Molecular Plant Advance Access published April 9, 2014



# Meta-Analysis of Retrograde Signaling in *Arabidopsis thaliana* reveals a core module of genes embedded in complex cellular signaling networks

**Running title: Meta-Analysis of Retrograde Signaling**

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**Short Summary**

Meta-analysis of transcriptional response in retrograde signaling dissects communalities and differences among different triggers and pathways. A shared core transcriptional response module has been found and molecular interfaces to a variety of intersecting pathways were analysed.

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## Abstract

Plastid-to-nucleus signaling is essential for the coordination and adjustment of cellular metabolism in response to environmental and developmental cues of plant cells. A variety of operational retrograde signaling pathways have been described that are thought to be triggered by reactive oxygen species, photosynthesis redox imbalance, tetrapyrrole intermediates and other metabolic traits. Here we report a meta-analysis based on transcriptome and protein interaction data. Comparing the output of these pathways reveals the commonalities and peculiarities stimulated by six different sources impinging on operational retrograde signaling. Our study provides novel insights into the interplay of these pathways, supporting the existence of a yet unknown core response module of genes being regulated under all conditions tested. Our analysis further highlights affiliated regulatory *cis*-elements and classifies abscisic acid and auxin-based signaling as secondary components involved in the response cascades following a plastidial signal. Our study provides a global analysis of structure and interfaces of different pathways involved in plastid to nucleus signaling and a new view on this complex cellular communication network.

168 words


Keywords: Retrograde signaling, meta-analysis, abscisic acid, auxin

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## Introduction

Besides their important role in photosynthesis, chloroplasts are central organelles in starch, amino acid and lipid metabolism (McFadden, 2001; Infanger et al., 2011). Plastids emerged about 1,500 million years ago by incorporation of an ancient photosynthetic active bacterium into ancestral eukaryotes. Due to this endosymbiontic event, many genes primarily located in plastids were lost in the plastidial genome and transferred to the nuclear genome (McFadden, 2001; Stoebe and Meier, 2002; Martin et al., 2002; Timmis et al., 2004). Thus, the modern genome of plant chloroplasts only encodes about 100-130 genes (Sato et al., 1999), while the vast majority of essential proteins are encoded by the nuclear genome and have to be imported into the chloroplast. As a result, a number of protein complexes located in the chloroplast such as the photosystems are composed of both nuclear- and chloroplast-encoded subunits (Race et al., 1999). The correct stoichiometric subunit composition of these complexes requires tightly coordinated gene expression in both nucleus and chloroplast. This intracellular coordination is orchestrated by anterograde signals originating from the nucleus and by retrograde signals, which emerge from the chloroplast (Woodson and Chory, 2008).

To date, several distinct pathways involved in retrograde signaling in *Arabidopsis thaliana* (Arabidopsis) have been proposed (Woodson and Chory, 2008; Kleine et al., 2009; Pfannschmidt, 2010; Estavillo et al., 2011; Sun et al., 2011; Ramel et al., 2012; Xiao et al., 2012; recently reviewed in Leister, 2012 and Chi et al., 2013). Using genome uncoupled mutants (*gun2* to *gun5*) it has been shown that the tetrapyrrole biosynthetic pathway possibly contributes to retrograde signaling (Nott et al., 2006). Further, the steady state levels of Mg porphyrins (Mg protoporphyrin IX and its monomethylester) are modulated upon chlorophyll biosynthesis and photooxidative stress (Alawady and Grimm, 2005; Stenbaek et al., 2008).

Although Mg protoporphyrin IX was discussed as potential candidate for a retrograde signaling molecule (Nott et al., 2006), its role as such was challenged in more recent studies (Moulin et al., 2008; Mochizuki et al., 2008). Rather novel data suggest that heme and 5 aminolevulinic acid might work as the potential signaling molecule from the tetrapyrrole biosynthesis pathway (Woodson et al, 2011; Czarnecki et al., 2012). Reactive oxygen species (ROS) including singlet oxygen are considered as possible source for retrograde signals as well. ROS-induced retrograde signaling was shown to be negatively

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controlled by antioxidants, apoptosis proteins or facilitator proteins like EXECUTER1 or EXECUTER2 (Lee et al., 2007). A related pathway includes redox signals originating from the reduction state of the photosynthetic electron transport chain, i.e. the plastoquinone pool and pools of electron end acceptors. These redox signals arise from unbalanced excitation of photosystems I and II, decreasing the photosynthetic efficiency. They contribute to light intensity regulation of nuclear-encoded marker genes for light-harvesting chlorophyll binding proteins (Escoubas et al., 1995). The kinase STATE TRANSITION 7 (STN7) has been shown to play a major role in the counterbalancing state transition reactions, the short-term response, and photosystem stoichiometry adjustment, the long-term response (Pesaresi et al., 2009). The latter includes the regulation of many nuclear genes and STN7, thus, is likely involved in the redox-dependent pathway of retrograde signaling. Specific transcription factors like a basic leucine zipper transcription factor (bZIP-G) are involved in redox-regulated expression of the light harvesting complex protein (LHCB2.4) (Shaikhali et al., 2012). Thus knowledge on upstream and downstream signalling components appear to prove the existence of retrograde redox signalling in retrograde control.

Plant hormones are also thought to play important roles in retrograde signaling, such as the plant hormone abscisic acid (ABA). ABA is related to stress signaling (Zeevaart and Creelman, 1988; Yamaguchi-Shinozaki and Shinozaki, 1993) and involved in plant growth regulation (Finkelstein et al., 2002) and its involvement in retrograde signaling has been demonstrated in various studies. For instance, many nuclear genes encoding plastid proteins contain ABA-responsive regulatory elements in their promoters (Weatherwax et al., 1996; Rodriguez Milla et al., 2003), an ABA-responsive transcription factor, ABA-insensitive4 (ABI4), participates in genome uncoupled 1 (GUN1)-dependent retrograde signaling (Koussevitzky et al., 2007). Recently it was shown that this pathway involves the action of the plant homeodomain (PHD) transcription factor PTM, which is released from the chloroplast envelope membrane upon an internal signal (Sun et al., 2011) and is both localized in the nucleus and the chloroplast.

Furthermore, ABI4 also provides a linkage between ABA and sugar signals through its sensitivity to sugar signaling (Finkelstein et al., 2011). Sugar signals mediated by glucose, sucrose as well as trehalose-6-phosphate do not only apply for a number of physiological cellular processes (Rolland et al., 2006), but were also shown to regulate photosynthetic

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gene expression (Zhang et al., 2010). Some authors argue that sugar signals might overlap with retrograde signaling pathways (Armbruster et al., 2010) or that metabolic signatures might be recognized as retrograde signal (Pfannschmidt, 2010). Thus, sugar signals have been linked to plastidial signaling (Oswald et al., 2001; Stettler et al., 2009). Another metabolite identified as plastidial signal is 3´-phosphoadenosine-5´-phosphate (PAP) which accumulates in the plastid upon drought or high light stress (Estavillo et al., 2011), and methylerythritol cyclodiphosphate (MecPP), a precursor of plastid isoprenoid biosynthesis which accumulates under different stresses (Xiao et al., 2012). Both add to the increasingly complex picture of metabolic signals from plastids.

Although all above mentioned metabolites and components have been shown to regulate nuclear gene expression it remains elusive how different signals are integrated into retrograde signaling pathways and which kind of components participate in signal transduction. The dissection of such a signaling cascade is further complicated by the crosstalk of distinct stimuli. As example, ABI4, involved in ABA signaling, binds to an S-box in the promoter of the *RBCS* gene encoding the ribulose-1,5-bisphosphate carboxylase/oxygenase small subunit. The S-Box is closely associated with a light-responsive G-Box (Acevedo-Hernández et al., 2005). Moreover, ABI4 was shown to be involved in cross-talk between ABA and sugar signaling (Rook et al., 2006), and thus interlinks light, sugar, and ABA signaling. Even alterations in mitochondrial metabolism and physiology can largely alter gene expression of nuclear-encoded photosynthetic genes (Schwarzländer et al., 2012). Such an effect might be explained by the direct connection and interdependence of mitochondrial and plastidial metabolic pathways (Strodtkötter et al., 2009). It remains to be elucidated how such a signaling cascade can be shaped by the trade-off of different hypothetical signaling molecules (Biehl et al., 2005; Pfannschmidt, 2010; Ramel et al., 2012; Sun et al., 2011).

Here we apply a meta-analysis of six different microarray experiments, each monitoring the transcriptional response on disturbances of chloroplast performance by chemical treatment or mutation of the different pathways mentioned above resulting in rapid adjustments of energy metabolism to maintain an optimum of production (operational control, Pogson et al., 2008).

Transcriptomics have been successfully applied to identification of regulators or signaling pathways (Xin et al., 2005; Buchanan-Wollaston et al., 2005). The observed signals are

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monitored by the changes in the transcript profiles in response to a specific stimulus on a level of differential expression. Specifically regulated genes are subsequently analyzed for promoter elements and their implication in metabolic pathways and have been further analyzed for their embedding in protein-protein interaction (PPI) and probabilistic networks at a systems level.

## Results

### Characterization of pathways involved in plastidial retrograde signaling

To analyze putative retrograde signals and their target genes, we analyzed microarrays affecting or inducing plastidial signaling via mutations or treatments in *Arabidopsis thaliana.* These analyses enabled us to monitor the stimulus by modified gene expression compared to the corresponding control condition. All experiments used for this meta-analysis aimed at perturbations of chloroplast performance and hence in a differential release of retrograde signals (Figure 1). The tetrapyrrole pathway was included in the analyses by application of gabaculin, an inhibitor of the 5-aminolevulinic acid synthesis, and by using the *gun4* mutant, which is unable to activate Mg-chelatase and thus displays a disturbance in the tetrapyrrole biosynthesis (Susek et al., 1993; Papenbrock et al., 2000, Larkin et al., 2003). Both conditions resulted in a reduced synthesis of 5-aminolevulnic acid and subsequently in a reduced amount of tetrapyrrole and chlorophyll concentration and are denoted as experiment 1 (Czarnecki et al., 2012). Furthermore an additional experiment (experiment 2) affecting the tetrapyrrole pathway used two inducible transgenic lines, which exhibit opposing de-regulation of two enzymes contributing to the first enzymatic steps of the Mg branch towards chlorophyll synthesis. Upon short term dexametasone induction for 6 hours, the RNAi-line for *CHLD-1* displays a reduced amount of magnesium chelatase subunit D (CHLD) transcripts. In contrast, the inducible line *CHLM-1* overexpressor line exhibits an up-regulation of the gene encoding S-adenosyl-L-methionine:Mg-protoporphyrin IX methyltransferase (CHLM) upon induction with ß-estradiol causing an increased amount of chlorophyll. The third experiment included in the meta-analysis was based on the transition of low light acclimated plants to high light (Oelze et al. 2012). These plants reorganize their transcriptome within 6 h to a similar state, irrespective whether they were acclimated to extremely low light (8 µmol quanta/m$^2$s) or normal growth light (80 µmol quanta/m$^2$s) and experienced a 100-fold or only 10-fold light intensity increase upon transfer to the same high light condition (800 µmol

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quanta/m$^2$s). Transcriptome analysis was performed both in wild type and in a mutant allele of the AP2/DREB-type transcription factor RELATED TO APETALA 2.4 (RAP2.4), *rap2.4* (Shaikhali et al., 2008). RAP2.4 has been shown to act as a trans-regulator of the *2-Cys peroxiredoxin-A* promoter, which regulates the expression of an antioxidant enzyme in response to oxidative stress (Baier et al., 2004).

Experiment 4 addressed the consequence of a diminished day- and night-path of photoassimilate export from the chloroplast in a double mutant defective in both the triosephosphate/phosphate translocator of the inner envelope membrane (TPT; i.e. the day-path of photoassimilate export) and in ADPglucose pyrophosphosphorylase (ADG1) leading to a lack of starch and hence in a block of the nocturnal delivery of starch degradation products from the chloroplast (i.e. the night-path of photoassimilate export) (Schneider et al., 2002). The resulting *adg1-1/tpt-2* double mutant was retarded in growth and exhibited a high-chlorophyll fluorescence (HCF) phenotype similar to the *adg1-1/tpt-1* allele (Häusler et al. 2009), only when grown under high light conditions (Schmitz et al., 2012). Plants grown under low light conditions were indistinguishable from wild-type plants and the respective single mutants. Moreover, growth on sugars (sucrose or glucose) could rescue both the growth- and HCF phenotype of the double mutant under high light conditions (Schmitz et al., 2012).

Lastly, two experiments monitoring the redox-dependent pathway of retrograde signaling were included. Experiment 5 affected this pathway by manipulating the electron flow between the photosystems via light quality treatments and blocking the corresponding signal by mutation of the thylakoid protein kinase STN7 (Bonardi et al., 2005; Wagner et al., 2008; Pesaresi et al., 2009). Likewise, the sixth experiment dealt with redox imbalance by using two T-DNA inactivation photosynthesis mutants (Pesaresi et al., 2009). The mutant *psad1-1* exhibits a deficiency in the subunit D1 of photosystem I, whereas the mutant *psae1-3* displays a defect in the subunit E1 of the same photosystem. Both mutations lead to a permanently reduced activity of the photosynthetic electron transport chain and a more reduced plastoquinon pool than wild type, which activates the STN7 kinase. The mutant allele *stn7* and the double mutations *psad1-1 stn7* and *psae1-3 stn7* were assessed in this context as negative controls.

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## Identification of a common response module

To investigate which genes are significantly differentially expressed in each experiment, the transcriptional response of mutant plants or treated mutant plants in comparison with the response of untreated or wild type plants was analyzed taking into account only those genes showing at least a 1.5-fold expression change and a adjusted p-value of $\leq 0.05$ as measure of significance for the observed fold change (primary data Table S1). These overlaps were used to monitor shared subsets of responding genes among the different experiments and identify response modules, which are common in all experiments. These modules are referred to as core response moduls. An overview of the experimental work-flow is given in Figure S1.

The Venn diagram (Figure 2A) depicts shared sets of genes in all various combinations (Table S2, Figure S2). The six experiments shared in total a common and significant set of 39 transcripts (Table 1, Table S3), whereas only one gene would have been expected to be differentially expressed in all experiments by chance ($p=2.57 \times 10^{-5}$). This finding indicates a core response module of retrograde signaling, consisting of 39 genes. The existence of such a core module suggests that several retrograde signaling pathways share common components. To get new insight into the underlying stimuli, this core module of 39 transcripts was subsequently analyzed in more detail.

## The putative retrograde core response module indicates cross-talk between sugar, ROS, ABA, and auxin signaling pathways

To understand the functionality of these 39 transcripts in retrograde signaling as well as the metabolic and signaling pathways they are contributing to, their responsiveness to certain stimuli and their functional role in different pathways was investigated (Table 1).

The 39 identified genes of the core response module encode proteins of diverse functional categories. Genes encoding proteins involved in cell wall establishment or modification (AT4G19380, ATTPPA (AT5G51460), AT5G64640), as well as developmental processes (ATTPPA (AT5G51460), LBD37 (AT5G67420)), stress responsiveness (AT5G63190, LBD37 (AT5G67420)), responsiveness to salicylic acid (WRR4 (AT1G56510)) and

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involvement in defense reactions (ATTPPA (AT5G51460)) were identified. The other identified genes indicate that specific metabolic stimuli were involved (Figure 2B). Five out of the 39 genes are known to be involved in auxin signaling or at least to be responsive to auxin as stimulus (LAX3 (AT1G77690), IAA2 (AT3G23030), AT4G28270, IAA29 (AT4G32280), AT4G34770*;* Table 1). Moreover five of the identified genes are known to be responsive to or involved in ROS signaling (EXPA5 (AT3G29030), AT3G44450, AT3G62950, EDS5 (AT4G39030), AT5G19120) or ABA signaling (AT1G66100, AT1G49230, MEE14 (AT2G15890), AT2G05540, AT4G17245). Four genes were shown to be involved in sugar signals or are responsive to sugars (STP1 (AT1G11260), UGE3 (AT1G63180), AT5G22920, LSU2 (AT5G24660)), while one gene was denoted as calcium-dependent (CCL (AT3G26740)). Ten of the 39 genes (AKINBETA-1 (AT5G21170), HIS1-3 (AT2G18050), DIN10 (AT5G20250), AT5G08350, AT1G68440, DNAJ (AT2G17880), AT3G15630, CAX7 (AT5G17860), PP2C (AT5G02760), TCH2 (AT5G37770)) were determined to be responsive to multiple of these stimuli. Taken together, 29 out of 39 genes can be denoted as responsive to four distinct stimuli: ROS, ABA, auxin and sugar. As calcium is a common element in different signaling pathways some genes were identified which were shown to be involved in calcium signaling before: for instance *COLD CIRCADIAN RHYTHM-LIKE* (CCL (AT3G26740)). The interdependence of signaling pathways was also reflected in some of the identified genes, which were described to be responsive to more than one signal; e.g., *HISTONE1-3* (HIS1-3 (AT2G18050)) is described as responsive to sugar (Usadel et al., 2008) and to ABA (Fujita et al., 2005). Another example is the protein phosphatase 2C gene, which has been shown to be auxin- as well as sugar-responsive (Zhao et al., 2003; Osuna et al., 2007). These results indicate that the core module consists of genes that probably respond to a common feature of these four distinct stimuli. Besides their different cellular functions, the proteins encoded by the 39 genes also have various subcellular localizations. Only 6 of these are actually located in the chloroplast (MEE14 (AT2G15890), DNAJ (AT2G17880), CCL (AT3G26740), DIN10 (AT5G20250), AKINBETA-1 (AT5G21170), ATTPPA). All six genes were shown to react to ABA, ROS and sugars before, but not to auxin (Figure 2B).

The 39 genes were further analyzed for their association with regulatory elements. For the regulatory element analysis the “Finding Informative Regulatory Elements” (FIRE) algorithm was conducted (Elemento et al., 2007).

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One regulatory element, CGF1ATCAB2 (TATATAT for kmer 6, ATATATA for kmer 7), was identified which is over-represented in the 39 transcripts (Figure S3, Table S4). This motif was first described as the binding-site for CHLOROPHYLL A/B BINDING PROTEIN GATA FACTOR 1 (CGF1) in the *chlorophyll a/b binding protein 2* (*cab2*) gene promoter (Anderson and Kay, 1995).

**Identification of lateral gene sets responsive to retrograde signaling**

To gain a deeper insight into distinct modules of plastidial signaling we aimed to broaden our focus towards genes that are responsive to only a subset of stimuli rather than to all stimuli analyzed in this study. We selected genes that showed a modulated expression in at least three experiments. Applying the k-means clustering algorithm (Hartigan and Wong, 1978), genes being differentially expressed in at least three different experiments were grouped into 15 clusters according to their log fold change and its direction (Table S5). These clusters include a minimum of 86 genes (cluster 1, Table S5) and a maximum of 668 genes (cluster 8). These 15 clusters were the basis for subsequent analyses. Their characteristics and involvement in cellular signaling networks are subsequently denoted as lateral response modules.

***Cis*-element analysis identifies distinct promoter elements associated with retrograde signaling**

To identify regulatory mechanisms, all genes in each cluster were analyzed for common *cis*-elements. For this purpose, a motif discovery search was conducted (Figure S4, S5, Table S6) using FIRE.

Besides 14 novel motifs, several promoter elements linked to ABA signaling were detected. The motif ABREATRD22 (GCAC) was one of these elements (Figure S5). It was first described as ABA-responsive *cis*-element in the dehydration-responsive gene responsive to desiccation 22 (rd22) (Iwasaki et al., 1995). This motif is often found to be associated

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with pathways related to abiotic stresses (Li et al., 2006). ABREATRD22 was shown to be recognized by the MYB and MYC transcription factor families (Abe et al., 1997). The latter also binds to the motif ATMYC2-RD22 ([A|C|G]ACATG for kmer 5, [A|G|T][A|C][C|G]CATGTG for kmer 8), a promoter element first described in rd22 as well (Abe et al., 1997). Some MYCs act as transcription factors in ABA-regulated gene expression under drought and salt stress (Abe et al., 2003). Another motif, ABRE-like ([A|G|T][A|C]CACGT[G|T][A|G|T]), has been described to be involved in the ABA-mediated response to drought (Yamaguchi-Shinozaki and Shinozaki, 1994; Simpson et al., 2003). It is recognized by G-Box proteins belonging to the bZip-family (Giraudat et al., 1994). The ATHB6 binding site motif (AATAATA), which is found in the promoter of *ARABIDOPSIS THALIANA HOMEOBOX PROTEIN 6* (ATHB6), also reflects the ABA-dependent retrograde signaling pathway. ATHB6 is responsive to drought, osmotic stress and ABA mediated via ABI1 (Söderman et al., 1999; Himmelbach et al., 2002).

FIRE also identified a W-Box (A[A|T]GTTGAC, Figure S5). The W-Box WBOXATNPR1 was shown to be present in genes responding to ABA in other studies as well (Yazaki et al., 2003). Through NONEXPRESSOR OF PATHOGENESIS-RELATED 1 (NPR1) this motif might also be related to defense reactions (Després et al., 2003). W-Boxes are bound by WRKY transcription factors (Eulgem et al., 2000).

Promoter elements associated with light-signaling pathways were identified as well. CGF1ATCAB2 ([A|T]TGGATAA[A|C]) is such an example (Anderson et al., 1994). This motif was also identified to be over-represented in the putative core response module. Another motif which is found in genes for the light-harvesting chlorophyll a/b binding protein is the I-Box ([C|G|T]C[C|T]TATCC for kmer 7, CTTATC[C|T][A|G|T] for kmer 8; Donald and Cashmore, 1990). It is also present in RuBisCO genes of the small subunit and as such linked to light-signaling pathways. The last motif belonging to the group of light responsive motifs is HEXAT ([A|C|T]CACG[G|T]C[A|T][C|G|T]), a modified G-Box motif. This motif is a binding-site for TGA1, named for its core binding sequence TGACG (Després et al., 2003), and for the G-BOX BINDING FACTOR 1 (GBF1). Both belong to the leucine-zipper class (Schindler et al., 1992).

The Telo-Box1 ([A|G|T]AA[A|G]CCCTA for kmer 7, [A|G|T]AA[A|G]CCCTA[A|C|G] for kmer 8) does not belong to any of the three groups presented above. It was first described as characteristic sequence found in the *ELONGATION FACTOR1*-α genes (Axelos et al.,

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1989) and as homologous to the telomeric repeat in higher eukaryotes. It might interact with the nuclear scaffold (Curie et al., 1993) and is involved in activation of gene expression (Tremousaygue et al., 1999). Furthermore, the exact motif defined by FIRE has been shown to be a central sugar responsive motif (Li et al., 2006). This might indicate that this element is involved in translating sugar signals into transcriptional response. The FIRE-analysis also reveals that some clusters display distinctive over- or under-representation of particular motifs. The telo-box has been implicated in cluster 6 and 15, which exhibit significant under-representation of all motifs. This might indicate that these clusters are sugar-responsive and might not be direct targets of ABA or light signals. The analyses also demonstrate that most clusters contain over-represented motifs connected to ABA as well as light. This corresponds to previous findings indicating that ABA and light signaling pathways show a strong overlap (Kusnetsov et al, 1996; Galvez-Valdivieso et al., 2009; Garcia-Mata and Lamattina, 2007; den Os et al., 2007).

Several transcription factor families recognize the motifs identified. Some representatives of these are also differentially expressed in at least three experiments (Table 2; Table S5).

In conclusion, FIRE identified *cis*-elements echoing ABA, light, and sugar as putative signaling components for plastid-derived processes. The elements might also reflect transcription initiation and defense response as lateral modules of retrograde signaling.

**GO enrichment analyses indicate lateral pathways triggered through retrograde signals**

To analyze for gene functions that are enriched in the lateral clusters a Gene Ontology (GO, Ashburner et al., 2000) enrichment analysis was conducted for each cluster (Table S7a). Results were reduced for those terms that either represent a child term or that represent closely connected terms (Table S7b). GO enriched terms might reflect responses to plastid signals and depict pathways connected to the retrograde signaling cascade. For a better understanding, terms that describe the same or similar pathways are grouped into one category (Table S8).

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The identified *cis*-regulatory elements indicate the involvement of ABA response, light signaling pathways, sugar signaling as well as defense reactions and transcription initiation as possible regulatory mechanisms and reactions to a plastid signal. Over-represented terms indicating such stimuli are not confined to clusters supporting the respective promoter elements, but are also represented in other clusters. This finding indicates a strong connectivity between the different modules potentially mediated through common signals (Table S6).

The majority of terms belong to the categories transcription and translation (Table 3, Table S8). Sugar signals are also reflected in categories e.g. "response to sucrose stimulus". Besides sugar signals, one cluster (cluster 11, Table S7b) also contains terms enriched for transcription.

ABA signaling is indicated in the GO analyses as well in terms like "abscisic acid-mediated signaling pathway". Clusters, in which *cis*-elements connected to ABA signaling were identified, are mainly enriched for transcription and light-connected pathways. These signals are summarized together with "response to gibberellin stimulus", "jasmonic acid biosynthetic process" and "response to ethylene stimulus" as hormonal signals. The light signaling pathway indicated by the presence of an I-Box, a G-Box, and HEXAT in the identified *cis*-elements is also reflected in enriched GO terms. Clusters, which are denoted for under- or over-representation of these light-signaling *cis*-elements not only show GO term enrichments connected to light-signaling pathways, but also for transcription (Table S7b). Lastly, defense reactions as indicated by the *cis*-element analysis are also represented in the enriched terms. The GO term "response to wounding" was categorized together with defense reaction as putatively related.

Though these categories are strictly divided, the clusters do in majority not belong to only one category (Table S8). This result might indicate a pronounced interference presented in the lateral modules.

In conclusion, we identified terms that might reflect light signals as well as ABA signals and sugar signaling as common elements of the lateral clusters. Two of these signals, namely ABA and sugar, are also found in the core response module detected in our analyses. Transcriptional processes present the major part of identified GO terms and also

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a *cis*-element, which is essential for initiating transcription, was identified. Further, the GO enrichment analysis indicates high interference between distinct clusters.

**The systems biology of the core response module and lateral response modules**

The analysis outlined above was focused on the transcriptional response upon triggering different retrograde signals. We were aiming to broaden our analysis towards a systems level. Besides considering transcriptional response, we analyzed for functional modules that might be involved in signaling and transmission of molecular responses upon disturbance of the plastidial signaling cascades and retrograde circuits as found in both the core response module and lateral modules. We therefore analyzed genes present in either the core response module or the lateral modules with regard to the connectivity of their protein products in a protein-protein interaction (PPI) map and within a probalistic network of Arabidopsis genes. We used the interaction map of the Arabidopsis Interactome Mapping Consortium (Arabidopsis Interactome Mapping Consortium, 2011), based on yeast-two-hybrid (Y2H) data. It contains 2661 proteins with 5664 binary interactions. In addition, the interaction map ANAP incorporating different databases for PPI, was used (Wang et al., 2012). Finally, a probabilistic network, AraNet (Lee et al., 2010), was used for the analysis of interacting components as well. AraNet contains Arabidopsis genes with 1,062,222 functional links. After filtering for a subnetwork based on connections up to first neighbor degree from the gene of interest, interaction communities were determined and communities consisting of at least five genes were analyzed in more detail.

Subnetworks of genes, defined as genes that are differentially expressed in at least three experiments and their direct interaction partners, were analyzed based on Y2H data. We found 4895 genes differentially expressed in at least three experimental datasets. 720 out of these were present in the Y2H dataset. After applying the linkcomm algorithm (Kalinka and Tomancak, 2011), 488 genes form a network with 1916 binary interactions and 1315 distinct identifiers (Figure S6, Table S9). Unique categories e.g. transport, phosphorylation and translation were detected. However the wide variety in detected categories indicates an intimate relationship between retrograde signaling and its responses and general plant functions. For instance, communities with GO enrichment for chloroplast as compartment

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also show enrichment for terms related to homeostasis, translation and gene expression (Table S10).

The data basis for the ANAP protein interaction database is broader and contains 201,699 interactions and 15,208 Arabidopsis genes in the PPI network. We analyzed the connections of the proteins encoded by the core response set of genes for their connectivity and embedding in the PPI network. 26 genes out of 39 encoded proteins (2/3) of the core response module are found in ANAP. After applying the linkcomm algorithm for identification of communities, 19 proteins (49%) form a subnetwork of 456 interactions with 354 identifiers (Figure 3A, Table S11). Among other categories, auxin and transcription, transporter activity, chloroplast, defense response, ABA, disaccharide metabolism and ribosome were detected (Table S12). We observed strong interconnectivity among the different modules. E.g., based on GO enriched terms in the communities one community shows the categories transcription, auxin, tropism, development and the nucleus as compartment. These genes have also been analyzed using the Y2H data, indicating similar results and adding the category redox homeostasis (Figure S7, Table S13, Table S14).

AraNet does not only include PPI data but also uses co-expression data (without the datasets used in this study) and orthology-based information to derive a whole genome probabilistic network. Usage of this dataset thus further expands the focus beyond PPI networks and potentially discovers network relationships not reflected in the PPI network analysis. From the core response module, 36 out of 39 (92%) encoded proteins were represented. The analysis of connections from encoded proteins in the core response module based on the AraNet interactome indicated a multifaceted network that is triggered by the retrograde stimuli. The subnetwork contains 2089 proteins and 2497 connections (Table S15) with 33 out of 39 query proteins included. One query protein, AT1G11260 (SUGAR TRANSPORTER 1), was shown to be a strong hub (Figure S8) and for better visualization left out (Figure 3B). Categories for interacting communities indicate transcription, auxin, oxidoreductases, translation, sugar binding, ABA, trehalose metabolism and the mitochondrion as well as the thylakoid as compartment amongst others (Table S16). Some communities do show various GO enriched terms. As example, jasmonic acid, ethylene, salicylic acid, gibberellin, ABA, auxin, transcription and cold are represented by only few communities. This observation suggests a high interference

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between different modules and reflects the complexity in the molecular interactions underlying retrograde signaling.

To complement our analysis on the embedding of the responding lateral gene set into the molecular circuits potentially linked to the retrograde signal transmission, we conducted a pathway analysis using the pathway identification tools KEGG Spider, R Spider and PPI Spider. Based on the KEGG database (Kanehisa and Goto, 2000), KEGG Spider (Antonov et al., 2008) links genes that encode proteins involved in reactions sharing common substrates. R Spider (Antonov et al., 2010) makes use of the Reactome database (Matthews et al., 2009) and combines the KEGG metabolic network with the signal network in Reactome. Lastly, PPI Spider (Antonov et al., 2009) was conducted. Unlike KEGG Spider and R Spider, it builds a network of PPI's from the IntAct database (Kerrien et al., 2007).

The results reflect a broad range of pathways (Table S17*,* Figure S9), that in part overlap with the analysis against PPI networks as outlined above. The most prominent pathways are connected to amino acid metabolism, pigment biosynthesis, translation and transcription. Again, the putative stimuli ABA, sugar*,* and light are found. Pathways connected to the chloroplast like "protein import into chloroplast stroma" might indicate signals that lead to chloroplast adaption. Interestingly, as indicated by the GO enrichment analysis based on the clusters, defense response is potentially a lateral response module to retrograde signaling.

**MicroRNAs are linked to the plastidial signaling network**

MicroRNAs (miRNAs) are known to modulate many biological processes in plants (reviewed in Jones-Rhoades et al., 2006). We therefore tested if miRNAs were associated with modules potentially accompanying retrograde signaling as detected by the analysis of PPI networks. We used information in miRBase (www.mirbase.org) and information on the respective miRNA target genes from psRNATarget (http://plantgrn.noble.org/psRNATarget/) to associate miRNAs with genes and modules in the PPI networks. In all networks miRNAs were found to be exclusively associated with

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several of the detected modules (Table S18). Modules that are not connected through PPI information (Y2H data and ANAP derived) were found to be frequently connected via miRNAs that target individual genes in two or more separate PPI modules (Figure S6, Figure 3A). Although most of the miRNAs connections to individual PPI networks and modules were found exclusively in networks generated from either the ANAP, Y2H or AraNet datasets (Table S18), the miRNA ath-miR858 was found connecting modules in all PPI networks (Figure S10). It targets a range of MYB family transcription factors like AtMYBL2 and AtMYB20. Interestingly AtMYBL2 has been shown to act as a negative regulator of flavonoid biosynthesis (Matsui et al., 2008), which is an interface to retrograde signaling studied in this analysis.

Thus, detected miRNAs might form candidates for potential regulatory players in the plastidial signaling network, which is an attractive hypothesis that, however, asks for further experimental testing.

## Discussion

Plastidial signaling has been demonstrated to be triggered by a number of different stimuli that are induced by a variety of environmental inputs (Woodson and Chory, 2008; Kleine et al., 2009; Pfannschmidt, 2010). In addition, a number of regulatory protein components involved in retrograde signaling have been analyzed and their role in retrograde signaling has been discussed. As example, genome uncoupled mutants (gun1 to gun6) have been shown to lack elements necessary for retrograde signals (Nott et al., 2006, Woodson et al., 2011). Additionally, metabolites like phosphonucleotide 3'-phosphoadenosine 5'-phosphate (PAP) (Estavillo et al., 2011), ß-cyclocitral (Ramel et al., 2012) and methylerythritol cyclodiphosphate (MEcPP) (Xiao et al., 2012) have been suggested as activators of retrograde signals.

However, thus far a systems level analysis that correlates molecular responses from different plastid-derived retrograde stimuli putting them into an integrative framework has been missing. Such an analysis might reveal potential interactions in the various types of operational plastidial signaling without necessarily being detectable if solely a single

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stimulus is investigated (Jung and Chory, 2010). The basic assumption of this study was that chloroplasts represent a central compartment of plant cells that is essential for metabolism and environmental sensing. Any change in chloroplast function, thus, should have an immediate impact on all other cellular functions including nuclear gene expression. In the past the existence of several distinct retrograde pathways has been discussed suggesting that they specifically control separate sets of genes. The approach we used clustered genes that are responsive to operational stimuli allowing us to reach a more detailed picture with to our opinion general significance.

Surprisingly, our analysis on transcriptome data from the various experiments indicated the existence of a core response module consisting of 39 genes with much higher significance than a random expectation ($p=2.57 \times 10^{-5}$) (Figure 2A). Also, these genes are not enriched for chloroplastidial genes. This strongly suggests that chloroplast function is integrated into a cellular network that activates the same nodes regardless of the stimulus. In comparison, analyses of lateral modules did not show an enrichment for photosynthetic pathways or related genes. These results support the suggestion that the integration of the chloroplast into the common cellular network has been show in our study. This does not exclude the existence of stimulus-specific gene sets, but indicates the existence of a basic overall framework which attaches chloroplast function in a general manner to the remaining cell. Such a framework might have been an early requirement for successful endosymbiosis and the results of our study provide novel ideas for further investigations of plastid evolution.

**The retrograde core response module places sugar and ROS-/redox-signals at the beginning of a plastidial signaling cascade**

Sugar, calcium and auxin have not been described yet to contribute to plastid signals, although auxin influences nuclear expression of chloroplastic genes (Leister et al., 2011). Calcium acts as second messenger in many signaling pathways (Echevarría et al., 2003), and, among other effects, contributes to the regulation of stomatal closure (reviewed in Dodd et al., 2010) through ABA (Pei et al., 2000). Also, the chloroplast directly regulates stomatal closure (Nomura et al., 2008). Thus, the potential calcium signal, as indicated

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from the core response module, might reflect a response to a plastid signal. It might also be related to a recently described chloroplast calcium signal which is involved in plant pathogen defense (Nomura et al., 2012) or might reflect mitochondrial retrograde signaling, which is known to show an overlap to chloroplastidial signaling (Schwarzländer et al., 2012).

Auxin, among its variety of regulatory roles, is also involved in regulation of stomata opening through gibberellin (Saibo et al., 2003). Adjustment of stomata opening range by auxin acts antagonistically to ABA. Since only auxin precursors are synthesized in the chloroplast via the shikimate pathway, auxin signals are likely to be secondary effects of the plastidial signal. It has been suggested that auxin-induced genes are also induced by ROS (Pasternak et al., 2005; Hirt, 2000; Mittler, 2002), suggesting a connection of auxin to retrograde signaling via ROS signals.

ABA has been discussed as affiliated with plastidial signals. ABA precursors are synthesized in the chloroplast, while synthesis is completed in the cytoplasm. Release of the ABA precursor xanthoxin to the cytosol may act as plastidial signal both in retrograde control as during stresses like water deprivation (Jia et al., 2002) or osmotic stress (Skriver and Mundy, 1990). Therefore, the observation of ABA responsive genes in the core responsive module allows speculating that the ABA synthesis is under control of a plastidial primary signal (Baier and Dietz 2005). In this scenario ABA would act as a secondary signal, a signal accompanying the retrograde signal. This is in line with downregulation of ABA marker transcripts e.g. in the low light/high light transfer experiment (Oelze et al. 2012).

Our observations also indicate that sugar status and ROS/redox-cues act as early plastidial signals in retrograde signaling. Here redox-signals are not those derived from plastoquinone redox state but redox information from electron acceptors downstream of photosystem, like thioredoxins and part of the thiol-/disulfide redox regulatory network which also senses ROS. Precursors for sugar synthesis are synthesized in the chloroplast and have been shown to act in strong association with ABA signals (Smeekens, 2000; Cho et al., 2010; Hey et al., 2010; Çakir et al., 2003).

Consequently, for some promoters embedding of both ABA and sugar signals have been shown (Rook et al., 2006). It might therefore be possible that ABA precursors, generating

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a secondary signal to the retrograde signal, are affected by primary metabolite signals such as altered sugar metabolism or specific sugar species. Correspondingly, the carbohydrate status would be suggested to be a primary candidate for a retrograde signal. However, our results did not indicate which sugar species could putatively transmit such a signal. ROS- and redox-signals also emerge in the chloroplast, suggesting ROS species or redox transmitters as primary retrograde signals (Gadjev et al., 2006). Accordingly, it is also possible that ABA synthesis is linked with ROS stimuli. Thus, the influence on ABA synthesis by ascorbate, a potential anti-oxidant in dependence of ROS has been shown (reviewed in Baier and Dietz, 2005). Also, a study on the 2-Cys peroxiredoxin-A promoter shows that ROS signals interact with ABA signals (Baier et al., 2004). However, our results did not allow distinguishing between sugar and ROS/redox cues as major signaling resource.

**The lateral modules reflect retrograde signals and add secondary pathways**

Genes contained in the core response module are involved in a variety of pathways and categories as indicated by analysis of associated regulatory elements and by literature. Most prominently genes involved in transcriptional regulation (AT1g49230, HIS1-3 (AT2G18050), AT4G17245, AT4G28270), defense response (WRR4 (AT1G56510), EDS5 (AT4G39030)) as well as growth, cell wall establishment, and cell wall synthesis (MEE14 (AT2G15890), AT5G64640, AKINBETA-1 (AT5G21170), AT3G47420, ATTPPA, UGE3 (AT1G63180)) were represented. These categories were also indicated by analyses based on lateral modules. Therefore, they might indicate pathways responsive to retrograde signaling being triggered by the stimuli auxin, ABA, ROS and sugar. Thus, auxin signals could onset growth processes as well as cell wall modifications (Cosgrove, 2005). Accordingly, ABA possibly triggers pathways of stress signals. The indicated light signaling pathways might be initiated by ROS signals, as well as pigment metabolism like anthocyanin and porphyrin metabolism as defense reaction to ROS. Since the FIRE analysis indicated a promoter element linked to both, sugar and transcription, a potential sugar derived signaling pathway that does not have commonalities with other stimuli found in the core response module might be suggested. As indicated by the presence of

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ATTPPA in the core response module, defense reactions might also be part of the plastidial signaling cascade. Accordingly, GO enriched terms indicating defense reactions have been identified. Putatively, the suggested jasmonic acid and salicylic acid metabolism could be in close connection to the triggered defense reaction. It remains speculative if this reaction is linked to ABA or ROS, since ABA has been shown to modulate pathogen defense (reviewed in Asselbergh et al., 2008) and oxidative bursts are one of the first reactions in defense (reviewed in Nanda et al., 2010).

The analyses further indicated that many clusters highlight a variety of different GO enriched terms. Thus, the high interference of different stimuli and pathways suggested by the core response module is also found in lateral modules. These findings suggest that the retrograde signaling cascade is not a linear process, but is able to involve a variety of parallel signal transduction pathways with intensive crosstalk, which can be modulated via single disturbances. This supports the view of a metabolite signature rather than (a) single compound(s) as responsible signals (Pfannschmidt*,* 2010)*.*

**The operational retrograde signal is embedded into a complex cellular signaling network**

Monitoring of transcriptional responses and definition of overlaps in responsive genes under different experimental conditions has proven to be a powerful approach to elucidate molecular mechanism driving the molecular response to retrograde signaling. However, transcription is not the only level of regulation that controls activity of proteins and, thus, transcriptionally inconspicuous genes still might be involved in the generation and transmission of retrograde signals. To bridge this gap we expanded our analysis towards a systems level analysis. We aimed to analyze the core responsive genes and lateral transcriptional gene modules in the context of molecular pathways. Further, we put them in context with new genome scale systems biology data that cover PPI interaction networks (ANAP and Y2H), a probabilistic network of gene interactions in Arabidopsis (AraNet), molecular and metabolic pathways (Reactome and MapMan) and with the targets of regulatory miRNAs. The analysis of genes that were found to constitute the core response module in PPI networks indicated multiple links between retrograde signaling and a variety

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of GO categories and the involvement of defined module substructures in the network (Figure 3). The putative stimuli sugar, ABA and auxin were represented in two out of three PPI network approaches. ROS/redox cues as important signals in retrograde signaling are reflected by the categories “redox homeostasis” and “oxidoreductase”, but did not emerge as specified stimulus. This might be related to the limitations of each network, not representing all protein interactions in Arabidopsis. Besides the categories “defense response”, “transcription” and “translation”, “salicylic acid” and “jasmonic acid” were found as well consistent with findings by GO enrichment analysis and regulatory element analysis on genes that are differentially expressed in at least three experiments. These observations suggest a tight link of these processes with the perception and transduction of a retrograde signal from plastids. All categories show strong interferences, suggesting that retrograde signaling is integrated in complex networks. Strikingly, all networks show enrichment for “chloroplast” or “thylakoid” as compartment supporting the basic function of plastidial signals in adjusting chloroplast functions and validating the reliabilty of the approach.

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**Material and Methods**

*Experimental procedures*

In experiment 1, gun4-1 and wildtype seeds (Col-0 background) were surface sterilized and plated onto 0.5x MS medium (Murashige and Skoog, 1962) supplemented with 1% (w/v) sucrose and 0.8% (w/v) agar. After 2 days vernalization at 4°C, pots were transferred to a growth chamber with light intensity of 100-120 µmol photons $m^{-2}s^{-1}$ at 22-23°C with a day/night cycle of 12 hours light/12 hours dark. To synchronize germination, etiolated seedlings were exposed to light for 2 hours followed by dark-incubation for 3 days. Ten micromolars of GAB (5-aminocyclohexa-1,3-diene-1-carboxylicacid) were supplied to the MS medium. 7-day-old plants were then harvested.

Experiment 2 used, besides wildtype, *CHLD-1* dexamethasone- and *CHLM-1* β-estradiol-inducible RNAi lines using vectors pOpOff2 and pMDC7, respectively. Arabidopsis wildtype (Col-0) and transgenic RNAi lines were grown on soil at 110 µmol photons $m^{-2}s^{-1}$ under short day (10 h light) conditions, acclimated for at least three days in continuous light (100 µmol photons m-2 s-1) and sprayed with 20 µg/ml dexamethasone or β-estradiol, respectively. 14-day-old plants were harvested.

In experiment 3, *rap2.4* and wildtype seeds (Col-0) were vernalized for 2 days at 4°C. After vernalization, seedlings were grown on soil at 80 µmol photons $m^{-2}s^{-1}$ under short day (10 h light) conditions for 3 weeks, then transferred to low light (8 µmol photons $m^{-2}s^{-1}$), high light (800 µmol photons $m^{-2}s^{-1}$) or normal light (110 µmol photons $m^{-2}s^{-}$) conditions for 10 days. Plants were subsequently transferred to high light. 4,5-week-old plants were harvested.

In experiment 4, mutant (*adg1-1, tpt-2 adg1-1xtpt-2*, Col-0) and wildtype seeds were vernalized for 2 days at 4°C and subsequently grown on soil for 4 weeks in a growth cabinet with a day/night cycle of 16 hours/8 hours. Light intensity was adjusted for high light conditions (300 µmol photons $m^{-2}s^{-}$) or low light (30 µmol photons $m^{-2}s^{-}$). At time points 3,5 hours before transferring to high light, 4 hours and 2 days in high light, approximately 4,5-week-old plants were harvested.

In experiment 5, wildtype and stn7 mutant seeds (Col-0) were grown on soil. After vernalization for 2 days at 4°C, plants were transferred to continuous white-light

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illuminaton for 20 days followed by 3 days in PSI-light conditions (red light filter, 20 µmol photons $m^{-2}s^{-}$) and subsequently shifted to PSII-light conditions (yellow filter, 30 µmol photons $m^{-2}s^{-}$). Leaves of approximately 4-week-old plants were harvested directly prior to light shift, or 30 or 60 minutes afterwards.

In experiment 6, wildtype (Col-0, Ws) and mutant plants (*psad1-1, stn7*: Col-0, *psae1-3*: Ws, *psae1-3 stn7*: Ws, *psad1-1 stn7*: Col-0) were vernalized for 3 days at 2-5°C. Subsequently, plants were grown in a growth chamber under short day conditions (10 hours light at 100 µmol photons $m^{-2}s^{-}$) and harvested after four weeks.

*Microarray hybridization and data analysis*

The microarray analysis was performed using the ATH1 *Arabidopsis* GeneChip. The quality control of RNA, preparation of biotinylated amplified RNA and hybridization was performed at KFB Regensburg (http://www.kfb-regensburg.de) using the GeneChip 3' IVT Express Kit and Affymetrix standard protocols. For experiments 1,2,3 and 5, three biological replicates for a mutant plant, a wild type plant and treatments of those were available, for experiment 4 and 6 two biological replicates per condition.

*Normalization and differential expression*

For all experiments, expression data from wild type and mutants or treated plants were compared as well as different treatments or mutants among each other. In experiments analyzing different time-points, wild type and mutant/treated plants the same time points were compared. Additionally, wild type plants at different time-points were compared among each other and mutants/treatments likewise. For analyzing differential expression, the LIMMA package (Smyth, 2004) in R and Bioconductor (Gentleman et al., 2004) was used. Spots were translated to gene names in TAIR9 annotation using the cdf file provided by http://nmg-r.bioinformatics.nl/NuGO_R.html. For computing expression measure, the function just.rma with standard settings (robust multi-array average expression measure,

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RMA (Irizarry et al., 2003) as background correction, quantile normalization) was employed. Differential expression was computed using an empirical Bayes linear modeling approach. The obtained p-values for multiple testing were corrected according to Benjamini and Yekutieli (Benjamini and Yekutieli, 2001).

Genes were considered to be significantly differentially expressed if their respective corrected p- value was $\leq 0.05$ and the log fold change was either $\leq \log(2/3)$ or $\geq \log(3/2)$.

*Venn diagram*

For each comparison, a list of significantly differentially expressed genes was obtained. Subsequently, these lists were combined according to the experiment they belonged to, thus obtaining a list of differentially expressed genes for each experiment based on the single comparisons made in one experiment. A customized program was used for calculating the intersections of differentially expressed genes per experiment. Assuming uncorrelated experiments, the probability *E* of a shared set of differentially expressed genes was calculated as

$$E = \prod_{k=1}^{j} \frac{\sigma_j}{\sigma_N}$$

with $\sigma_j$ as sum of differential expressed genes in experiment j and $\sigma_N$ as sum of genes represented on the Affymetrix Chip in TAIR9 annotation.

*GO analysis*

A customized program was used for calculating over-represented Gene Ontology terms (Ashburner et al., 2000) in a given set of genes. GO files (released 2010/05) were downloaded from the GO website (www.geneontology.org), GO annotations for Arabidopsis from the TAIR website (www.arabidopsis.org, release: TAIR9). The

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subsequent calculation was based on hypergeometric distribution with the hypergeometric probability *H*:

$$H = \frac{\binom{m}{k}\binom{N-m}{n-k}}{\binom{N}{n}}$$

with m as probability of success, k the total number of successes, N the population size and n as number of draws. The resulting p-value was corrected using the Bonferroni correction. GO terms, which have an error probability of < 0.05, were considered as significant.

*Clustering*

All genes, which were significantly differentially expressed in at least 3 experiments, were clustered according to their log fold change using a k-means clustering approach (Hartigan and Wong, 1978) in R. Except for creating 25 random starting sets, k-means clustering was used at default.

*Motif discovery*

For motif discovery we used the Finding Informative Regulatory Elements (FIRE) algorithm (Elemento et al., 2007). Based on the concept of mutual information, FIRE calculates putative *cis*-elements in a set of genes using the JASPAR database of promoter elements. Further, FIRE scores simple motif definitions in the form of k-mers, searching each combination for under- or over-representation in a defined set of genes. It is possible to define a set of genes using a continuous FIRE approach or using a pre-clustered set as discrete approach. For our analysis, we used a 2kb upstream promoter annotation based on TAIR9. We further used FIRE in a discrete analysis, with robustness index threshold of 6 and 3 to 10 k-mers.

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*Interactome data*

For analyzing the interactome based on the core genes, the interactome network contained all genes that are connected to the genes of interest up to direct interaction partners. Subsequently, communities were retrieved using the linkcomm algorithm (Kalinka and Tomancak, 2011) in R using standard settings with removing trivial communities. After filtering for communities that contained at least 5 genes, the communities were characterized using a GO enrichment analysis. Here, a customized code was conducted as previously described. For visualization, Cytoscape was used.

*Pathway analysis*

The analysis of pathways represented in clusters of genes being differentially expressed in at least three experiments was conducted using www.bioprofiling.de (Antonov, 2011). Only pathways that show a significant p-value < 0.05 are reported.

*miRNA detection*

A list of *A.thaliana* mature miRNA sequences in TAIR9 was downloaded from www.mirbase.org and subsequently scanned for targets using http://plantgrn.noble.org/psRNATarget and standard settings of 3.0 as maximum expectation, hpsize of 20, UPE of 25.0, a flanking length of 17 bp up- and 13 bp downstream and a mismatch range of 9 to 11 nucleotides. The list of targets was then compared with genes represented in modules of a network composed of at least five genes.

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Accession Numbers

Sequence data from this article can be found in the EMBL/GenBank data libraries under accession numbers GSE27704 (experiment 1), GSE41884 (experiment2), E-MTAB-1344 (experiment 3), E-MEXP-3791 (experiment 4), GSE42710 (experiment 5) and E-GEOD-15939 (experiment 6).

## Acknowledgments

The authors are grateful for financial support by the Deutsche Forschungsgemeinschaft (MA 2522/4-2).

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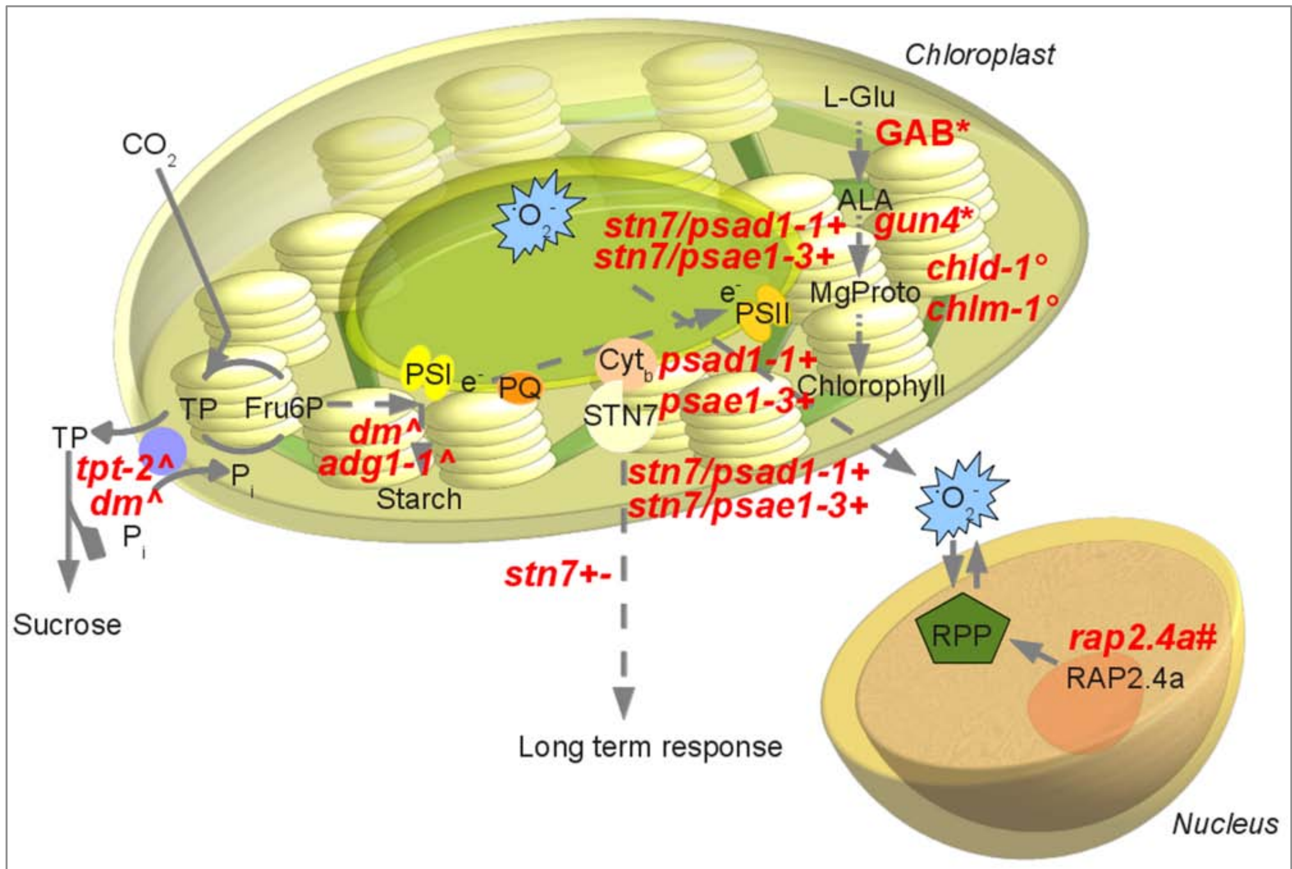
## Figure legends

**Figure 1.** Schematic overview of experiments used in the meta-analysis. Mutants affecting a specific pathway are denoted in red.




PSII: Photosystem 2; PSI: Photosystem 1; PQ: plastoquinone; Cytb6f: Cytochrome b6f; ALA: 5-Aminolevulnic acid, MgProto: Mg-Protoporphyrin IX; MgProtoMe: Mg-Protoporphyrin IX monomethyl ester; RPP: ROS protective protein; TP: triose phosphate; Fru6P: fructose-6-phosphate; ADPG: ADP-glucose

To distinguish between the different experiments, all mutants are marked with an experiment-specific sign and are highlighted in bold.

*: Experiment 1, affecting the tetrapyrrole pathway

°: Experiment 2, affecting the magnesium chelatase

#: Experiment 3, ROS protective protein/light acclimation

^: Experiment 4, starch synthesis and triose-phosphate transport, dm = *adg1-1/tpt-2* double mutant

-: Experiment 5, redox signaling

+: Experiment 6, light acclimation

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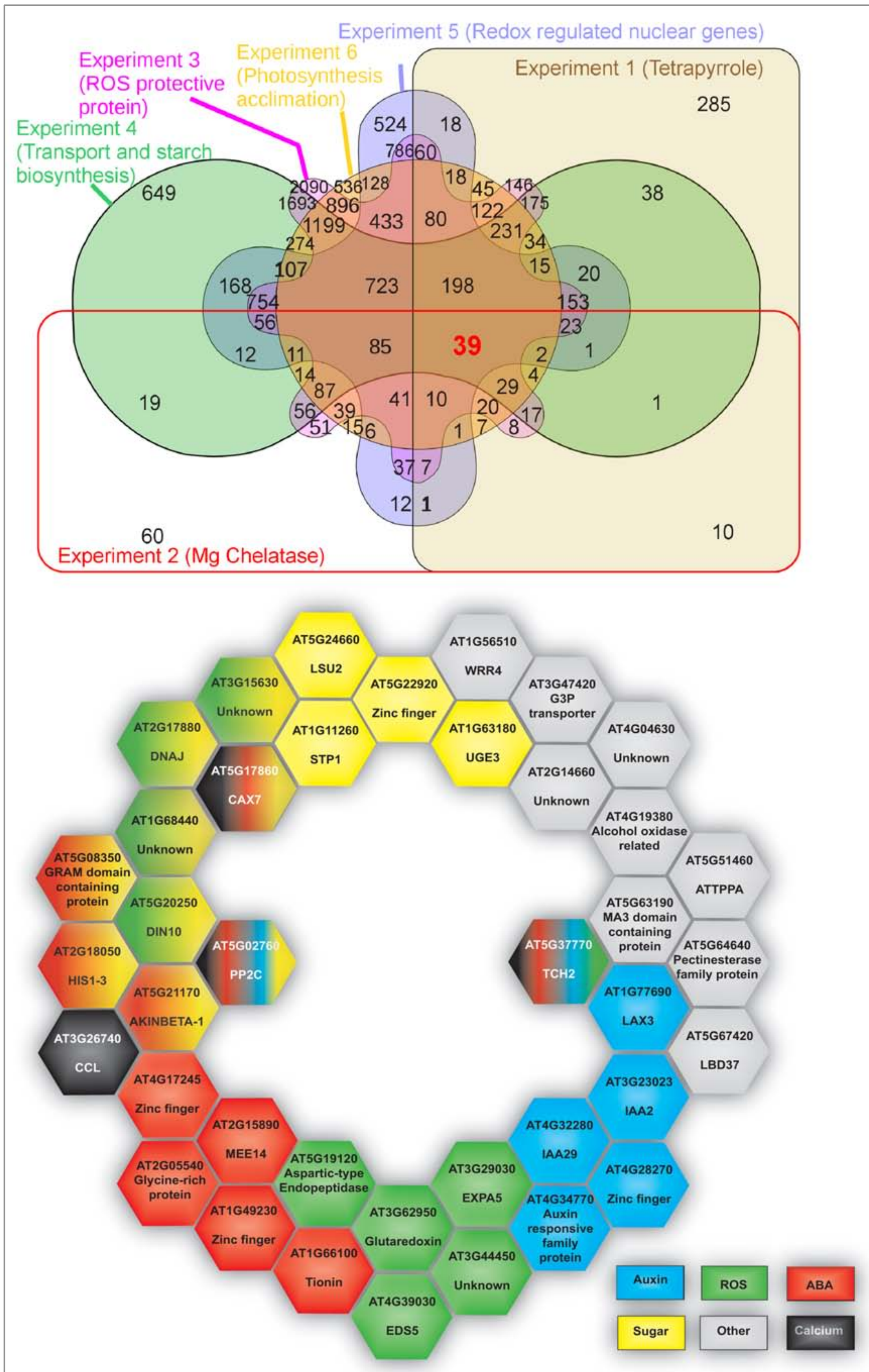
**Figure 2.** Intersections of transcriptional responsive genes among all experiments.

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A) A Venn diagram, depicting the intersections of the experiments. Each intersection gives the number of genes involved in the intersection. 39 genes are responsive in all experiments and highlighted in red. B) Stimuli to gene associations of the core 39 responding genes have been identified by literature survey. Auxin responsive genes are depicted in blue, sugar responsive genes in yellow. Genes that have been shown to respond to ROS or related to ROS pathways are colored in green and genes related to ABA signals are denoted in red. Calcium dependent genes or genes responsive to calcium are depicted in black. Genes that are assigned to other pathways or stimuli are colored in gray. Genes that have been reported to react to more than one stimuli are colored accordingly. E.g., TOUCH2 (TCH2 (AT5G37770)) has been characterized as calcium dependent and responsive to ABA, auxin and ROS and is therefore colored in black, red, blue and green.

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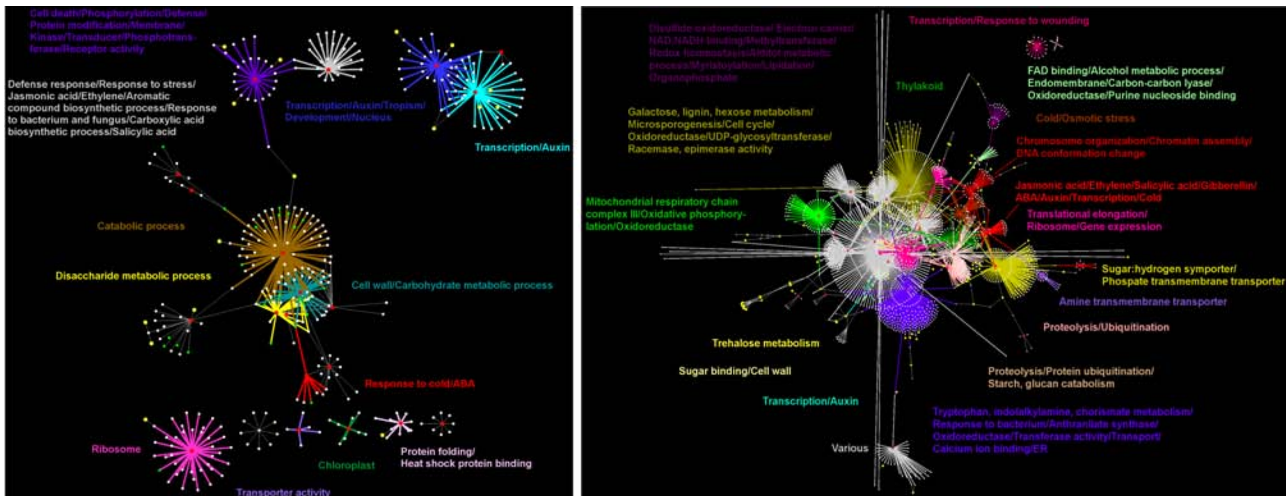
**Figure 3.** Embedding of core responsive genes in PPI and probabilistic networks




The network consists of those genes that shape the putative core response module and their direct interaction partners. The network was clustered for linked communities, which were subsequently analyzed for GO enriched terms. Terms being similar were categorized for better insight. Additionally, miRNAs targeting genes that link to communities are given. A) Network analysis using ANAP (PPI). Red, bold dots denote query genes, green dots genes that do not have a TAIR identifier. Yellow, bold nodes denote miRNAs. B) Network analysis using the probabilistic network AraNet. One hub, SUGAR TRANSPORTER1, was left out for visualization (Supplemental Figure S8). The category "various" describes highly complex categories. Red, bold dots denote query genes, while yellow, bold nodes denote miRNAs.

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## Tables

**Table 1.** Genes that were differentially expressed in all six experiments provoking retrograde signaling. Six different experiments considering retrograde signaling were analyzed in terms of their similarities and intersections in genetic expression. The intersection of all experiments with regard to their differentially expressed genes is presented. [A] The gene product is located to the chloroplast.

| **Locus ID** | **Short description** | **Functional Characteristics** | **References** |
|---|---|---|---|
| AT1G11260 | STP1 (SUGAR TRANSPORTER 1) | Sugar transporter<br><br>Responsive to salt stress | Sharma et al., 2007<br><br>Hsu et al., 2009 |
| AT1G49230 | Zinc finger (C3HC4-type RING finger) family protein | Responsive to ABA, cADPR<br><br>Responsive to ROS? | Sánchez et al., 2004<br><br>Charron et al., 2008 |
| AT1G56510 | WRR4 (WHITE RUST RESISTANCE 4) | Disease resistance<br><br>Responsive to salicylic acid | Zheng et al., 2006<br><br>Tan et al., 2007 |
| AT1G63180 | UGE3 (UDP-D-glucose/UDP-D-galactose 4-epimerase 3) | Sugar responsive<br><br>Cell wall structure and growth<br><br>Responsive to heat | Nicolaï et al., 2006<br><br>Mølhøj et al., 2004; Seifert et al., 2002; Rösti et al., 2007<br><br>Busch et al., 2005 |
| AT1G66100 | Thionin, putative | ABA responsive | Osakabe et al., 2005 |
| AT1G68440 | Unknown protein | Responsive to oxidative | Baxter et al., 2007 |

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| | | | |
|---|---|---|---|
| | | stress<br><br>Responsive to Sucrose after starvation | <br><br>Nicolaï et al., 2006 |
| AT1G77690 | LAX3 (LIKE AUX1 3) | Auxin influx-carrier<br><br>Involved in cell pattern in apex and hook<br><br>development | Péret et al., 2012<br><br>Ugartechea-Chirino et al.,<br><br>2010; Vandenbussche et<br><br>al., 2010; Swarup et al.,<br><br>2008 |
| AT2G05540 | Glycine-rich protein | Component of cell wall<br><br>Stress responsive, ABA-responsive | Ringli et al., 2001; Martínez and Chrispeels, 2001<br><br>Suzuki et al., 2005; Xin et al., 2005 |
| AT2G14660 | Unknown protein | Undescribed | |
| AT2G15890 [A] | MEE14 (maternal effect embryo arrest 14) | ABA responsive, stress inducible<br><br>Responsive to APETALA3 | Leonhardt et al., 2004; Bräutigam et al., 2009<br><br>Zik and Irish, 2003 |
| AT2G17880 [A] | DNAJ heat shock protein, putative | Responsive to sugar after starvation<br><br>Mediates tolerance to oxidative stress? | Usadel et al., 2008<br><br>Chen et al., 2010 |
| AT2G18050 | HIS1-3 (HISTONE H1-3) | ABA responsive, stress inducible<br><br>Drought responsive<br><br>Responsive to sugar after | Fujita et al., 2005<br><br>Ascenzi and Gantt, 1997<br><br>Osuna et al., 2007 |

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| | | | |
|---|---|---|---|
| | | starvation<br>Responsive to cADPR | <br>Sánchez et al., 2004 |
| AT3G15630 | Unknown protein | Responsive to sugar after starvation<br>Cell wall modification<br>Sensible to ROS stress | Usadel et al., 2008<br>Jakoby et al., 2008<br>Boyce et al., 2003 |
| AT3G23030 | IAA2 (INDOLE-3-ACETIC ACID INDUCIBLE 2) | Auxin induced | Overvoorde et al., 2005 |
| AT3G26740 [A] | CCL (CCR-LIKE) | Responsive to Calcium | Kaplan et al., 2006 |
| AT3G29030 | EXPA5 (EXPANSIN A5) | Cell wall modification<br>ROS responsive | Li et al., 2002<br>Davletova et al., 2005 |
| AT3G44450 | Unknown protein | ROS responsive<br>Sugar responsive after starvation | Brown et al., 2005<br>Usadel et al., 2008 |
| AT3G47420 | Glycerol-3-phosphate transporter, putative | Pi-starvation responsive | Bari et al., 2006 |
| AT3G62950 | Glutaredoxin family protein | Redox signaling<br>Responsible to salt<br>Defense reaction? | Rouhier et al., 2008; Nagata et al., 2005; Kasukabe et al., 2004<br>Sottosanto et al., 2004<br>Sattler et al., 2006 |
| AT4G04630 | Unknown protein | Undescribed | |
| AT4G17245 | Zinc finger (C3HC4-type RING finger) family protein | Responsive to the SWI/SNF-ATPases BRAHMA and SPLAYED | Bezhani et al., 2007 |

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| | | | |
|---|---|---|---|
| AT4G19380 | Alcohol oxidase-related | Defense reaction? | Kachroo and Kachroo, 2009 |
| AT4G28270 | Zinc finger (C3HC4-type RING finger) family protein | Auxin responsive<br><br>Drought stress | Huang et al., 2008<br><br>Son et al., 2010 |
| AT4G32280 | IAA29 (INDOLE-3-ACETIC ACID INDUCIBLE 29) | Auxin induced | Overvoorde et al., 2005 |
| AT4G34770 | Auxin-responsive family protein | Auxin responsive<br><br>Responsive to cold | Schwager et al., 2007<br><br>Lee et al., 2005 |
| AT4G39030 | EDS5 (ENHANCED DISEASE SUSCEPTIBILITY 5) | Defense response, involved in salicylic acid pathway<br><br>ROS responsive | Nawrath et al., 2002<br><br>Ogawa et al., 2007 |
| AT5G02760 | PP2C family protein | Stress responsive, ABA responsive<br><br>Auxin responsive<br><br>Sugar responsive<br><br>Calcium responsive | Xue et al., 2008<br><br>Zhao et al., 2003<br><br>Osuna et al., 2007<br><br>Sugimoto et al., 1997 |
| AT5G08350 | GRAM domain-containing protein / ABA-responsive protein-related | Sugar responsive<br><br>ABA responsive, RGA responsive | Usadel et al., 2008<br><br>Efetova et al., 2007; Hou et al., 2008; Jiang et al., 2008 |

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| AT5G17860 | CAX7 (calcium exchanger 7) | Interaction with calcium<br><br>ABA responsive<br><br>RGA regulated<br><br>Sugar responsive after starvation | Delk et al., 2005<br><br>Efetova et al., 2007<br><br>Hou et al., 2008<br><br>Usadel et al., 2008 |
|---|---|---|---|
| AT5G19120 | Aspartic-type endopeptidase | ROS responsive<br><br>Sensible to chilling stress<br><br>Response to APETALA3 | Nagata et al., 2005<br><br>Kasukabe et al., 2004<br><br>Zik and Irish, 2003 |
| AT5G20250 [A] | DIN10 (DARK INDUCIBLE 10) | Antioxidant<br><br>Sugar responsive | Nishizawa et al., 2008<br><br>Fujiki et al., 2000 |
| AT5G21170 [A] | 5'-AMP-activated protein kinase beta-2 subunit, putative | Responsive to sugar starvation<br><br>ABA | Li et al., 2009<br><br>Jossier et al., 2009; Hey et al., 2010 |
| AT5G22920 | Zinc finger (C3HC4-type RING finger) family protein | Sugar starvation<br><br>RGA responsive | Usadel et al., 2008<br><br>Hou et al., 2008 |
| AT5G24660 | LSU2 (RESPONSE TO LOW SULFUR 2) | ROS responsive?<br><br>Responsive to lack of sulfur<br><br>Response to sugar after starvation | Davletova et al., 2005<br><br>Lewandowska et al., 2010<br><br>Usadel et al., 2008 |

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| | | | |
|---|---|---|---|
| AT5G37770 | TCH2 (TOUCH 2) | Interaction with Calcium, response to ABA, Auxin, eventually involved in redox signaling and responsive to ROS | Delk et al., 2005 |
| AT5G51460 [A] | ATTPPA | Involved in developmental process<br><br>Through T6P connected to cell wall modification, defense reaction | Vogel et al., 1998<br><br>Schluepmann et al., 2004 |
| AT5G63190 | MA3 domain-containing protein | Stress responsive | Sharma et al., 2007 |
| AT5G64640 | Pectinesterase family protein | Cell wall modification | Louvet et al., 2006 |
| AT5G67420 | LBD37 (LOB DOMAIN-CONTAINING PROTEIN 37) | Organ development, stress responsive | Shuai et al., 2002 |

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**Table 2.** Differentially expressed transcription factors, which putatively bind to the identified promoter elements.

| Gene ID | Shortname | Motif putatively bound |
|---|---|---|
| AT1G13450<br>AT1G69010 | GT-1<br>BIM2 | ABREATRD22 (GCAC) |
| AT1G69010 | BIM2 | ATMYC2-RD22<br>([A\|C\|G]ACATG for kmer 5, [A\|G\|T][A\|C][C\|G]CATGTG for kmer 8) |
| AT4G01120<br>AT2G46270<br>AT1G03970<br>AT4G34590 | GBF2<br>GBF3<br>GBF4<br>GBF6 | ABRE-like<br>([A\|G\|T][A\|C]CACGT[G\|T][A\|G\|T]) |
| AT2G22430 | ATHB6 | ATHB6 bindingsite motif<br>(AATAATA) |
| AT2G03340<br>AT4G31800<br>AT5G07100<br>AT4G30935<br>AT2G38470<br>AT3G04670<br>AT1G80840<br>AT3G01970<br>AT2G46400<br>AT4G23810 | WRKY3<br>WRKY18<br>WRKY26<br>WRKY32<br>WRKY33<br>WRKY39<br>WRKY40<br>WRKY45<br>WRKY46<br>WRKY53 | WBOXATNPR1<br>(A[A\|T]GTTGAC) |

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| | | |
|---|---|---|
| AT3G56400 | WRKY70 | |
| AT5G65210 | TGA1 | I-Box ([C|G|T]C[C|T]TATCC for kmer 7, CTTATC[C|T][A|G|T] for kmer 8) |

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**Table 3.** Categories of GO terms in all k-means derived clusters. Over all clusters, the identified enriched terms were grouped for similarities (Table S6). Subsequently, the percentage of terms supporting such a group was calculated in relation to all identified enriched terms. The total sum of terms supporting a specific group is given as well as the percentage for each group.

| **Category** | **% of all terms** |
|---|---|
| Transcription and translation | 24.21% |
| Miscellaneous | 9.47% |
| Compartments | 10.00% |
| Sugar-related | 6.32% |
| Hormones | 5.79% |
| Growth and development | 5.27% |
| Lipids, cell wall establishment | 4.74% |
| Stresses | 4.21% |
| Transport | 4.21% |
| Wounding and defense reaction | 4.21% |
| Light and circadian rhythm | 4.21% |
| Pigments | 2.63% |
| Metal ions | 2.63% |
| Oxidoreductases | 2.11% |
| Protein folding and assembly | 1.58% |
| Amino acid metabolism | 1.58% |
| Phosphorylation | 1.58% |
| Degradation | 1.05% |
| Nitrogen compound biosynthetic process | 1.05% |
| Sulfur | 1.05% |
| Kinases | 1.05% |
| Vitamin biosynthesis | 1.05% |

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