different part of seedlings were treated with 1% H_2O_2 for 3 hours. The specific activity was decreased as compared to untreated seedling. These results suggest that the most of signaling pathways may be influenced by oxidative stress of protein tyrosine phosphatases, consequently leading to an aberrant phosphorylation state of cellular proteins and role of protein tyrosine phosphatases in stress-related cellular processes.

Keywords: *Arachis hypogaea* L, Peanut, PTPase, protein kinases, protein phosphorylation and dephosphorylation, oxidative stress.

INTRODUCTION

The reversible phosphorylation of proteins is involved in the regulation of a cellular processes in eukaryotes (Hunter T 1995, 2000), including signaling pathways (Chernoff T.1999, Iten M Hoffman & T. Grill 1999), environmental stresses (Ischimura *et al.,* 2000) and developmental processes (Den Hertog J. 1999). Protein tyrosine phosphatase (PTPase) is central player in many biological processes (Michel, L Tremblay 2009). Phosphorylation on tyrosine residues is a key signal transduction mechanism known to regulate intracellular and intercellular communication in multi-cellular organism (Isabelle R. *et al.,* 2009). The major role of the PTPases is Cell growth, replication, mitosis, transformation of oncogenes, and receptor endocytosis (Dutta *et al.,* 2015). Natural plant phytochemicals also showed high efficiency in binding with the active site of the PTPases in prostate cancer in silico docking analysis (Singh AN *et al.,* 2017). The protein tyrosine phosphatases involve in the developing of new innovative drugs against various classes of target enzymes (Venkata Raghavan R, *et al.,* 2018).

Protein kinases and protein phosphatases that catalyze these processes and modulate the phosphorylation of the target proteins, are classified into two major groups, depending their substrate specificities (i) protein serine / threonine kinases / phosphatases and (ii) protein tyrosine kinases / phosphatases while serine / threonine protein kinases / phosphatases are well characterized and play a prominent role in various processes of plant growth and development (Luan S. 2003).

In nature, plants are exposed to various stresses, which affect their physiology, morphology and development (Shu, Hsien Hung *et al.,* 2005). Some protein phosphatases are induced by heat shock, cold shock, draught and high salt concentration (Tahtiharuja S, and Palva T, 2001). These are found to be regulated developmentally (Casamayor A *et al.,* 1994).

Studies of protein kinases/phosphatases have shown that mitogen activated protein kinases (MAPKs) are activated by H_2O_2 in both animals and plants, which could lead to the modulation of gene expression (Torres, M and H J Forman 2003). In addition to protein kinases, tyrosine phosphatases have been shown to be inactivated by hydrogen peroxide in mammals (Cho, S H *et al.,* 2004) and phosphatases may be involved in H_2O_2 signaling in plants too. The Arabidopsis protein phosphatase 2C enzymes

ABI1 and ABI2 and the protein tyrosine phosphatase AtPTP have been suggested to play such a role (Gupta R, Luan S, 2003). Interestingly, AtPTP regulates the activity of MAPKs, suggesting a tight link between H_2O_2, kinases and phosphatases.

Recently, Cheong, *et al.,* 2002, have reported that wounding and other stress conditions regulate protein phosphatases of genes. Bose and Taneja, (1998), have reported the germination specific induction of low molecular mass protein tyrosine phophatase in lentil (*Lens esculenta*) seeds. They also showed that the level of protein tyrosine phosphatase activity varied greatly in different parts of the seedling, indicating tissue specific localization of protein tyrosine phosphatases.

There is growing recognition that reactive oxygen species as well as reactive nitrogen and sulphur species, are as fundamental part of the basic communication chemistry of cells and organism as calcium (Ghezzi P *et al.,* 2005). Production of ROS serves highly localized and specific signaling functions both in stress response and in hormonal physiological processes as well as development (Wu, J I, and Bennutt 2005). Phosphatases contain readily oxidizable (Low Pka) active site cysteins residues (Stone J R., 2004) because phosphatases are involved in regulation of kinases; redox regulation of phosphatase activity can in turn regulate the activity of its target kinases (N K Tonks, 2005).

H_2O_2 can play a dual role in cells. During oxidative stress, H_2O_2 is a strong oxidant causing a cell damage or even cell death. At the same time it serves conversely as a signaling molecule to activate a rescue / defense system for restoring the redox homeostasis in plant cells. In addition, H_2O_2 is involved in mediating biological process (Desikan R, 1998). ABA mediated stomata closure (Pei, Z-M, 2000), auxin-regulated gravitropic response (Joo, J H, *et al.,* 2001) interestingly, despite clear evidence for involvement of H_2O_2 in the intracellular regulation of PTPs, in vitro experiments reveal that H_2O_2 at physiological concentrations, rather sluggish PTP inactivators (Ross, S H, *et al.,* 2007).

Reactive oxygen species (ROS) play basic role in the regulation of biological processes and behave as signaling molecule in mediating response to various stimuli (Laloi C *et al.,* 2004). It is recognized that ROS especially H_2O_2 have a major role in cellular signaling pathways, across a wide range of organisms, including plants (Droge W, 2002; Foyer, C H and Noctor G 2005b). ROS can be generated in plants via the leakage of electrons from mitochondria or photosynthesis, or can be synthesized by a variety of dedicated enzymes, such as peroxidases and NADPH oxidases (Neill, S *et al.,* 2002).

Some 40-odd genes in mammals encode phosphor-tyrosine specific, 'classical' Protein Tyrosine Phosphatases (W J Hendriks *et al.,* 2008), and several comprehensive reviews on PTPs chemistry have been published so far (N K Tonks, 2006; F Liang, S. Kumar, Z-Y. Zhang. 2007). Structurally, PTPs possess a conserved 230 amino acid domain with an essential Cys residue in the active site with a lower pKa than of Cys thiol. At neutral pH, the Cys-thiol groups were deprotonated being susceptible to oxidation by reactive oxygen species (ROS). Moreover, the signaling properties of ROS are largely attributable to the reversible oxidation of the redox-sensitive cysteine of PTPs (J-I. Abe, C- H. Woo, 2009). Oxidation inhibits the nucleophilic property of PTPs required for substrate dephosphorylation, and makes these enzymes inactive (N K Tonks, 2005; J-I Abe & C- H Woo 2009).

Control of key metabolic enzymes by reversible phosphorylation has been studied extensively in plants (Ranjeeva R and Bouder A M, 1987) for example, sucrose phosphate syntheses and nitrate reductase are activated by decrease in the phosphorylation status (Hurber S C *et al.,* 1994), and in contrast phosphoenol pyruvate carboxylase is activated by phosphorylation. Since sucrose phosphate syntheses, nitrate reductase and phosphoenol pyruvate carboxylase are key enzymes that control nitrogen and carbon assimilation in plants mechanism must exist to regulate their relative activities in response to environmental and metabolic conditions. Coordination of these pathways might control the activities in cytosol. So, protein phosphatases and protein kinases respond differently to signals in the cells. Here we report the development tissue specific localization and effect of the oxidative stress on the level of protein tyrosine phosphatases in peanut seedlings.

MATERIALS AND METHODS

Peanut seeds were collected from seed storage, washed with double distilled water and surface sterilized with 1% (w/v) $HgCl_2$ solution and allowed to germinate under aseptic conditions for 0-14 days according to previously description (Devi S I, *et al.,* 2005) various (Fig. 1) plant parts (root, hypocotyls, epicotyls and cotyledon) were excised manually and the crude enzyme extract was prepared by homogenizing the different tissues of plants (10 gm fresh weight each in 30 ml) in the homogenizing the different buffer (100mm Tris-HCl, pH 7.6, containing 10mm EDTA, .04% β-mercaptoethanol) at 0-4˚C. The homogenate was filtered through 4 layers of autoclaved cheesecloth. The filtrate was centrifuged at 9000 rpm for 30 minutes at 0-4˚C. The supernatant (crude enzymes extract) was collected and used for enzyme assays.

Protein tyrosine phosphatase activity was assayed by using O-phospho-L-tyrosine (Sigma) as a substrate the reaction mixture contained the following components in a total volume of 200 µl: enzyme (20-200 µg protein), 100mm Tris-HCl (pH 7.6), 0.5mM EDTA and 0.5mM O-phospho-L-tyrosine substrate. After 30-minute

incubation at 30˚C the reaction was terminated by adding 250µl 10 % trichloro acetic acid (TCA) and the migratory was kept in ice bath for 30 minute to allow complete precipitation of protein. The insoluble matter was removed by centrifugation at 9000 rpm for 10 minutes in refrigerated centrifuge at 0-4˚C**.** An aliquot (100 µl) of the clear supernatant of the reaction mixture was assayed for inorganic phosphate (Pi) by the malachite green method which was described by Lenzetta, *et.al.,* 1979) with the exception that Sterox was omitted for the determination of protein tyrosine phosphatase (PTPase) was carried out in similar way using, O-phospho-L-tyrosine as substrates, respectively, instead of Casein (10mg/ml). One unit was defined as "the amount of protein (mg) that liberated one nanomole of inorganic phosphate (Pi) per minute under assay condition".

The oxidative stress was applied by immersing the seedlings in 1% H_2O_2 for 0-6 hrs than immersing different parts of seedling (root, hypocotyl, epicotyl and cotyledon) in 1% H_2O_2 for 3 hours. Protein concentration was measured by the methods of Lowry *et al.,* (1951) using bovine serum albumin (as standard). Interaction between catechin and native and modified bovine serum albumin has been studies by J.P.S Arora, *et al.,* 1989.

RESULTS AND DISCUSSION

The specific activity (units / mg-protein) of protein tyrosine phosphatase have increased at least 2.5 fold between 6-10 days of germination period. After 8 days the increase in the level of PTPase activity started to decline, indicating that the biosynthesis of the enzyme was dependent on germination period (Fig. 2). Table-1 shows the level of PTPase activity in different parts of peanut seedlings, viz. root, hypocotyl, epicotyl and cotyledon, the highest specific activity of PTPase (Units / mg-protein) was found in hypocotyl followed by root, epicotyl and cotyledon. The distribution of the PTPase for instance the enzyme activity was highest in cotyledon followed by hypocotyl, epicotyl and root. Interestingly distribution patterns of protein tyrosine phosphatase in all parts of the seedlings were nearly identical (data not shown). Figure-3 represents the protein band profile of PTPase using SDS-PAGE. For example, the root contained two molecular forms of PTPase corresponding to proteins of molecular masses of at least 67.60kDa and 29.15kDa, the hypocotyls contained two molecular forms of PTPase corresponding to apparent molecular masses 66.7kDa and 29.10kDa, the epicotyls contained relatively low levels of PTPase migrating the marker proteins of 67.70kDa and 28.50kDa and the cotyledon contained both a high molecular form of PTPase, the former co-migrated with the higher forms of PTPase 116.0kDa, 67.60kDa and 20.4kDa.

The PTPase activity (Units/mg-protein) in the whole seedling was increased approximately 2.0 fold during the first 3h of treatment, followed by a rapid decline in the PTPase activity level due to the oxidative stress (Fig.4). Figure-5 represents the protein band profile of PTPase after treatment of the peanut seedlings by 1% H2O2 for different hours using SDS-PAGE. Some protein bands were expressed and some other reduced after oxidative stress. The effect of oxidative stress on PTPase activity in different parts of the seedling shows that the PTPase activity decreased PTPase activity decreased significantly in hypocotyls, while in cotyledon, epicotyls and roots the PTPase activity increased by 20-30% (Fig. 6). These results clearly indicate that the oxidative stress had a profound effect on the specific activities of PTPase in the germinating peanut seedlings.

Although a number of PTPases have been identified, isolated, purified and characterized. The chemistry by which oxidative species regulate PTPase is relatively well characterized, but the exact mechanism (s) by which these species themselves are produced and regulated remain unclear (Rhee S G, 2006). Limited information is available regarding their function or role in plant development and physiology. The present study demonstrates that both PTPase and total activity of peanut seedlings increased by approximately 2.5 fold, respectively during germination period of 0-14 days at 28±2 ˚C in dark. Further the levels of PTPase activity in different parts of the seedlings vary greatly. Peanut seedlings are known to show high sensitivity to environmental stresses especially to hours and oxidative stress (Ketring D L 1984). We have also observed in vivo oxidative stress on PTPase activity. H_2O_2 can play a dual role in cells. During oxidative stress, H_2O_2 is a strong oxidant causing all damage or even cell death. At the same time, it serves conversely as a signaling molecule to activate a rescue / defence system for restoring the redox homeostasis in plant cells. In addition, H_2O_2 is involved in mediating biological process (Desikan *et al.,* 1999). The peanut seedlings showed two distinct effects, which were time dependent. There was a marked increment approx (2.0 fold) in the PTPase activity of the peanut seedlings up to 3 hours of 1% H_2O_2 treatment, whereas oxidative stress is longer than 3 hours resulted in slowly decline of the PTPase activity, which induced PPase as well.

H_2O_2 inhibits phosphatase activities, probably by the direct oxidation of cysteine in the active site of these enzymes. H_2O_2 may activate transcription by directly oxidizing. H_2O_2 responsive transcription factors via oxidation of thiols of cysteine residues in proteins. Since H_2O_2 activated mitosis activated protein lineage cascade (MAPLC) in plants. Xu, Q, *et al.,* 1998 reported a tyrosine specific protein phosphatase encoded by a stresses responsive gene, in Arabidopsis, and suggested that PTPase may represent a primary targets for the oxidative stress in higher plants inbeing cellular processes which require PTPase activity like stomated closure (Mac Robbie, E A C 2002). Den Hertog, J. Groen, A. and van der Wijk, T., 2005) reported based upon the studied of oxidative stress

Fig-1 A population of 0-14 days old germinating seedlings. Peanut (*Arachis hypogaea* L.) Were germinated on whatman (3mm) filter paper moistened with sterile double distilled water in dark at 28 ± 2°C under aseptic conditions in a seed germinated chamber. Note the different anatomical parts which are clearly visible in the seedlings only healthy seedling were used.

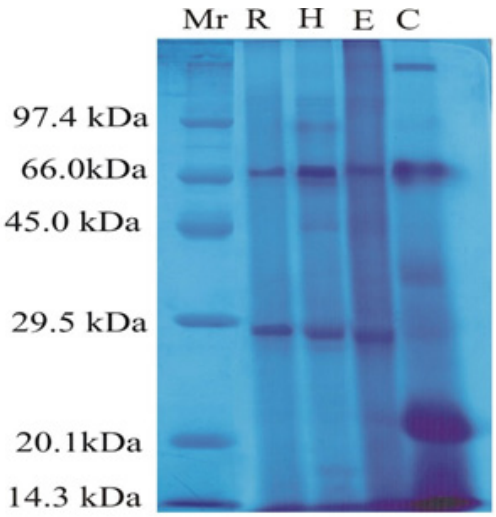

Fig.3- Comparisons of protein bands profile by SDS-PAGE of different part of 8 days old germinated peanut (*Arachis hypogaea* L.) Seedlings. Protein were stained by CBBR-250 dye. The standard marker are as follows:- 14.3K.Da- ysozyme, 20.1 kDa- Trypsin inhibitor, 29.5 kDa-Carbonic anhydrase, 45.0 kDa- oval albumin, 66.0kDa - BSA, 97.4 kDa - phosporylase-b.

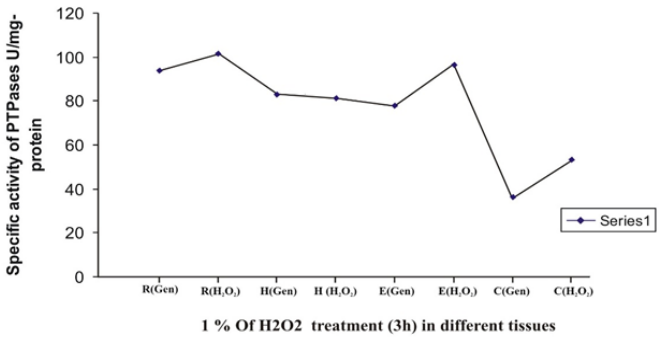

Fig. 6 Specific activity of PTPases in different part of seedlings using 1% o H2O2 after 3hours treatment.

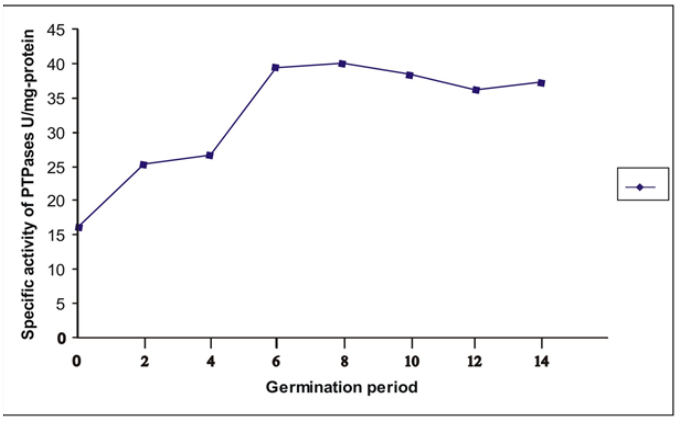

Fig-2 Induction of Specific activity of PTPasc during germination period (0-14 days) in peanut (*Arachis hypogea* L.) Seedlings were germinated on what man filter paper (3-4 layers) moistened with double distelled water at 28± 2°C in dark under aseptic, condition for the indicated periods. Seedlings were harvested and immediately Processed. The PTPase activity was measured using O-phospho L- tyrosine as substrate.

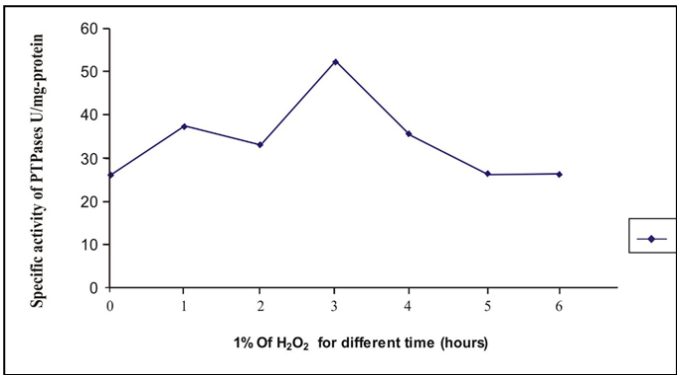

Fig. 4 Specific activity of PTPases after treatment with 1% of H2O2 for different hours on 8days old germinating seedlings

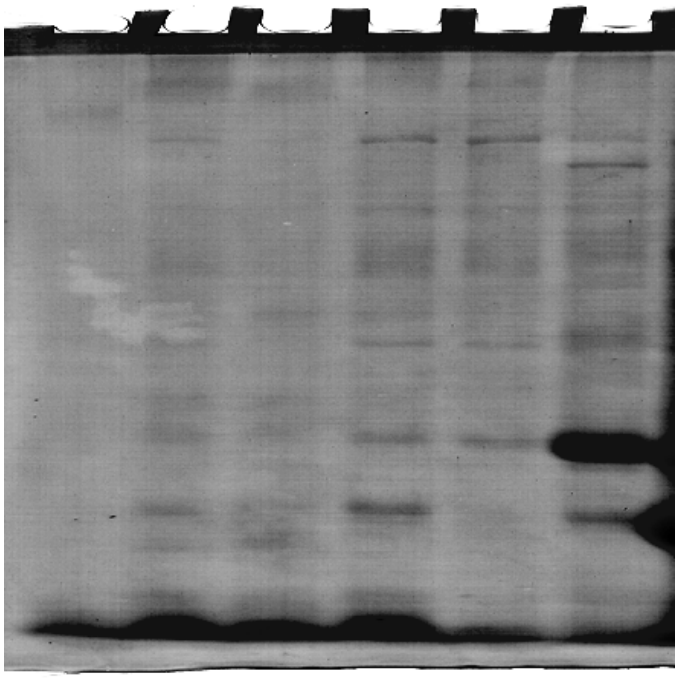

Fig. 5 Comparison of protein band profile using SDS-PAGE. 8 days old germinated seedlings of *Arachis Hypogea* were stressed in 3% of H2O2 for different hours.

Table.1-Distribution of specific activity of PTPase in well developed parts of 8 days old germinated peanut (*Arachis hypogaea L.*) seedling.

S. No	Plant tissues	Specific activity of PTPases (U/mg-protein)
1	Root	81.0
2	Hypocotyl	83.0
3	Epicotyl	78.0
4	Cotyledon	32.0

Table.2-Specific activity of PTPase after treated with 1% hydrogen peroxide for 3 hours in different tissues of peanut (*Arachis hypogaea L.*) seedlings.

S. No	Different Tissues	Specific activity of PT-Pases (U/mg-protein)
1	Root (Gen)	93.97
2	Root (H_2O_2)	101.9
3	Hypocotyl (Gen)	82.98
4	Hypocotyl (H_2O_2)	81.67
5	Epicotyl (Gen)	77.80
6	Epicotyl (H_2O_2)	96.53
7	Cotyledon (Gen)	36.34
8	Cotyledon (H_2O_2)	53.10

that an oxidation / reduction cycle of PTPase can serve as a molecular switch of sorts, that regulates catalytic activity. Alka Shankar *et al.,* 2015 also reported the role of protein tyrosine phosphatases in the regulation of post-translational modification in plant physiology and development.

Future Perspectives

Phosphorylation or dephosphorylation of signaling molecules can cause many complications and diseases. The use of inhibitors can modulate the activity of specific phosphatases or kinases which may be further used for the study of cell signaling, development of drugs. These results show the role of oxidative stress-related kinases and phosphatases in a cell may provide unique and generic possibilities for the future development of therapeutic strategies by targeting the dys-regulated protein kinases and phosphatases in a clinical setting.

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