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Full Length Research Paper

Significant pathway analysis of *Arabidopsis thaliana* following treatment with paraquat (PQ)

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Paraquat (PQ), as a non-selective herbicide, has been used worldwide for weed control in agriculture. However, some medicine plant would be also weeded in this process. Thereby, herbicide antidote is advocated. In this study, we performed two pathway analysis methods, namely, component-based approaches and protein-protein interaction (PPI)-based approach, to identify more significant pathways associated with PQ application. The results showed that eight pathways were identified in component-based analysis, but twenty-two pathways were in PPI-based approach. Among them, phenylalanine metabolism and ribosome pathways were significant in two analysis methods. We anticipate that more PQ antidote would be developed based on our analysis.

Key words: Paraquat, significant pathway enrichment, *Arabidopsis thaliana.*

INTRODUCTION

Paraquat (1,10-dimethyl-4,40-bypiridilium, PQ), as a non-selective rapid-action bipyridyl herbicide, has been used worldwide since 1960 for the control of broadleaf weeds in agriculture (Qian et al., 2009). PQ exerts a phytotoxic effect by transferring electrons from photosystem I (PSI) of the chloroplast membrane to molecular oxygen. This action leads to the formation of superoxide anions, singlet oxygen and hydroxyl and peroxyl radicals (Yu et al., 2009). In turn, excess superoxide results in the production of deleterious hydroxyl radicals and hydrogen peroxide by a variety of reactions such as deoxyribonucleic acid (DNA) damage, protein degradation and lipid peroxidation. Thereby it affects key components of plant cell metabolism and initiates the accumulation of oxidative stress. PQ belongs to a non-translocated herbicide when it is applied foliar, but PQ's derived toxic products are able to diffuse within the cell from their site of production in the chloroplast to the tonoplast and plasmalemma where their actions stimulate the visible symptoms of wilting and necrosis (Yonova et al., 2009). Although, there is evident that Chinese herbal medicine is tolerant to PQ (Chun et al., 1997; Piao et al., 2008), field experiment still finds unavoidable weeding, such as *Scutellaria baicalensis* and *Purple perilla*. In consideration of this phenomenon, there is a continuous need for the development of selective herbicide or more herbicide tolerance of sensitive cultural plants.

The second way may be realized by using herbicide antidotes. Currently, limited evidences in the literature are presented on PQ antidotes. Foliar spray of *Arabidopsis thaliana* with 1.0 mM salicylic acid (SA) significantly improved their tolerance to subsequent PQ -induced oxidative damage and effectively retarded rapid decreases in the activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase(CAT), ascorbate peroxidase (APX), guaiacol pemxidase (POX) and peroxidase (POD) (Kim et al., 2003). Identically, these results were demonstrated in barley plants when pretreatment with SA (Ananieva et al., 2004). Studies have shown that some polyamines (putrescine, cadaverine and spermidine) when applied concomitantly with PQ could reduce the toxic effects of PQ (Kurepa et al., 1998; Soar et al., 2004). The protective effect of a cytokinin benzyladenine (BA) against paraquat toxicity was investigated in the leaves of maize. Pre-treatment with BA retarded PQ-induced decreases in chlorophyll, carotenoid, ascorbic acid contents, SOD activity and POD activity (Durmu and Kadiolu, 2005).

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Elevated ultraviolet (UV-B) treatment increased the leaf surface wax and decreased the absorption of PQ, affecting the effectiveness of PQ (Wang et al., 2007). Protective effect of exogenous proline was also most profound in the case of PQ treatment. Exogenous proline decreased the rate of lipid peroxidation, the content of superoxide radical and consequently, SOD activity and increased the content of chlorophylls in leaves of adult plants (Shevyakova et al., 2009). A synthetic compound - (4-fluorophenylthiocarbamoyl)-4-methyl-piperazine (FTMP) pretreatment resulted in a lower level of oxidative stress in leaves and higher in roots compared with PQ only. And the best concentration was 5×10-6 M that completely eliminated the PQ-induced oxidative damages in leaves and roots of barley plants (Yonova et al., 2009). Foliar-treatment of young pea plants with 2.5 mM H_2O_2 before PQ (0.2 mM) application stimulated antioxidant potential in both the chloroplasts and the other compartments of the cell (Moskova et al., 2009). Further study suggested that the γ-aminobutyric acid (GABA) shunt pathway and the accumulation of GABA metabolites might contribute to antioxidant machinery associated with reactive oxygen species and in the acquisition of tolerance in response to induced oxidative stress (PQ and H_2O_2 treatments) in Arabidopsis seedlings (AL-Quraan et al., 2011).

However, the development of more herbicide antidotes is still advocated. Many antioxidant related genes was identified in responses to PQ treatment by microarray analysis (op den Camp et al., 2003). Based on this study, we merged the component-based and the PPI-based approach (Huang et al., 2009) to further the comprehensive significant pathways for the PQ stimulation. We hope our analysis may lay a theoretical basis for developing more herbicide antidotes.

MATERIALS AND METHODS

Data sources

We downloaded all the pathways from Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa, 2002) and PPI datasets from Intact (Aranda et al., 2010), Texas Association for Institutional Research (TAIR) (Swarbreck et al., 2008), BIND (Bader and Hogue, 2000) and BioGrid (Winter et al., 2011) databases. An ensemble PPI network was constructed by integrating two above existing PPI databases in human. Total 138724 PPI pairs were collected in which 72268 unique PPI pairs involved 7402 proteins used for analysis. For the dataset GSE10464 (Przybyla et al., 2003), flu mutants of *Arabidopsis thaliana* ecotype Landsberg erecta (Ler) were grown under continuous light until they reached the rosette leaf stage. For the analysis of changes in the expression of genes after PQ treatment, flu mutants were sprayed either with a solution of 20 µM PQ (methyl viologen;Sigma) in 0.1% Tween or with Tween alone, and rosette leaves were harvested at 1, 2, and 4 h after spraying.

For each sample, the rosette leaves of five to six mutants were collected for ribonucleic acid (RNA) extraction. Then hybridization to the Affymetrix GeneChip Arabidopsis ATHI Genome Array, which contains > 22,500 probe sets representing ~24,000 genes. Total 6 chips including 3 PQ treated and 3 Tween treated at 1, 2 and 4 h were collected. The limma method (Smyth, 2004) was used to identify differentially expressed genes (DEGs) to find the difference after PQ treatment. The original expression datasets from all conditions were processed into expression estimates using the Robust Multi-array Analysis (RMA) (Irizarry et al., 2003) method with the default settings implemented in Bioconductor, and then to construct the linear model. The DEGs only with the fold change value larger than 2 and p-value less than 0.05 were selected (Bakay et al., 2002; Zhou et al., 2003; Nakagawa et al., 2004).

Traditional significant pathway analysis

The pathway annotations were based on KEGG annotations. P-values for the pathway enrichment were calculated based on a hypergeometric distribution (Fury et al., 2006). The local false-discovery rate (FDR) was determined with the 'fdrtool' package (Strimmer, 2008). The significance level was set at FDR<0.1. We reported significant pathway enrichments for groups with at least two members and FDR<0.1.

New significant pathways analysis based on PPI datasets

First, to determine the co-expressed significance of a gene pair in disease cases, we used the Pearson correlated coefficient (PCC) test to calculate the p-value. Those p-values were mapped to the nodes and edges in the PPI network collected from PPI related databases. The following formula was used to define a function as the combination of statistical significance of an interaction by a scoring scheme. The detail description could be seen in Liu et al. (2010).

$$S(e) = f(dif(x), cor(x, y), dif(y))$$

$$= -2\sum_{i=1}^{k} \log_e(p_i)$$

The dif(x) and dif(y) are differential expression assessments of gene x and gene y, respectively. Cor (x,y) represents their correlation between gene x and gene y. f is a general data integration method that can handle multiple data sources differing in statistical power. Where k = 3, p1 and p2 are the p-values of differential expression of two nodes, p3 is the p-value of their co-expression.

$$Sp = \sum_{e \in P} S(e)$$

Then, to estimate the significance of the pathways, we sample randomly 10^5 times of the same size pathways in the edges of pathway network and calculates their overlapping scores. The frequency of scores that are larger than Sp was used as the significance p-value of pathway P to describe its importance. To evaluate the significance of pathways, FDR also was calculated using the fdrtool packages. The same parameter (numbers >=2 and FDR<0.1) to traditional method were calculated to evaluate the significance of pathways.

RESULTS

Based on the GSE10464 dataset of the Arabidopsis flu mutation with PQ treatment, total 395 DEGs were

Table 1. Significant pathway analyses use the hypergeometric distribution.

Term	Name	Count	P-value	FDR
Ath 01110	Biosynthesis of secondary metabolites	12	1.81E-28	8.28E-27
Ath 03010	Ribosome	2	3.04E-10	6.95E-09
Ath 04075	Plant hormone signal transduction	3	1.63E-08	2.49E-07
Ath 00520	Amino sugar and nucleotide sugar metabolism	2	0.002422	0.003893
Ath 00010	Glycolysis / Gluconeogenesis	3	0.005638	0.007591
Ath 00940	Phenylpropanoid biosynthesis	5	0.038996	0.03204
Ath 00945	Stilbenoid, diarylheptanoid and gingerol biosynthesis	3	0.1103	0.067059
Ath 00903	Limonene and pinene degradation	3	0.113764	0.068427
Ath 00360	Phenylalanine metabolism	5	0.121992	0.071563

Table 2. Significant pathway of PQ treated.

Path	Description	Size	Node	Edge	Score	P-Value	Fdr
Ath 00071	Fatty acid metabolism	41	7	52	378.996	0	0
Ath 00510	N-Glycan biosynthesis	44	25	221	1358.963	0	0
Ath 00860	Porphyrin and chlorophyll metabolism	47	3	6	80.536	0	0
Ath 03008	Ribosome biogenesis in eukaryotes	90	69	1259	8646.76	0	0
Ath 03010	*Ribosome*	*246*	*173*	*2914*	*16649.04*	*0*	*0*
Ath 03020	RNA polymerase	35	28	439	2689.158	0	0
Ath 03440	Homologous recombination	34	25	422	2525.52	0	0
Ath 04712	Circadian rhythm - plant	30	23	95	642.9047	0	0
Ath 04122	Sulfur relay system	14	4	37	262.2817	4.00E-05	0.000178
Ath 00053	Ascorbate and aldarate metabolism	34	3	26	192.2713	1.00E-04	0.000406
Ath 00230	Purine metabolism	140	68	564	3178.393	0.00014	0.000538
Ath 03430	Mismatch repair	33	14	129	789.5793	0.00021	0.000757
Ath 03450	Non-homologous end-joining	8	8	199	1146.108	0.00275	0.009021
Ath 00350	Tyrosine metabolism	27	2	3	25.22507	0.00341	0.01093
Ath 00360	*Phenylalanine metabolism*	*92*	*2*	*7*	*51.06044*	*0.00828*	*0.024272*
Ath 04120	Ubiquitin mediated proteolysis	105	77	771	4170.787	0.01658	0.043482
Ath 03022	Basal transcription factors	47	36	637	3451.774	0.02172	0.054485
Ath 00590	Arachidonic acid metabolism	15	2	10	63.83358	0.03501	0.079331
Ath 03420	Nucleotide excision repair	59	19	217	1198.613	0.04071	0.088574
Ath 00562	Inositol phosphate metabolism	54	23	149	831.6264	0.04177	0.090213
Ath 00130	Ubiquinone and other terpenoid-quinone biosynthesis	26	11	85	483.8384	0.04311	0.092838
Ath 04130	SNARE interactions in vesicular transport	48	36	206	1136.218	0.04637	0.099162

The rows italic marked mean the pathway was also in the traditional significant pathway list, simultaneously.

detected, using the limma method.

Traditional significant pathway analysis

Using the DAVID with the DEGs, significant pathways analysis was performed. Only one pathway Phenylalanine metabolism (ath00360) was enriched with the FDR = 0.07 and Ribosome (ath03010) was enriched with the FDR = 6.95E-09. The total result of FDR<0.1 was listed in the Table 1.

New significant pathway analysis based on PPI datasets

We also used the Sp to evaluate the importance of pathways. Total 22 pathways were detected with the FDR<0.1 and node counts at least 2 members. We found 22 total significant pathways in PQ stimulation. Phenylalanine metabolism (ath00360) and Ribosome (ath03010) were also significant in our data (Table 2).

DISCUSSION

Using component-based and the PPI-based approach, we identified some significant pathways associated with PQ application. Eight pathways were identified in component-based analysis, but 22 pathways were in PPI-based approach. Of them, phenylalanine metabolism and ribosome pathways were shown significant in two analysis methods. Phenylalanine metabolism, phenylpropanoid biosynthesis, Biosynthesis of secondary

metabolites and plant hormone signal transduction pathway were suggested closely connection based on previous reports. Acteoside, a phenolic compound present in the plant, has been shown to inhibit paraquat in *Rehmannia glutinosa*. Phenylpropanoid biosynthesis pathway is one of the important secondary metabolism pathways and produces a large number of biologically important secondary metabolites, such as acteoside moiety. Phenylalanine ammonia-lyase(PAL), which is the first enzyme in phenylpropanoid biosynthesis pathway, links primary and secondary metabolism by catalyzing the conversion of L-phenylalanine to cinnamic acid, the initial and also a rate-limiting step of phenylpropanoid metabolism (Song and Wang, 2009). The transcript level and enzyme activity of RgPAL1 increased gradually from 6 to 24 h after exposure to paraquat or jasmonic acid.

Induction of RgPAL1 by paraquat and stress-related phytohormones suggests that it is involved in the regulation of the phenylpropanoid pathway under oxidative stress (Lee et al., 2003). These results indicated phytohormones as potential PQ antidote. As expected, pre-treatment with SA and MeJA improved the capacity of the antioxidative enzyme system and increased PQ tolerance (Popova et al., 2003). As we all known, the mechanisms of PQ toxicity involve the generation of the superoxide anion, which can lead to the formation of more toxic reactive oxygen species, such as hydrogen peroxide and hydroxyl radical through a variety of reactions such as DNA damage, protein degradation and lipid peroxidation. Thereby it affects key components of plant cell metabolism and initiates the accumulation of oxidative stress. Our study identified related pathway in response to above damage, such as DNA repair pathway (mismatch repair, nucleotide excision repair and non-homologous end-joining), protein synthesis and transport pathway (RNA polymerase, Ribosome, Ribosome biogenesis in eukaryotes, Sulfur relay system, and SNARE interactions in vesicular transport), and lipid metabolism (fatty acid metabolism, and arachidonic acid metabolism), glycometabolism pathway(N-Glycan biosynthesis, Inositol phosphate metabolism, and Glycolysis/Gluconeogenesis).

Although, ribosome protein increases after PQ treatment, few studies were reported about that in plant. Previous study found genes encoding the ribosomal proteins acidic ribosomal phosphoprotein PO, S4, S19, S28, L5, L7 and L21 were uniquely up-regulated in the old vs. young rat hearts following PQ exposure. It is unclear why transcription of these ribosomal protein genes would increase following PQ treatment, but it may signify more ribosomal biogenesis in response to the damaging agent (Edwards et al., 2003). In addition, ubiquitin mediated proteolysis is the primary cytosolic proteolytic machinery for the selective degradation of various forms of damaged proteins (Shang and Taylor, 2011). More importantly, antioxidant potential in both the chloroplasts and the other compartments of the cell is improved through increasing all kinds of antioxidant enzymes, such as SOD, CAT, APX, POX and POD.

Thereby, ascorbate and aldarate metabolism pathway, and tyrosine metabolism may be involved. Tyrosine aminotransferase gene (TAT) was suggested to be involved in rosmarinic acid biosynthesis and to indirectly promote plant antioxidant. The enzyme TAT catalyzes the ultimate step in L-Tyrosine biosynthesis by the conversion of 4-hydroxyphenylpyruvate to L-Tyrosine (Pranav, 2010). Further expression analysis revealed that MeJA, abscisic acid (ABA), SA and UV-B, up-regulated the TAT transcript levels over the control, predicting tyrosine may be another PQ antidote as praline (Huang et al., 2008). PQ application resulted in a serial of metabolism changes in plant and caused weed control to some extent. However, profitable weed, such as Chinese herbal medicine would be weeded by accident. We anticipate more PQ antidote would be developed based on our analysis.

Conclusion

In this paper, a PPI-based approach was used to analyze the significance among PQ response pathways. New significant pathways are found and analyzed using the PPI datasets and expression profiles. The results are inconsistent with our prior knowledge of PQ but with the 2 same significant pathways (ath00360 and ath00940). The new significant pathways present new alternative insights for PQ application. Our work shows that comprehensive and system-wide analysis provides evidence for PQ and complements the traditional component-based approaches.

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