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Central Metabolic Changes to O_3 and Herbivory in *B. nigra* Affect Photosynthesis and Stomata Closure

Running title: Omics Multiple Stress Responses in *Brassica nigra*

Stefano PAPAZIAN[a], Eliezer KHALING[b], Christelle BONNET[c], Steve LASSUEUR[c], Philippe REYMOND[c], Thomas MORITZ[d], James D. BLANDE[b,1], Benedicte R. ALBRECTSEN[a,1]

[a.] Umeå Plant Science Centre, Department of Plant Physiology, Umeå University, 90187 Umeå, Sweden
[b.] Department of Environmental and Biological Sciences, University of Eastern Finland, P.O. Box 1627, FIN-70211, Kuopio, Finland.
[c.] Department of Plant Molecular Biology, University of Lausanne, 1015 Lausanne, Switzerland
[d.] Umeå Plant Science Centre, Department of Forest Genetic and Plant Physiology, Swedish University of Agricultural Sciences, 90187 Umeå, Sweden

[1]Address correspondence to:
Benedicte Albrectsen benedicte.albrectsen@umu.se
and James Blande james.blande@uef.fi

One sentence summary:

When facing a scenario of sequential abiotic and biotic stress, black mustard regulates glycerol and central energy metabolism to prioritize processes of photosynthesis and stomatal osmoregulation.

ABSTRACT

Plants evolved adaptive mechanisms which allow them to encounter a continuous range of abiotic and biotic stressors. Tropospheric ozone (O_3) is a global anthropogenic pollutant that directly affects living organisms and ecosystems, including plant-herbivore interactions. In this study we investigate the stress responses of the wild black mustard (*Brassica nigra*) exposed consecutively to O_3 and the specialist herbivore *Pieris brassicae.* Transcriptomics and metabolomics data were evaluated via multivariate, correlation and network analyses for the O_3 and herbivory responses. O_3 stress symptoms resembled those of senescence and phosphate starvation, while sequential shift from O_3 to herbivory induced characteristic plant defense responses, including decrease in central metabolism, induction of the JA/ET pathways, and emission of volatiles. Omics network and pathway analyses predicted a link between glycerol and central energy metabolism, with impact on processes of osmotic stress response and stomatal closure. Further physiological measurements confirmed that, while O_3 stress inhibited photosystem and carbon assimilation, sequential herbivory counteracted the initial responses induced by O_3, resulting in a phenotype which was similar to the one observed after herbivory alone. Overall, this study addresses the consequences of multiple stress interactions on a plant metabolic system, but it also represents an example of how omics data can be integrated to generate new hypotheses in ecology and plant physiology.

INTRODUCTION

Under natural conditions plants are continuously exposed to abiotic and biotic stresses. When studied in the laboratory, individual stresses trigger a variety of molecular, cellular, and physiological responses (**Ben Rejeb et al., 2014; Suzuki et al., 2014**). However, the way plants protect themselves in nature cannot be predicted on the basis of responses to individual stresses alone, as combined stresses may elicit antagonistic, neutral, or synergistic effects (**Rizsky et al., 2002, 2004; Mittler, 2006; Pandey et al., 2015**). Thus, there is increasing interest in plant responses to multiple stress conditions, and while most studies have focused on multiple abiotic factors (**Suzuki et al*.,* 2014**), biotic factors are usually limited to pathogen infection (**Sharma et al., 1996; Xiong and Yang, 2003; Anderson, 2004; Prasch and Sonnewald, 2013;** but see **Atkinson and Urwin, 2012; Atkinson et al., 2013**).

Global warming encompasses a range of interrelated abiotic phenomena, including increases in the Earth´s average temperature and changes in the greenhouse gas [e.g. methane, carbon dioxide (CO_2), and ozone (O_3)] composition of the atmosphere. Burning of fossil fuels releases nitrogen oxides and hydrocarbons, which in the presence of sunlight react to form tropospheric O_3, the most significant pollutant in the atmosphere in terms of phytotoxicity (**Ludwikow and Sadowski, 2008; Renaut et al*.,* 2009; Van Dingenen et al., 2009**). Plant responses to O_3 vary according to the intensity and duration of the exposure, but generally concur with deleterious effects on plant fitness, disturbing the processes of photosynthesis, energy and carbon metabolism, cellular detoxification, and transpiration (**Bagard et al., 2008; Dizengremel et al., 2008; Fares et al., 2010; Goumenaki et al., 2010; Salvatori et al., 2015**). However, while acute

74 exposure to high O_3 levels can rapidly cause induction of cell death and chlorosis (for
75 reviews see **Ashmore 2005**; **Kangasjärvi et al., 2005; Vainonen and Kangasjarvi,**
76 **2015**), negative yield responses are not always correlated with the severity of symptoms
77 in leaves, and exposure to O_3 can affect the plant metabolic processes prior to any
78 visible injury (**Long and Naidu 2002**; **Dizengremel et al., 2009; Sawada & Kohno,**
79 **2009; Pinto et al., 2010**).

80 Damage to plants caused by herbivory is also predicted to increase in response to
81 global change, either through direct effects on the herbivore behavior and survival, or
82 through indirect effects on the host plant condition (**Bale et al., 2002; Fuhrer, 2003;**
83 **Ditchkoff et al., 2009; Lindroth, 2010; Khaling et al., 2015**). Negative effects of
84 herbivory and defoliation on plant fitness include systemic down-regulation of
85 photosynthesis and reduced CO_2 assimilation (**Zangerl et al., 2002; Hui et al. 2003;**
86 **Ralph et al., 2006; Tang et al., 2006**). Thus, to protect against herbivores, plants
87 evaluate priorities and allocate resources between growth and defense (**Koricheva,**
88 **2002; Schwachtje and Baldwin, 2008; Firn and Jones, 2009; Havko et al., 2016**).

89 In Brassicaceae, leaf-chewing herbivores activate phytohormone signaling, where
90 crosstalk between JA and ET pathways fine-tunes the defense response (**de Vos et al.,**
91 **2005**; **Pieterse et al., 2012**). The large cabbage white (*Pieris brassicae*) is a specialist
92 Brassicaceae-feeding herbivore and is an important pest of black mustard (*Brassica*
93 *nigra*). *P. brassicae* oviposition on the host plant is influenced by glucosinolates (sulfur
94 and nitrogen containing glucosides) that function as chemical cues for the butterfly
95 (**Fahey et al., 2001**; **Petersen et al., 2002**; **Halkier and Gershenzon, 2006**; **Textor and**
96 **Gershenzon, 2008**). Young caterpillars primarily feed on mature leaves of *B. nigra*, but

97 after the third instar they move to fresh tissues with higher glucosinolate content, such
98 as flowers and buds (**Smallegange et al., 2007**). Plant-herbivore interactions are thus
99 frequently described with an emphasis on specialized (secondary) metabolism
100 (**Simmonds, 2003**; **van Dam et al., 2004**; **Poelman et al., 2010; Boeckler et al., 2011**;
101 **Lof et al., 2013**; **Onkokesung et al., 2014**). However, plant metabolism has a large
102 functional overlap between growth and defense traits, and reconfiguration at the level of
103 primary and energy metabolism can play a central role in the processes of stress
104 tolerance, signal transmission, and direct defense (**Both et al 2005; Rolland et al.,**
105 **2006; Schwachtje and Baldwin 2008; Fernandez et al., 2010)**.

106 The metabolomics approach has already been applied to different areas of plant biology
107 and ecology (for reviews see **Sardans et al., 2011** and **Weckwerth, 2011**), where it has
108 helped in understanding the regulation of pathways during plant-herbivore interactions
109 (**Jansen et al., 2008; Misra et al., 2010**) and plant stress responses (**Shulaev et al.,**
110 **2008**; **Nakabayashi and Saito, 2015**). What typically distinguishes metabolomics from
111 targeted analyses, or general metabolic profiling, is the ambition to integrate with other
112 omics sciences (**Fiehn, 2002; Barah and Bones, 2014**). Combined with the 'guilt-by-
113 association' principle (**Bino et al., 2004**; **Saito et al., 2008**), omics analyses allow
114 prediction of unknown gene and metabolite functions. For instance, the systematic
115 metabolomics approach has been successful in determining the biosynthetic regulation
116 of glucosinolates by MYB transcription factors (**Hirai et al., 2007; Sønderby et al., 2007**)
117 and in the modelling of the costs of glucosinolate biosynthesis in terms of primary
118 metabolism (**Bekaert et al., 2012**). New hypotheses generated by this data driven ("top-
119 down") strategy can thus guide the understanding of regulatory and metabolic pathways,

120 and eventually predict the emergence of certain phenotypes (**Fukushima et al., 2009;**
121 **Saito and Matsuda, 2010**).

122 Through integrated transcriptomics and metabolomics analyses in our study, we sought
123 to understand the systems regulation of *B. nigra* when exposed to sequential stress by
124 O_3 and *P. brassicae* herbivory. We found that shift from abiotic to biotic stress responses
125 differentially regulated glycerol and energy metabolic networks. In our model, these
126 pathways were functionally associated with photosystem and mitochondrial activity, and
127 were further predicted to involve physiological responses related to osmotic stress
128 tolerance and stomatal closure. Altogether, these results suggest an important role of
129 these central processes in the plant adaptation to sequential abiotic and biotic stresses.
130 The impact of the stresses on the plant physiology was assessed in an additional
131 experiment with measurements of photosynthesis and gas exchange, which confirmed a
132 negative effect of *P. brassicae* herbivory on the plant ability to regulate stomatal closure
133 and transpiration in response to O_3.

134

135

136 **RESULTS**

137 Black mustard was subjected to the following stress scenarios: O_3 fumigation at 70 ppb
138 for five days (O); herbivore-feeding by first instar *P. brassicae* caterpillars for 24 hours
139 (P); exposure to O_3 followed by herbivory (OP). Leaf samples were shared for omics
140 analyses (**Figure 1**: "Experiment 1"). Transcriptomics screening was based on
141 *Arabidopsis* CATMAv4 whole-genome microarrays (**Sclep et al., 2007**), while
142 metabolomics screening combined GC-MS, LC-MS, and VOCs collected via dynamic
143 headspace sampling and analysed by GC-MS (See **Supplemental Datasets S1** and
144 **S2**). Omics data were first examined separately and then integrated via network and GO
145 analyses. Molecular and metabolic responses were framed in a model which predicted
146 opposite regulatory dynamics between O_3 and sequential herbivory. This hypothesis was
147 tested in a follow-up experiment (**Figure 1**: "Experiment 2"), where physiological data of
148 chlorophyll content, photosynthesis rate, and gas exchange, were measured for the
149 same stress conditions (O, P, OP), and for a long term O_3 exposure of 16 days (OL).
150

151 **Transcriptome Responses**

152 Hierarchical cluster and gene ontology (GO) analyses of 970 differentially expressed
153 genes (*P*-value < 0.05) (**Figure 2A, 2B**) separated the O_3 stress treatment (O) from
154 herbivory (P) and the sequential stress treatment (OP). After GO enrichment, the
155 strongest response was represented by energy metabolic processes, including
156 photosystem and the mitochondria electron transport chain (ETC) (**Figure 2A, 2B**).
157 Overall, expressions in O were highly homogenous (Pearson´s coefficient, ρ = 0.6-0.8),
158 while P and OP showed lower correlation within their clusters (ρ = 0.2-0.5; **Figure 2C**).
159 MapMan pathway analysis confirmed similar responses at several biological levels

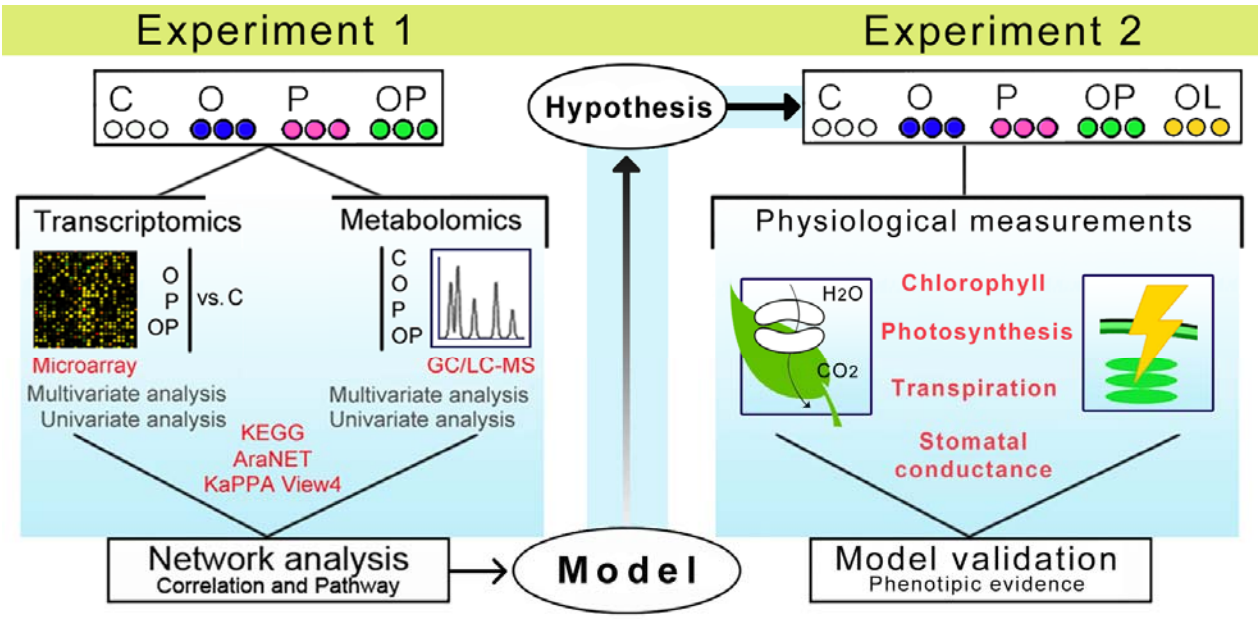

Figure 1. Design of omics experiments, hypothesis generation and validation via physiological evidence. Experiment 1: five weeks old Brassica nigra plants were exposed to abiotic and/or biotic stresses, including O3 fumigation at 70 ppb for five days (O), herbivore-feeding with 30 first instar P. brassicae caterpillars for 24 hours (P), sequential stress of O3 followed by herbivore-feeding (OP), or no treatment as controls (C). To obtain a comprehensive understanding of metabolome and transcriptome responses to the treatments, leaves of equal developmental stage were sampled from the same plants from which volatile emissions (VOCs) had been obtained. Statistical and network analyses combined omics data in a model which connected the metabolic responses with physiological adaptation to the multiple stress condition. B. nigra responses were further evaluated in Experiment 2: physiological parameters were measured for the same stress treatments (O, P, OP) and for a long term exposure to O3 at 70 ppb for 16 days (OL). The initial hypothesis was thus verified through validation of the omics model, which predicted differential physiological responses of photosystem, carbon assimilation and stomatal regulation.

(**Figure 2D**), while Venn diagrams based on Log2 fold changes ≥ 0.585 (for *P*-value < 0.05) indicated a dominance of up- and down- regulated genes in O, with the least impact in OP (**Figure 2E**).

Genes involved in photosystem and carbon assimilation were down-regulated in response to all stress scenarios but particularly in O (**Figure 2D**, **2F**), which also resulted in up-regulation of non-photochemical quenching *NPQ1* (**Figure 2F**). Other primary processes such as amino acid and carbohydrate metabolism generally showed opposite patterns of regulation for O_3 and herbivory (**Figure 2D, 2G**). In the sequential treatment (OP), *B. nigra* activated defense responses characteristic to herbivory alone

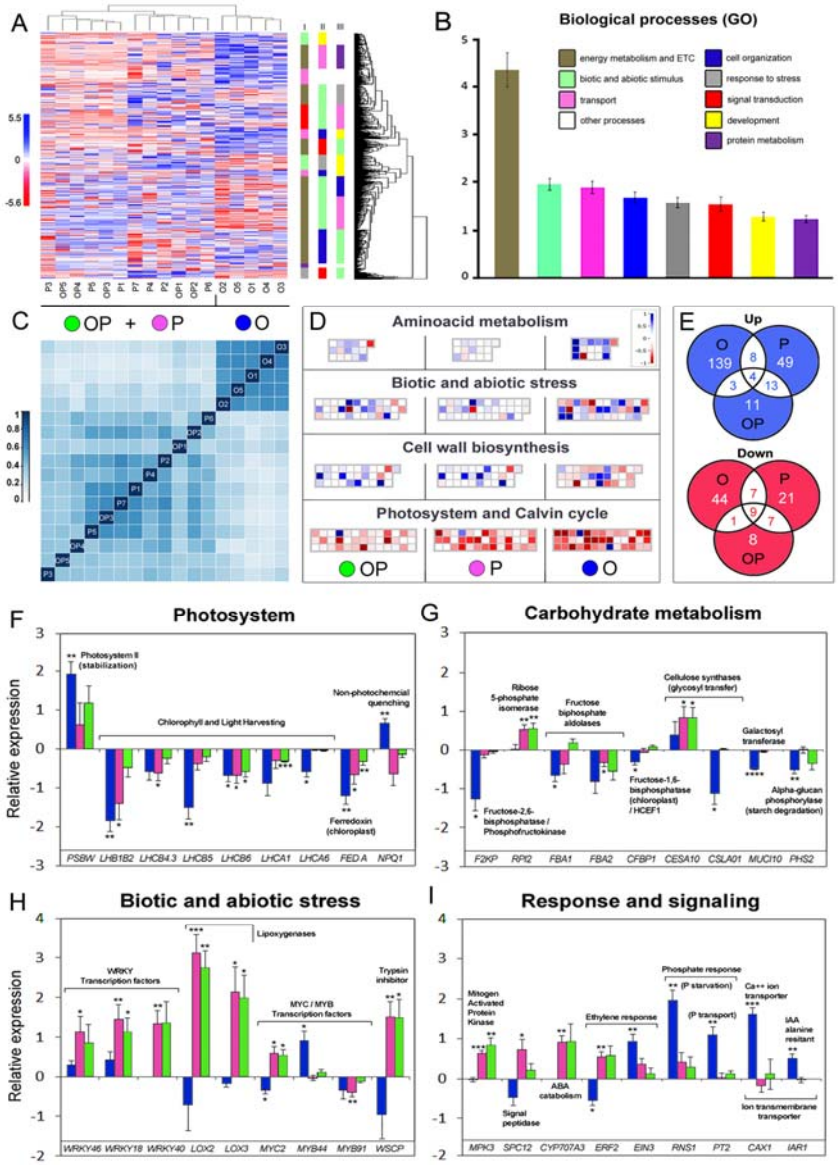

Figure 2. Transcriptome responses in B. nigra under multiple O3 and herbivory stress treatments: O3 stress (O), herbivory by P. brassicae (P), sequential treatment (OP). A, Heat-map for expression profiles of 970 genes, P-value ≤ 0.05 (rows) versus samples (columns) sorted by hierarchical clustering. Red indicates down-regulation, and blue up-regulation. GO enriched biological processes for each clusters was ranked (I, II, III) for their relative abundance and colored as in B, Summary of total GO processes significantly enriched in all the gene clusters, ordered by their relative abundance (for all 970 genes). C, Heat-map of Pearson´s correlation coefficient (ρ) as calculated for each sample pairs from the corresponding hierarchical clustering; darker blue shade indicates higher correlation ρ. D, Mapman biological functions (bins) showing the effect of the stress treatments on gene expression relative to amino acid metabolism, biotic and abiotic stress, cell wall biosynthesis, photosystem and Calvin cycle. E, Venn-diagrams (MapMan generated) comparing genes up- and down-regulated in response to the treatments, for Log2 fold-change thresholds > 0.585 (P-value ≤ 0.05). Lower panels show univariate analysis relevant to regulation of central metabolism and stress responses: F, processes of photosystem and light harvesting. G, carbohydrate metabolism. H, biotic and abiotic stress. F, response and signaling. Relative expressions are reported as log2 values. Significance relative to the controls (zero-level) is reported as student t-test P-values of * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001. Error bars= S.E. Treatments: ozone (O) in white; herbivory by P.brassicae (P) in grey; sequential treatment (OP) in black.

(P) (**Figure 2H, 2I**) - e.g. lipoxygenases *LOX2* and *LOX3* (**Felton et al., 1993; Halitschke and Baldwin, 2003**), trypsin inhibitor *WSCP* (**Zavala and Baldwin, 2004; Boex-Fontvieille et al., 2015**) and mitogen-activated protein kinase *MPK3* (**Pitzschke**

172 **and Hirt, 2008**). Notably, genes involved in stress responses and phytohormone
173 signaling were differentially regulated for the single O_3 stress and the herbivory
174 treatments (e.g. *WRKYs, MYC2, ERF2*), and only in O were abiotic stress responses
175 induced, such as drought (*MYB44),* senescence (*EIN3),* and phosphate starvation
176 (*RNS1*, *PT2*/*PHT1.4*) (**Figure 2H, 2I**).
177
178 **Metabolome Responses**
179 A multivariate analysis of the metabolome profile explained 65% of the metabolic
180 variation, and 95% of the treatment effects (PLS-DA, **Figure 3A, Supplemental Figure**
181 **S1** and **Supplemental Table S1**). Both O_3 stress and herbivory caused a shift from the
182 basal metabolic state of the untreated plants, inducing unique profiles as single
183 treatments in O and P. However, the effect of herbivory largely overshadowed the effect
184 of O_3 in the sequential treatment OP, indicated by the swarm overlap with P (**Figure 3A**).
185 Despite the importance of several metabolite pools in the multivariate model (**Figure 3B**
186 and **Supplemental Table S2**; 70 compounds for VIP scores > 1.00), single univariate
187 effects were only confirmed for a subset of these (**Figure 3C**, ANOVA post-hoc Tukey
188 tests).
189 Opposite effects of O_3 and herbivory were observed on pools of primary metabolites -
190 sugars, amino acids, and organic acids - which increased in O and decreased in P and
191 OP (**Figure 3B** and **Supplemental Table S2**). However, a common response to all
192 treatments was a three-fold induction of γ-aminobutyric acid (GABA; **Figure 3B, 3C**),
193 which partly correlated with its precursor α-ketoglutarate (α-KG) (**Figure 3B**). Most
194 noticeably, glycerol increased to 155% in O (**Figure 3B, 3C**), but was restored to steady-
195 state levels in the sequential treatment OP. A similar trend was observed for

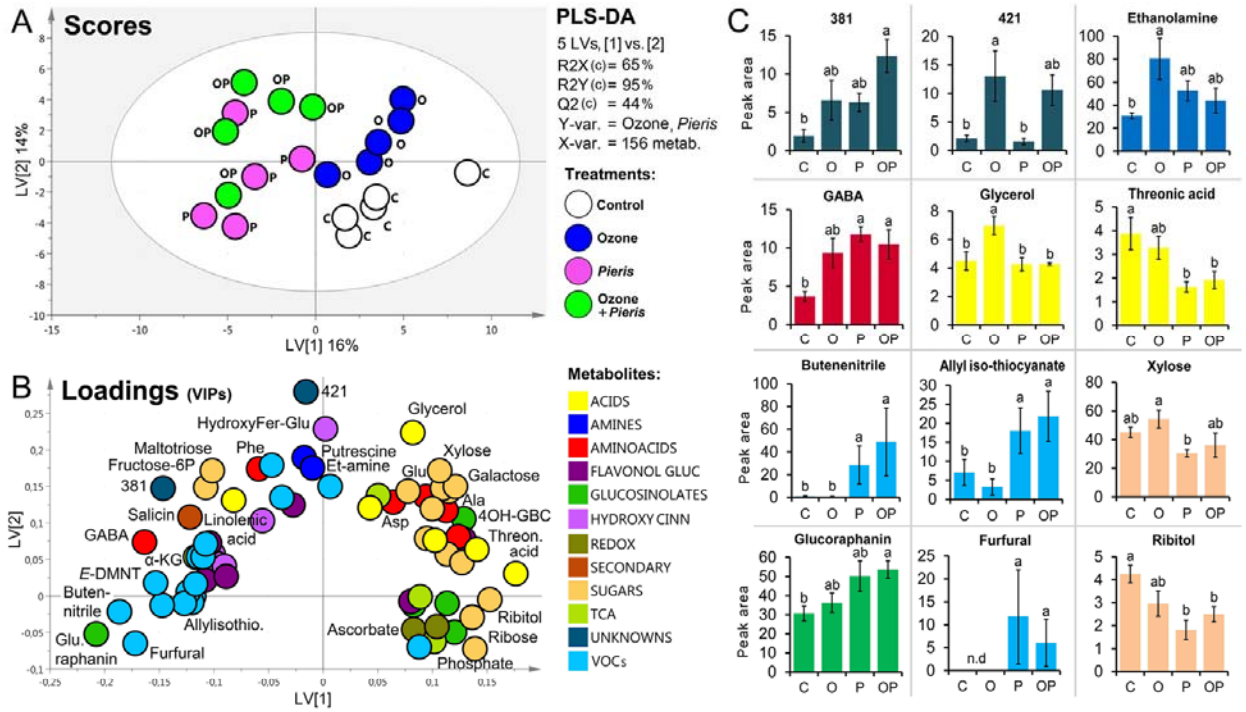

Figure 3. Metabolome responses in B. nigra under multiple O3 and herbivory stress treatments. O3 stress (O), herbivory by P. brassicae (P), sequential treatment (OP), and untreated plants (C). Leaf bound metabolites were analysed through LC-MS and GC-MS, while VOCs were collected via head-space and analysed with GC-MS. Five LVs cumulatively explained 65% variation in X (R2X[c]), and 95% of the treatment response (R2[c]Y), with 44% of total model predictability (Q2[c]). See model statistics and metabolite indentities in Supplemental Table S1 and S2. A, PLS-DA score plot of first and second latent variables, [LV1] vs. [LV2]. See Supplemental Fig S1 for score plots relative to [LV3]. B, PLS-DA loading plot showing important metabolites for the model (VIPs > 1.00). C, ANOVAs with post-hoc Tuckey comparisons to test treatment effects for selected compounds (different letters indicate different response means). Error bars= SE.

ethanolamine, another metabolite of the glycerophospholipid pathway and a component of lipid membranes (**Figure 3C**). Phenolic compounds, such as flavonols and cinnamic acid ester derivatives (**Lin et al, 2011; Shao et al., 2014**) increased in all treatments. Glucosinolate levels were stable or reduced (with glucoraphanin the only exception), while VOCs were emitted upon herbivore damage (P, OP), including glucosinolate derivatives and green leaf volatiles (GLVs) (**Figure 3B, 3C** and **Supplemental Table S2**). Two unidentified secondary compounds, previously described by **Khaling et al. 2015** (i.e. “421” [M-H]- m/z 485.13, and “381” [M-H]- m/z 349.15), were also induced, confirming their importance respectively in O and OP (**Figure 3C**).

206 **Omics Integrative Network Correlation Analysis**

207 Transcriptomic and metabolomic profiles were integrated in a scale-free correlation
208 network (**Figure 4**) (see topology in **Supplemental Figure S2**). The network was
209 dominated by assortative high-degree nodes (*hubs*), with major hubs involved in
210 processes such as stress signaling, cellulose biosynthesis, chloroplast activity and
211 stomatal regulation (**Table I**). Several primary metabolites clustered around the central
212 region of the network, while distinct modules of secondary metabolites clustered at the
213 periphery – i.e. glucosinolates, flavonol glucosides, hydroxycinnamic acid derivatives,
214 and VOCs (**Figure 4A-C**). Most glucosinolates connected to *CYP71,* a cytochrome
215 involved in herbivore-induced responses and formation of nitriles (At5g25120 /
216 At5g25180; **Bennett et al., 1993**, **Irmisch et al., 2014**). Glucobrassicin and
217 neoglucobrassicin (indolics) directly clustered with VOCs (nitriles and GLVs) and
218 positively correlated with *WRKY40* (involved in indolic glucosinolate biosynthesis and
219 GLV emissions; **Schön et al., 2013; Mirabella et al., 2015**)*, WRKY46* and *CYP707A3*
220 (both involved in ABA metabolism; **Saito et al., 2004; Liu et al., 2012; Geilen and**
221 **Bohmer, 2015**) (**Figure 4C**). The herbivory response (P) linked to glycerol via four
222 nodes, including two genes coding for flavin monooxygenases *NOGC1* (At1g62580) and
223 *FMO* (At1g12200), which negatively correlated with glycerol (ρ = -0.86, *P*-value < 0.001)
224 and positively correlated with each other (ρ = 0.85, *P*-value < 0.001) (**Figure 4A, 4B**).
225 *MYB44* linked to the same module and negatively correlated with *NOGC1* (ρ = -0.91, *P*-
226 value < 0.0001) while it positively correlated with glycerol (ρ = 0.68, *P*-value =
227 0.006)(**Figure 4B**). Notably, both *MYB44* and *NOGC1* are involved in osmotic stress
228 response and regulation of stomatal closure.

229

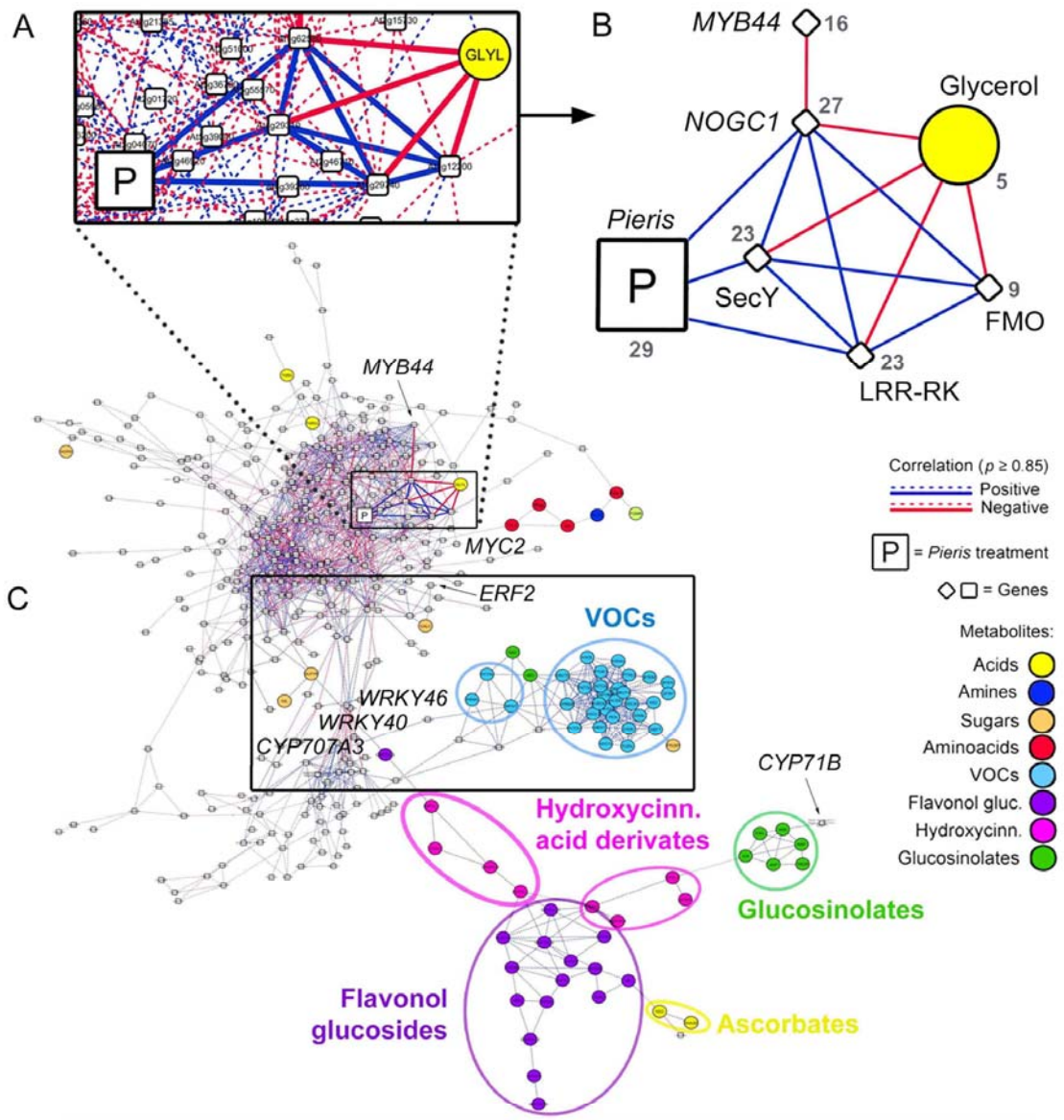

Figure 4. Omics integrative network correlation analysis for multiple stress responses in B. nigra. Gene expression profiles for 970 genes (P-value < 0.05) were correlated with the metabolome profile (156 compounds) considering all the treatments conditions of O3 stress and P. brassicae herbivory. The resulting graph was rendered as a network which was generated in Cytoscape. Edges: Pearson´s correlation coefficient (ρ ≥ 0.85) for positive (blue) and negative (red) correlation. Nodes: genes (white squares/diamonds), metabolites (colored circles). Herbivore variable for the effect of P. brassicae treatment is indicated by the bold letter (P), white square. A, Network of gene-to-gene, gene-to-metabolite, and metabolite-to-metabolite correlations. B, Zoom-in on the gene-to-metabolite subnet highlighting the effect of (P) on glycerol and co-expressed genes (MYB44, flavin monoxygenases NOGC1 and FMO, a LRR-RK receptor and a SecY protein). C, VOCs subnet, connecting central metabolism to secondary metabolism (glucosinolates, hydroxycinnamic acid derivates and flavonol glucosides) via WRK40, WRK46, and CYP707A3.

Responses Relative to Energy and Glycerol Metabolic Networks

Energy metabolic processes (photosystem and mitochondria) were the most affected by the stress treatments (**Figure 2A, 2B**). Based on these energy genes (functionally

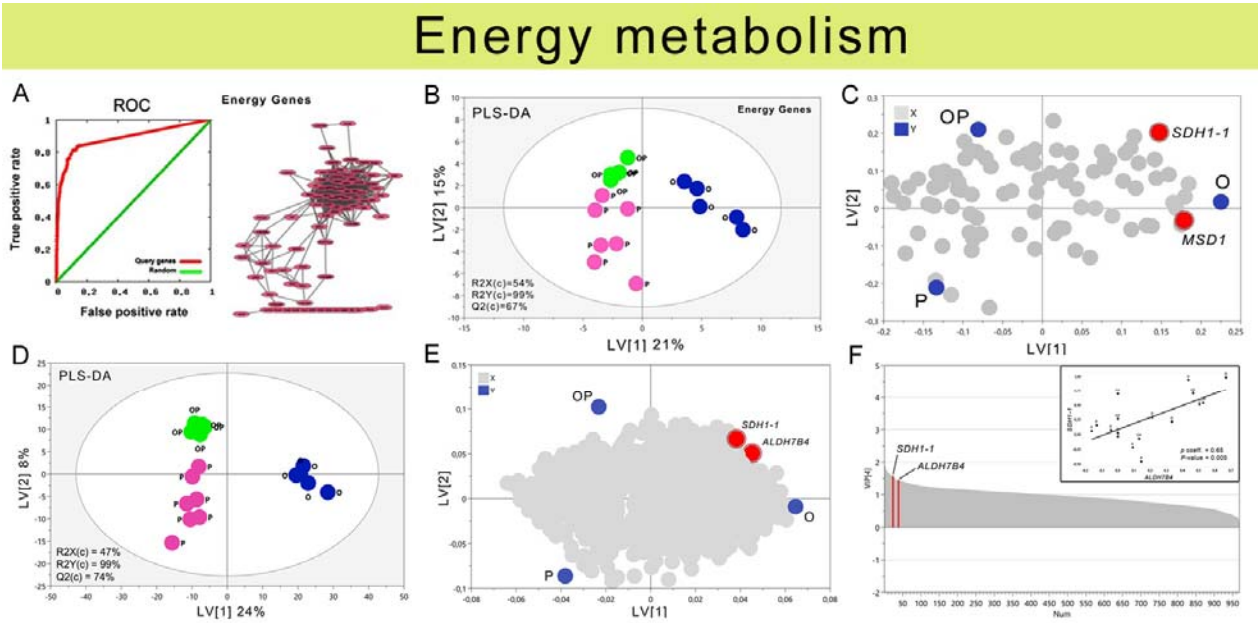

Figure 5 Regulation of energy metabolic networks in B. nigra, under multiple O3 and herbivory stress treatments. A, Network model (AraNet) assessing gene connectivity between the 85 genes enriched in energy metabolic processes. Model fitness was calculated by genes inter-connectivity of the receiver operating characteristic (ROC), for true-positives and false-positives rate between the entry genes (red curve) and a randomly generated gene-set (green curve). The network scored high area under the curve (AUC = 0.89; P-value = 1.82 E-62). B-C, Multivariate analysis evaluating the change in expression of energy genes in the network, during the multiple stress treatments: O3 (O), herbivory by P. brassicae (P), and sequential treatment (OP). PLS-DA score and loading plots of first and second latent variables [LV1] vs. [LV2] are shown. Treatments: O, P and OP. Five LVs cumulatively explained 54% variation in X (R2X[c]), and 99% of the treatment response (R2[c]Y), with 67% of total model predictability (Q2[c]). The importance of mitochondrial genes SDH1-1 and MSD1 in the model is highlighted (in red; VIP = 1.40 and 1.34; see in Supplemental Table S4 and S5). D-E, Multivariate analysis for general model (970 genes; P-value ≤ 0.05). Treatments: O, P, and OP. PLS-DA score and loading plots of first and second latent variables [LV1] vs. [LV2] are shown (see Supplemental Table 6 and 7). In red, SDH1-1 (VIP= 1.57) and ALDH7B4 (VIP =1.45), are important for O3 treatments (O, OP), as also shown in F, distribution of VIP values for all 970 genes, and correlation between expression of SDH1-1 and ALDH7B4 throughout all treatment conditions, Pearson´s coefficient (ρ) = 0.65, P-value = 0.005.

connected in AraNet; **Figure 5A**), a PLS-DA strongly separated the stress treatments O, P and OP , explaining 54% of the variation in gene expression, and 99% of the treatment effects (**Figure 5B** and **Supplemental Table S4**). In response to O_3 stress, the mitochondrial ETC Complex II succinate dehydrogenase subunit *SDH1-1* (At5g66760) and the mitochondrial superoxide dismutase *MSD1* (At3g10920), were both up-regulated (**Figure 5C, Supplemental Table S5**). In the general model for expression of all 970 genes (**Figure 5D, 5E,** and **Supplemental Table S6** and **S7**), *SDH1-1* again strongly described the effect of O_3 (O, OP) while it positively correlated with *ALDH7B4*

241 (At1g54100; Pearson´s coefficient ρ = 0.65, *P*-value = 0.005; **Figure 5E, 5F**), aldehyde
242 dehydrogenase involved in glycerol metabolism.
243 Visualization of the entire glycerolipid pathway in KEGG/KaPPA-View4 confirmed up-
244 regulation in O of *ALDH7B4* (*P*-value = 0.005; **Supplemental Figure S5**) and of the
245 adjacent aldo-keto reductase *AKR4C10* (At2g37790; *P*-value < 0.05), which together
246 with *ALDH7B4* reversibly converts glycerate into glyceraldehyde and glycerol (see paths
247 in **Supplemental Figure S6** and **S7**). Interestingly, both *AKR4C10* and *ALDH7B4* are
248 involved in oxidative and osmotic stress tolerance during abiotic and biotic responses
249 (**Kotchoni et al. 2006, Missihoun et al., 2014; Sengupta et al., 2015**).
250 On the basis of genes annotated for GO enzyme substrate "glycerol-" (**Supplemental**
251 **Table S8**) which functionally connected in AraNet (**Figure 6A**), a PLS-DA could
252 separate the treatments O from P and OP, explaining 28% of the variation in gene
253 expression, and 60% of the treatment effects (**Figure 6B** and **Supplemental Table S9**).
254 In an OPLS-DA, the single and sequential O_3 treatments (O, OP) could be further
255 divided the by the activity of eight genes (VIP > 1.00): *LIP1*, *GPDHc1*, *SDP6*, *PLT5*,
256 *PDAT*, *DGD1*, *SQD2*, and *PAD4* (**Figure 6C, 6D**; see model statistics **in Supplemental**
257 **Table S10**). Particularly, the triacylglycerol lipase *LIP1* (At2g15230; fatty acids
258 catabolism, **El-Kouhen et al., 2005**) was up-regulated in O compared to OP (*P*-value <
259 0.05; **Figure 6E, 6F**), while the sulfolipid synthase *SQD2* (At5g01220; biosynthesis of
260 photosynthetic membranes components) was significantly down-regulated in O (*P*-value
261 = 0.02) but not in OP (**Figure 6E**, **6F** and KEGG/KaPPA View4 paths in **Supplemental**
262 **Figure S6 and S7**). Moreover, the glycerol 3-phosphate (G3P) dehydrogenases
263 *GPDHc1* and *SDP6* (At2g41540 and At3g10370; **Shen et al., 2006**) were both up-
264 regulated in O and negatively affected by herbivory in OP (*P*-value < 0.05; **Figure 5E**).

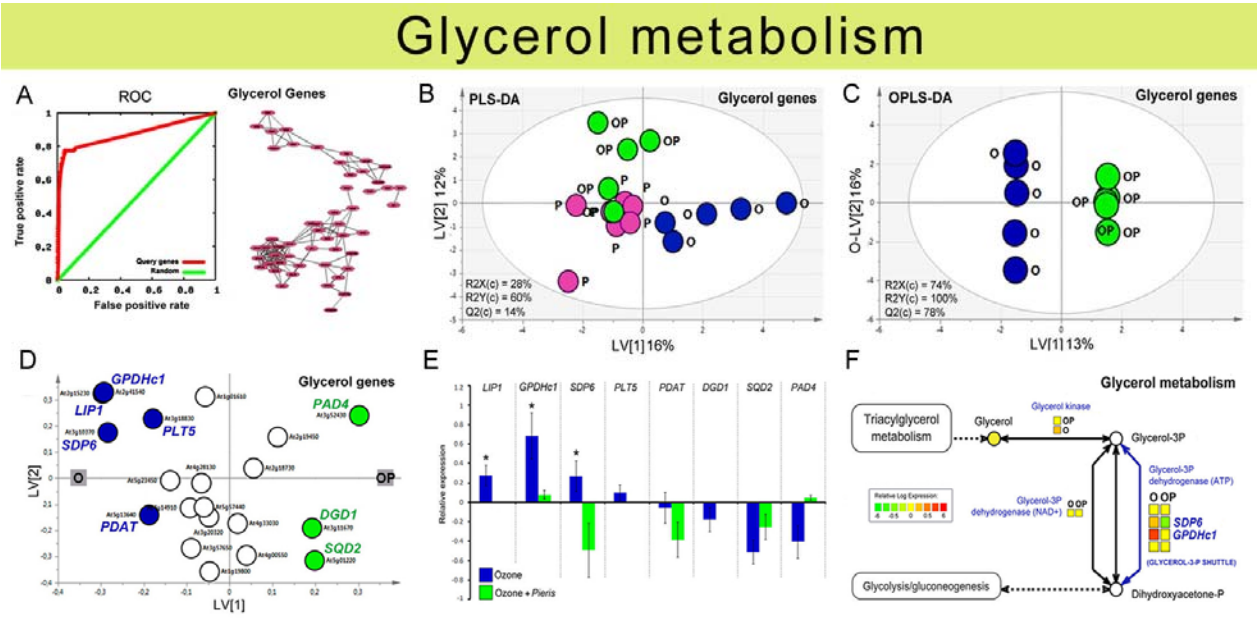

Figure 6 Regulation of glycerol metabolic networks in B. nigra, under multiple O3 and herbivory stress treatments. A, Network model (AraNet) assessing gene connectivity between the 78 genes enriched in glycerol metabolic processes. The network inter-connectivity scored high model fitness (AUC = 0.99; P-value = 9.3 E-57), for true-positives and false-positives rate between the entry genes (red curve) and a randomly generated gene-set (green curve). B, Multivariate analysis (PLS-DA) evaluating the change in expression of glycerol genes in the network, during the multiple stress treatments: O3 (O), herbivory by P. brassicae (P), and sequential treatment (OP). Five LVs cumulatively explained 74% variation in X (R2X[c]), and 100% of the treatment response (R2[c]Y), with 78% of total model predictability (Q2[c]) (see Supplemental Table 8 and 9). C, OPLS-DA modelling differences for glycerol genes, between (O) and (OP) (see Supplemental Table 10). D, OPLS-DA loading plot related to (C), VIPs >1.00 colored in blue or green, respectively for their abundance in (O) and (OP). E, Univariate analysis of genes selected from the OPLS-DA model. * indicates two-tails student-t test significance of P-value < 0.05 between (O) and (OP). Error bars= SE. F, Pathway analysis in KaPPA-View4 for glycerol metabolism highlighting the two G3P dehydrogenases GDPDHc1 (cytosolic) and SDP6 (mitochondrial) of the mitochondrial G3P shuttle. Color code indicates up- (red) and down- (green) regulation (Log expression).

Pathway visualization in KEGG/KaPPA-View4 (**Figure 6F**) showed that *GPDHc1* and *SDP6* (respectively located in the cytosol and on the mitochondrial membrane) constitute the G3P shuttle which is responsible for transport of reducing equivalents to the mitochondrial ETC via recycling of dihydroxyacetone phosphate (**Shen et al., 2003; Shen et al., 2006; Quettier et al., 2008**).

Predictive Interactions of GO Functional Networks

During shift between O_3 stress and herbivory, *B. nigra* actively regulated energy and glycerol metabolic processes (**Figure 2, 3, 5, 6**), possibly in connection with osmotic

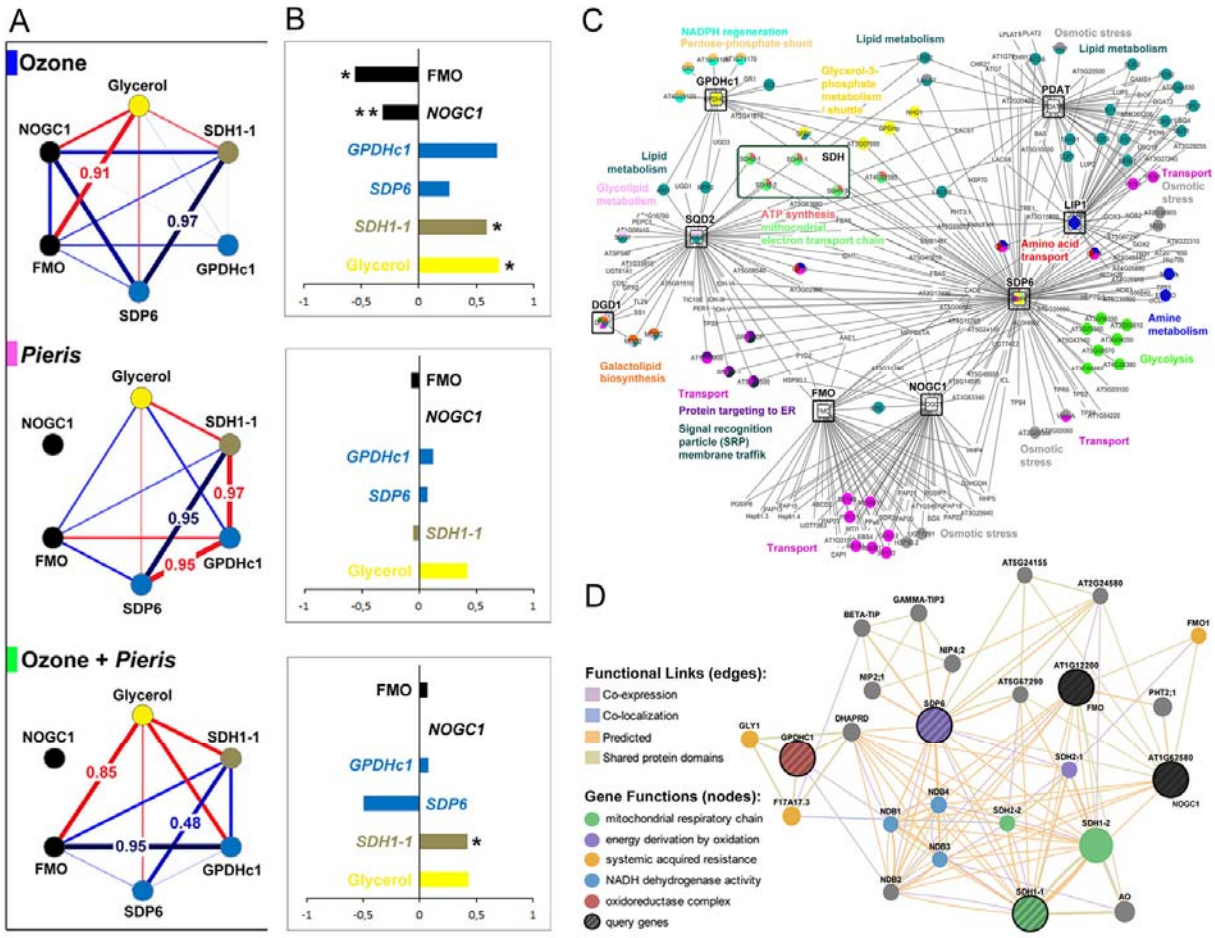

Figure 7 Components of glycerol metabolic network and mitochondrial ETC, under multiple O3 and herbivory stress treatments.Comparative correlation analysis and predictive GO network interactions (AraNet and GeneMANIA). A, Comparative correlation analysis between glycerol, components of G3P shuttle (GPDHC1 and SDP6), mitochondrial ETC Complex II (SDH1-1), and flavin monoxygenases (NOGC1 and FMO). Treatments: O, P and OP. Edges indicate Pearson´s coefficient (ρ) for positive (blue) and negative (red) correlations. All correlation values reported were significant (between P-value <0.05 and <0.001), beside the two correlations in the sequential (OP) of glycerol/FMO (ρ = 0.85), and SDP6 /SDH1 (ρ = 0.48) which were not significant. B, Average of relative gene expressions (Log2), and glycerol abundance, for each treatments (O, P, OP) and corresponding student t-test significance (P-value = * < 0.05, ** < 0.01) when compared to the control conditions. C, Gene interactions predicted in AraNet, for the glycerol metabolic network. Entry genes (in black squares) and emerging new members of a pathway are colored by GO categories after enrichment analysis (GOlorize/Cytoscape). Predicted interactions with members of the mitochondrial ETC Complex II, succinate dehydrogenase (SDH) are highlighted in the window. D, Gene interactions generated in GeneMANIA, between query genes SDH1-1, SDP6, GPDHc1, NOGC1 and FMO. Node functions related the genes to processes of energy and mitchonodria metabolism. Functional links indicated co-expression (purple), co-localization (blue), predicted interaction (orange), and shared protein domains (brown), between the network components.

stress response and stomatal regulation (**Figure 4**). To better describe the system transition during the stress treatments (O, P, OP), we performed a comparative correlation analysis (**Steuer, 2006**) between regulation of glycerol, G3P shuttle

277 (*GPDHc1/SDP6*), mitochondria ETC (*SDH1*), and stomatal closure (*NOGC1/FMO*),
278 (**Figure 7A, 7B**), while GO network analyses (AraNet and GeneMANIA) provided
279 biological insights for possible functional relationships of these processes (**Figure 7C,**
280 **7D**). In AraNet, GO functional associations were predicted for genes of glycerol
281 metabolism which most strongly responded to the dynamics of the sequential treatment
282 (see **Figure 5**). Overall, the network was enriched in processes of fatty acid biosynthesis,
283 mitochondria metabolism (G3P shuttle), photosynthesis (chlorophyll biosynthesis,
284 sulfolipids, and photosystem stabilization), response to phosphate starvation, and
285 stomatal closure (**Table II**). New functional links between these processes highlighted
286 the connection between glycerol metabolism (particularly via the G3P shuttle; *GPDHc1*
287 and *SDP6*) and central energy metabolism - e.g. pentose phosphate shunt, NADPH
288 regeneration, glycolysis, ATP synthesis and mitochondrial ETC (**Figure 7C**). In AraNet,
289 *SDP6* linked to *SDH1-1* (**Figure 7C**), while GeneMANIA specifically predicted their
290 protein interaction and co-expression (**Figure 7D**). Consistently, we found that *SDH1-1*
291 and *SDP6* co-expressed most strongly during O_3 stress in O (ρ = 0.97, *P*-value = 0.005),
292 but also upon herbivory in P (ρ = 0.95, *P*-value = 0.01; **Figure 7A**). Up-regulation of
293 *SDH1-1* persisted in the sequential treatment OP (**Figure 7B**) but its co-expression with
294 *SDP6* was reduced (ρ = 0.48, *P*-value = 0.07; **Figure 7A**). Glycerol metabolism was
295 further associated to osmotic stress, stomatal closure and ABA response, via *SDP6*
296 interaction with flavin monoxygenases *NOGC1*/*FMO* and *SRE1*/*ABA2* (At1g52340;
297 **Nambara et al., 1998**) (**Figure 7C**). *NOGC1* and *FMO* were negatively correlated with
298 glycerol accumulation during O_3 stress in O (especially *FMO*, ρ = -0.91; P-value = 0.03)
299 but not in OP (**Figure 7A, 7B**). Moreover, *SDP6* interacted with water-glycerol protein

300 channels (*NIP* aquaglyceroporins, vacuole *BETA-TIP* and *GAMMA-TIP3*) and via
301 *NOGC1*/*FMO,* to the phosphate transporter *PHT2;1*(**Figure 7D**).
302
303 **Physiological Measurements of Photosynthesis and Gas Exchange**
304 Combined omics and network analysis highlighted the connection of glycerol and energy
305 metabolism with regulation of osmotic stress response and stomatal closure. In order to
306 assess the actual impact of O_3 and herbivory on *B. nigra*, we performed a second
307 experiment where we measured phenotypic and physiological parameters for plants
308 exposed to the stress treatments O, P and OP, and also for an additional long term O_3
309 stress of 16 days (OL) (**Figure 8A**). Although few individuals showed visible symptoms
310 of early senescence and chlorosis, chlorophyll content of the three youngest fully
311 expanded leaves (L5-L7) decreased by 9.5% after five days O_3 exposure (*P*-value <
312 0.05, n = 20) (**Figure 8B**). Herbivory alone did not directly affect chlorophyll levels, but
313 plants previously exposed to O_3 in the sequential treatment OP had 13.8 % lower
314 chorophyll content compared to P (*P*-value < 0.05, n = 10) (**Figure 8B**). The deleterious
315 effect of O_3 was even more evident in the long term exposure (OL), where plants
316 revealed strong symptoms of senescence and chlorosis, particularly on the central fully
317 expanded leaves (L5-L7) (**Figure 8A**). Consistently, plants in OL showed a drastic 47.8%
318 decrease in chlorophyll compared to plants of the same age in C (*P*-value < 0.001, n =
319 10) (**Figure 8B**).
320 Five days of O_3 stress (O) to *B. nigra* plants also reduced photosynthetic activity,
321 decreased intracellular CO2, and negatively affected stomatal conductance and leaf
322 transpiration (**Table III**). After 16 days exposure (OL), stomatal conductance decreased
323 even further, but intracellular CO_2 levels increased. 24 hours herbivory by *P. brassicae*

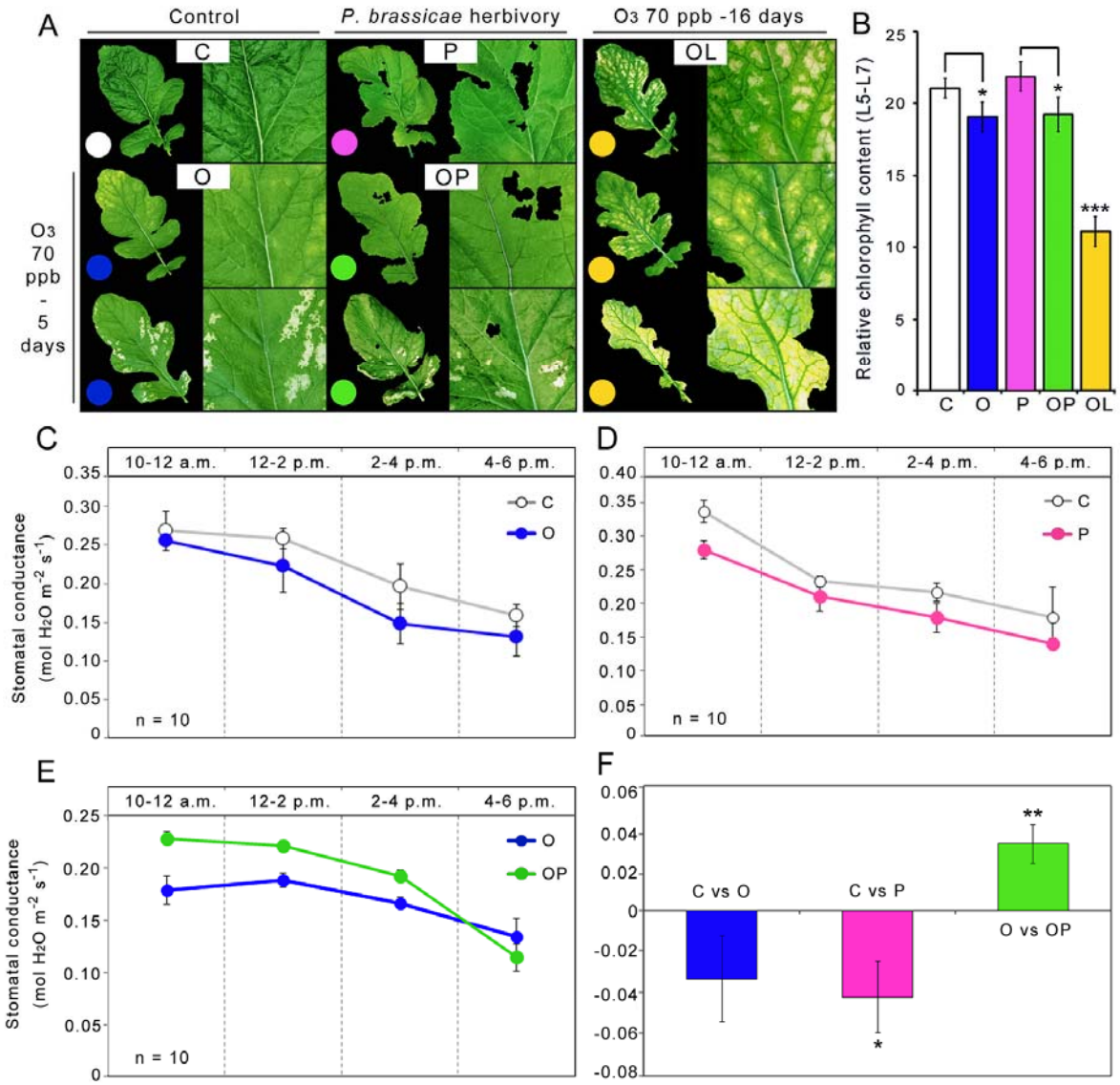

Figure 8 Physiological responses in B. nigra, under multiple O3 and herbivory stress treatments. A, Leaf phenotypes of five weeks old B. nigra exposed to O3 fumigation at 70 ppb for five days (O), herbivore-feeding with 30 first instar P. brassicae caterpillars for 24 hours (P), sequential stress of O3 followed by herbivore-feeding (OP), long term exposure to O3 at 70 ppb for 16 days (OL), or no treatment as controls (C). B, Relative chlorophyll content in leaf tissues was determined by optical absorbance at 653 nm for the three youngest fully expanded leaves (L5-L7). Student t-test shown between C and O (* P-value < 0.05; n= 20), P and OP (* P-value < 0.05; n = 10), C and OL (*** P-value < 0.001; n = 10). C-E, Stomatal conductance (µmol H2O m-2 s-1) of fully expanded leaves (L6) measured via steady-state porometry for three experimental setups during separate days (n=10 per treatment / day). F, Differences in stomatal conductance between the treatments and their controls were measured simultaneously. A one tailed t-tests evaluated if the mean difference between treatment responses was larger than zero: C versus O (P-value = 0.07); C versus P (P-value < 0.05; O versus OP (** P-value < 0.01). Bars = S.E.

(P) did not affect photosynthesis, but stomatal conductance and leaf transpiration decreased slightly compared to untreated controls (C). However, when herbivory followed (O) in the sequential treatment (OP), photosynthesis, stomatal conductance

327 and leaf transpiration were reactivated and thus expressed a reversed behaviour when
328 compared to the single stresses (**Table III**). As stomatal regulation follows the circadian
329 clock and decreases over the day, we further verified these conductance measurements
330 via steady-state porometry (**Figure 8C-D**). Similar to the previous results, conductance
331 decreased after single stress in O (*P*-value = 0.07; see also **Supplemental Figure 10**)
332 and in P (*P*-value = 0.02), whereas the sequential treatment OP induced stomatal re-
333 opening (*P*-value = 0.004) (**Figure 8F**).
334
335

336 **DISCUSSION**

337 Multiple stresses to plants may evoke unpredicted molecular responses with negative,
338 neutral or positive consequences for plant metabolism. We found molecular evidence of
339 photosystem and mitochondrial regulation in *B. nigra* in response to stress by O_3 and
340 sequential herbivory by *P. brassicae*. O_3 induced suppression of photosystem and
341 stomatal closure, but this response was re-directed to higher photosynthetic activity after
342 sequential addition of herbivores.Through omics multivariate and network analyses we
343 identified glycerol metabolism as a central driver of this shift. As predicted by the
344 combined omics -models, stomatal conductance and gas exchange were enhanced after
345 the sequential stress treatment, confirming a strategic change in *B. nigra* to emphasise
346 photosynthetic activity and energy metabolism. This response to sequential stresses
347 could not have been predicted from the individual stress responses, alone.

348

349 **Effects of O_3 stress on Photosynthesis and Stomatal Regulation**

350 O_3 stress negatively affects photosynthesis in plants (**Bagard et al., 2008; Salvatori et**
351 **al., 2015; Vainonen and Kangasjarvi, 2015**). It oxidizes thylakoid membranes in the
352 chloroplasts leading to symptoms like bleaching, chlorosis, and early leaf senescence
353 when chlorophyll is degraded (**Bergmann et al., 1999; Ranieri et al., 2001;**
354 **Goumenaki et al., 2010**). However, even before the symptoms appear, as
355 demonstrated in this study, the senescence process may be fully initiated with the down-
356 regulation of chlorophyll and light harvesting genes, and the induction of the
357 transcription factor *EIN3* that is involved leaf senescence (**Long and Naidu 2002**;
358 **Potuschak et al., 2003, Li et al., 2013**).

359 Besides photosystem suppression, chronic O_3 exposure above 40 ppb triggers a signal
360 cascade of reactive oxygen species (ROS) that causes stomatal closure to prevent O_3
361 from entering the leaf, but it also limits the CO_2 absorption (**Bergmann et al., 1999;**
362 **Castagna and Ranieri, 2009; Ranieri et al., 2001; Booker et al. 2009; Vahisalu et al.,**
363 **2010; Settele et al., 2014**). Our results confirmed a negative effect of O_3 on stomatal
364 conductance, leaf transpiration, and intracellular CO_2 levels, induced by stomatal closure
365 in *B. nigra*. After long-term exposure (70 ppb O_3 for 16 days) bleaching and chlorosis
366 also became obvious and the intracellular levels of CO_2 increased in agreement with
367 reduced assimilation rates and photosynthetic activity, which may further reinforce
368 stomatal closure (**Paoletti & Grulke 2005; Singh et al., 2009**).
369 O_3 stress also induced the expression of *MYB44*, which is thought to play a complex role
370 between abiotic and biotic responses such as drought and wounding (**Baldoni et al.,**
371 **2015**). During drought, overexpression of *MYB44* leads to enhanced tolerance through
372 regulation of stomatal closure in *Arabidopsis* mutants (**Jung et al., 2008**); however
373 *MYB44* also negatively regulates ABA responses (**Jaradat et al., 2013; Li et al., 2014**)
374 involved in stomatal closure, leaf senescence and ROS scavenging (**Persak and**
375 **Pitzschke, 2014**). In our study, expression of *MYB44* correlated positively with glycerol
376 levels, and negatively with *NOGC1*, an NO dependent guanylyl cyclase involved in
377 stomatal closure via Ca++ signaling (**Mulaudzi et al., 2011; Joudoi et al., 2013**). In
378 addition, *MYB44* positively correlated (ρ = 0.85, *P*-value = 0.001) with a chloroplastic
379 lipid transfer protein *LTPc1* (At2g10940), which together with *LTPc2* (At2g45180) was
380 up-regulated during O_3 stress, but not herbivory (**Supplemental Figure S3,S4,** and
381 **Supplemental Table S3**). *LTPs* are known to be active in transfer of glycerolipids
382 between cell membranes - e.g. from chloropasts to ER (**Xu et al., 2008**).

383 These results led us to suggest a coordinated regulation of *MYB44* and *NOGC1* in
384 response to O_3, which could serve as a feedback on ABA signaling and stomatal closure,
385 possibly connecting central energy metabolism and glycerolipid pathways involved in
386 osmotic stress responses.
387
388 **Importance of Glycerol and Energy Metabolism as Safety Valves**
389 Glycerol metabolism allows plants to adapt to a range of environmental stresses.
390 Spinach leaves for example accumulate triacylglycerol which is derived from membrane
391 galactolipids in response to O_3 fumigation (**Sakaki et al., 1990**). Regulation of
392 glycerolipid pathways is also induced in *Arabidopsis*, wheat, and saltbush in response to
393 temperature stress, which results in diacylglycerol trafficking from ER to chloroplast (**Li**
394 **et al., 2015**). In *Arabidopsis*, heat, salt, and drought also induce triacylglycerol
395 accumulation in the cytosol, as an adaptation that enables structural remodeling of
396 membrane lipids (**Mueller et al., 2015**). In our study, the combination of photosystem
397 suppression and decrease of chlorophyll content suggests that glycerol may originate
398 from degradation of chloroplasts and glycolipid membranes in response to O_3 stress.
399 Increased glycerol levels were further correlated with regulation of genes involved in
400 stomatal closure and osmotic stress responses (*MYB44, NOGC1,* and *FMO)*. Glycerol
401 has osmolyte properties, and its accumulation in mutants that lack glycerol kinase
402 enhances *Arabidopsis* resistance to dehydration stress (**Eastmond, 2004**).
403 GO network analyses further emphasized the presence of a connection between
404 osmotic stress response, glycerol metabolism, and central energy processes of
405 chloroplasts and mitochondria.

406 Without CO_2 to assimilate the photons harvested from photosynthesis, plants suppress
407 their photosystem and activate non-photochemical quenching to protect cellular
408 structures against excess excitation energy (**Niyogi, 2000; Murata et al., 2007**).
409 Mitochondria also act as sinks for excess electrons that follow oxidative stress, and
410 oxidize reducing equivalents via respiration (**Hoefnagel et al., 1998; Niyogi, 2000;**
411 **Scheibe et al., 2005; Noctor et al., 2007; Nunes-Nesi et al., 2008**).
412 In our study, increased activity of the mitochondrial manganese superoxide dismutase
413 *MSD1* (**Tsang et al., 1991; Martin et al., 2013**) (**Figure 5D**), suggests that mitochondria
414 also play a role in the oxidative stress response against O_3. This was further supported
415 by the increased activity of the mitochondrial succinate dehydrogenase *SDH1-1* and of
416 the glycerol-3P shuttle (*GPDHc1/SDP6*). In the mitochondrial ETC, *SDH1-1* acts as
417 binding site for coenzyme Q in Complex II (**Huang et al., 2013**), while the G3P shuttle is
418 pivotal in supplying the ETC with redox energy derived from NADH (**Shen et al., 2006;**
419 **McKenna et al., 2006; Berg et al., 2012; Mráček et al., 2013**). Curiously, we found that
420 the phosphate response genes (*RNS1, PT2*) were up-regulated, while our GO- network
421 analyses linked glycerolipid metabolism to phosphate starvation (*SQD2, DGD1*).
422 Phosphate starvation symptoms are similar to those of O_3 stress including down-
423 regulation of photosystem, low CO_2 assimilation, photo-oxidation of membrane lipids
424 (**Hernández and Munné-Bosch, 2015**), transfer of digalactosyldiacylglycerol from
425 chloroplast to mitochondria (**Jouhet et al., 2004**), and membrane lipid remodeling in
426 *Arabidopsis* with down-regulation of *SQD2* (**Jost et al., 2015**). Overall, cumulative
427 regulation of glycerol metabolism may reflect a flux reconfiguration to sustain
428 mitochondria activity, resulting in increased glycerol pools as an intermediate metabolite

429 in the pathway (**Kleijn et al., 2007; Morandini, 2013; Gomes de Oliveira Dal'Molin et**
430 **al., 2015**).
431
432 **Sequential Herbivory after O_3 Stress Induces Abiotic and Biotic Crosstalk**
433 Herbivory by *P. brassicae* induced down-regulation of photosystem and reduced carbon
434 assimilation rates, although with a less severe impact compared to O_3 stress. Chewing
435 herbivores systemically reduce photosynthetic activity in damaged leaves and in
436 neighboring tissues (**Zangerl 2002; Bilgin et al., 2010; Halitschke et al., 2011**),
437 whereas JA signaling and lipoxygenases (*LOX*s) directly affect photosystem and ETC
438 activity in chloroplasts (**Nabity et al., 2012; Havko et al., 2016**). The underlying
439 mechanisms that suppress photosynthesis in favor of induced-defense responses are
440 not fully understood, but a trade-off between allocation of resources to growth and
441 defense appear to determine how plants rearrange their metabolism and redirect
442 primary resources towards the production of specialized defensive compounds
443 (**Schwachtje and Baldwin, 2008; Tang et al., 2009; Meldau et al., 2012**). Upon
444 herbivory, *B. nigra* induced a slight stomatal closure, although we did not observe a
445 distinct up-regulation of *MYB44* expected after biotic stress and wounding (**Jung et al.,**
446 **2010**, **Shim et al., 2013; Persak and Pitzschke, 2013**). While *MYB44* was up-regulated
447 and stomata closed in the O_3 stressed plants, addition of herbivores in the sequential
448 stress caused stomata to reopen. Thus, the resulting phenotype resembled the one
449 observed after herbivore damage alone, with a relatively low stomatal conductance.
450 Sequential herbivory positively induced the expression of *MYC2* (JA-signaling) and
451 negatively affected *EIN3* (ET-signaling) previously induced by O_3. *MYC2* and *EIN3* are
452 key integrators of plant abiotic and biotic stress responses (**Abe et al., 2003; Anderson,**

453 **2004; Fujita et al., 2006; Dombrecht et al., 2007; Atkinson et al., 2013**). In a mutual
454 antagonistic interaction, JA-activated *MYC2* is known to repress transcription of
455 *EIN3/EIL1,* while induction of *EIN3/EIL1* reciprocally represses *MYC2* and JA responses
456 (**Song et al., 2014; Zhang et al., 2014; Song et al., 2015; Kim et al., 2015**).
457 Similarly, *ERF2*, which is involved in ET-signaling (**Fujimoto et al., 2000**) and in positive
458 regulation of JA-responses (**McGrath et al., 2005; Pré et al., 2008**) was down-regulated
459 after single O_3 stress, but it was induced during single and sequential herbivory. This
460 asymmetric regulation of ABA and JA/ET pathways, in connection with stomata behavior,
461 suggests a specific cross-talk that balanced the metabolic responses to O_3 and
462 herbivory in the sequential stress situation.
463

464 **O_3 and Herbivory Affect Central Metabolism in Opposite Ways**

465 In a previous study, we showed that interaction between O_3 stress and herbivory in *B.*
466 *nigra* induced changes in the plant secondary metabolism (glucosinolates and
467 phenolics), and while O_3 fumigation at 120 ppb promoted feeding damage by *P.*
468 *brassicae*, the performance and fitness of the caterpillars was characterized by delayed
469 development and lighter pupae (**Khaling et al., 2015**).

470 Here we show that central (primary) metabolism also plays a pivotal role in the plants
471 response to concurrent abiotic and biotic stressors. Both transcriptomics and
472 metabolomics indicated an alteration of the carbon and nitrogen metabolism in response
473 to O_3 stress. Pools of central metabolites increased, while the activity of many genes
474 involved in carbohydrate metabolism and cell-wall biosynthesis was reduced, including
475 down-regulation of *F2KP* (fructose-2,6 bisphosphatase/phosphofructokinase), the

476 central regulator of glycolysis and gluconeogenesis (**Draborg et al., 2001; Nielsen et al.,**
477 **2004; McCormick and Kruger, 2015**)(**Figure 5B**). Up-regulation of genes involved in
478 amino acid metabolism further supports an increased flux towards mitochondrial
479 metabolism and nitrogen mobilization, resembling patterns of senescence (**Bouché et**
480 **al., 2003; Li et al., 2006; Breeze et al., 2011; Debouba et al., 2013 Watanabe et al.,**
481 **2013**). Similar effects of O_3 stress on the central metabolism were reported in other
482 studies in which routes of detoxification and redox balance (e.g. aldehyde
483 dehydrogenase *ALDH,* chloroplastic *SOD* activity, NADH regeneration) were coupled to
484 stomatal closure, decrease in photosynthesis, and increase in mitochondrial respiration
485 (**Dizengremel et al., 2009; Yendrek et al., 2015**). However, once herbivory was applied
486 as a second stress, all these initial effects of O_3 were reversed, resulting in decreased
487 levels of sugars and amino acids and a reconfiguration of gene expression, including
488 down-regulation of the amino acid transporter *AAP2,* which promotes nitrogen
489 accumulation in siliques and seed development in *Arabidopsis* (**Hirner et al., 1998;**
490 **Ortiz-Lopez et al., 2000**).

491 Interestingly, a common response to both O_3 and herbivory was the increase in the
492 central metabolite GABA. In mitochondria, the GABA shunt delivers additional succinate
493 and NADH to the ETC, and provides an alternative route to the amino acid metabolism
494 (**Bouché et al., 2003**). During abiotic and biotic stresses, GABA concentrations can
495 rapidly spike, but its function in plant response is still under investigation (**Bouché and**
496 **Fromm, 2004; Fait et al., 2008**). Studies show that GABA is involved in stress signaling
497 processes, from leaf senescence (**Ansari et al., 2005**) to plant communication with
498 insects and microorganisms (**Shelp et al., 2006; Michaeli and Fromm, 2015**). Under

499 conditions of oxidative stress and inhibited photosynthesis, GABA participates in
500 scavenging ROS in support of normal growth and stress tolerance (**Bouché et al., 2003;**
501 **Dizengremel et al., 2012**). GABA has also been proposed to regulate the carbon and
502 amino acid metabolism of plants through interaction with GABA/glutamate receptors
503 (GLR) in concert with differential regulation of the ABA/ET signaling pathways (**Lancien**
504 **and Roberts, 2006; Forde and Lea, 2007**). Accordingly, in our study, increased levels
505 of GABA may play a role in maintenance of central metabolism, oxidative stress
506 response, and/or regulation of stomatal closure, possibly via GLR and Ca^{++} signaling.
507
508 In conclusion, we propose the presence of a tolerance mechanism in *B. nigra* (**Figure 9**)
509 where glycerol and central energy metabolism play a central role in the adaptation to the
510 sequential stress by O_3 and herbivory, and which enables *B. nigra* to prioritize demands
511 of stomatal osmoregulation and oxidative stress. The suppression of photosynthesis and
512 regulation of glycerol and mitochondrial metabolism during O_3 stress possibly dissipate
513 excess energy to avoid formation of oxidative radicals (**Hoefnagel et al., 1998**),
514 combining fast NAD+ recycling with maintenance of central metabolism and growth
515 (**Dizengremel et al., 2008, and 2012**). This hypothesis is supported by previous studies
516 on the physiological functions of glycerol metabolism in NADH/NAD+ homeostasis
517 (**Shen et al., 2006; Quettier et al., 2008**), osmotic stress response (**Biela et al., 1999;**
518 **Eastmond, 2004; Chen et al., 2011; Geijer et al., 2012**), and plant development (**Hu et**
519 **al., 2014**). These pathways were redirected in the sequential treatment, during which
520 glycerolipid resources may have been reallocated towards JA signaling and induction of
521 defense against herbivores (**Turner et al., 2002; Kachroo et al., 2004; Havko et al.,**
522 **2016**). Alternatively, these reversed effects may also represent a manipulation of the

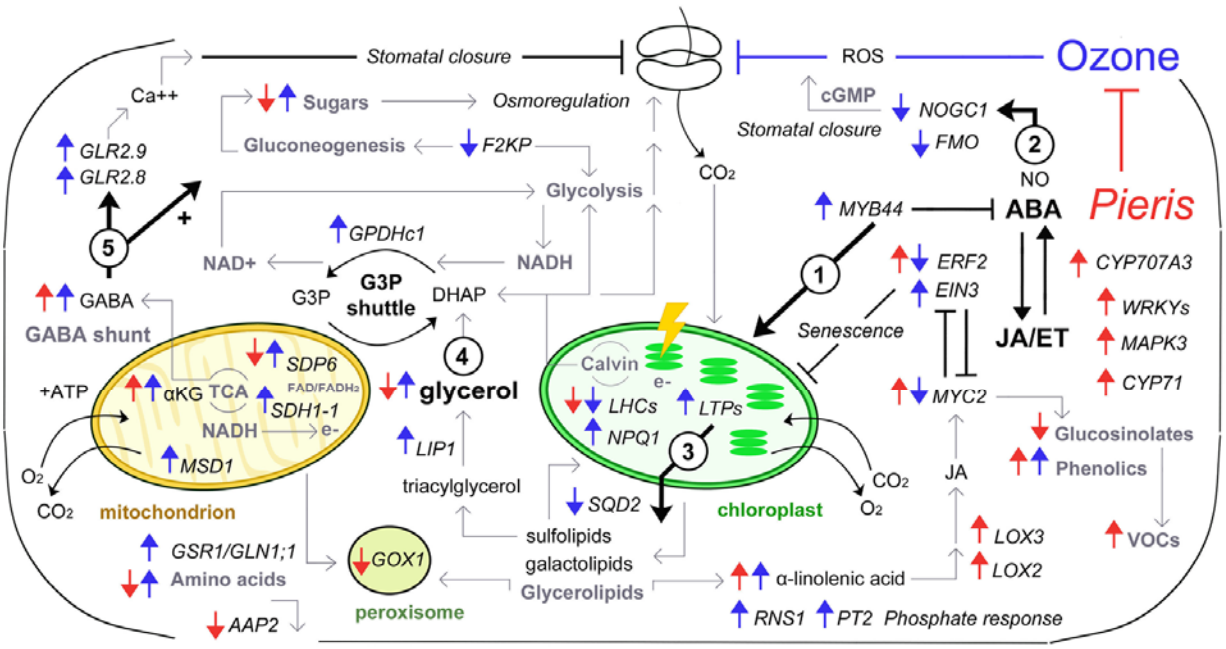

Figure 9 Summary of omics and physiological responses in B. nigra during sequential O3 and herbivory stress treatments. The model links metabolome and transcriptome fluctuations to physiological responses of photosystem, CO2 assimilation and stomatal opening. Stress adaptation mechanisms are proposed (1-5). Blue: O3 fumigation (5 days at 70ppb, 16h/day). Red: O3 followed by P. brassicae (24 h, 30 1st instar caterpillars). Upward arrows indicate up-regulation (genes) or increase (metabolites) and downward arrows the opposite. 1-2, Ozone induces abiotic stress responses of senescence (EIN3, ERF2) and stomatal closure (MYB44) with feedback on NO-guanylate cyclase/flavin monoxygenases (NOGC1, FMO). ABA and JA/ET crosstalk integrates responses between O3 and sequential herbivory (MYC2, ERF2), with opposite effect on stomatal closure. 3-4, Photosystem suppression (LHCs) and non-photochemical quenching (NPQ1) in response to O3 are linked to regulation of glycerolipid metabolism (LPTs, LIP1, SQD2). Glycerol derived from degraded chloroplast membranes enters the G3P shuttle (GPDHc1/SDP6) to sustain NAD+ recycle and mitochondrial activity (SDH1-1, MSD1, GABA) as anti-oxidative stress mechanism. A possible role of glycerol and sugars as osmolytes is also suggested. Sequential herbivory restores the glycerolipid pathway for alternative source-sink priorities - e.g. JA responses (LOXs/MYC2). 5, GABA plays multiple roles in plant stress adaptation, regulating Ca++ homeostasis, carbon-nitrogen metabolism, leaf senescence, ROS scavenging, and signaling of plant-insect interactions.

host metabolism by the herbivore (**Karban and Agrawal, 2002**), which can interfere with plant defense and water-stress response genes (**Reymond et al., 2000; Consales et al., 2012**).

527 **MATERIALS AND METHODS**

528 **Plants**

529 Seeds from black mustard plants (*Brassica nigra*) obtained from the Laboratory of
530 Entomology of Wageningen University (The Netherlands), were collected from a natural
531 population growing along the Rhine river in Wageningen.The seeds were planted
532 individually in plastic pots (9x9x9.5cm) filled with a 3:1:1 mix of peat, potting compost,
533 and sand. They were grown under greenhouse conditions at the University of Eastern
534 Finland, Kuopio, (FIN). The plants were watered intermittently with sprinklers for five
535 hours every day without chemical control for pests or diseases. The seedlings were
536 fertilized twice per week with 0.1% 5-Superex, (N: P: K 19:5:20) Kekkilä, Finland. When
537 the plants were four weeks old and had developed approximately 7 leaves, they were
538 taken to growth chambers (Weiss Bio 1300; Weiss Umwelttechnik Gmbh, Preskirchen-
539 Lindenstruth, Germany) and subjected to the different treatments for 6 days.

540

541 **Treatments**

542 Plants were subjected to one of four treatments: exposure to ambient air with and
543 without feeding by *Pieris brassicae* caterpillars (C and P), and O_3 fumigation with and
544 without subsequent feeding by *P. brassicae* caterpillars (O and OP). The experiment
545 was repeated five times (biological replicates) with each replicate including three plants
546 per treatment. Two extra replicates were produced for the evaluation of gene expression
547 after exposure to ambient air and *P. brassicae* feeding (seven replicates in total).

548

549

550 **O_3 Fumigation**

551 The plants (12 in total, three per treatment) were moved to plant growth chambers. The
552 chambers had been modified so that each had an independently controlled O_3
553 concentration. High O_3 chambers were set to 70 ppb from 4 AM to 8 PM and maintained
554 at a basal O_3 concentration of 30 ppb for the remaining hours each day. This was done
555 to imitate natural diurnal variation in O_3 concentration. In ambient chambers, the O_3
556 concentration fluctuated between 15 and 20 ppb. Chambers were maintained at a
557 temperature of 23 ± 3°C, relative humidity of 60% during the day and 80% at night and a
558 photoperiod of L16h:D8h with a light intensity of 300 µmol $m^{-2}s^{-1}$. The plants were
559 watered daily. The above conditions were maintained for five days, after which the
560 plants subjected to herbivore feeding were infested for a period of 24 hours.

561

562 **Herbivore Feeding**

563 The large cabbage white butterfly, *Pieris brassicae* (Lepidoptera: Pieridae), was
564 obtained from stocks at the Laboratory of Entomology, Wageningen University and
565 reared on Brussels sprouts plants (*Brassica oleracea var. gemmifera* L. cultivar Brilliant)
566 at the University of Eastern Finland under greenhouse conditions. Prior to experiments,
567 *P. brassicae* adults were presented with *B. nigra* plants for oviposition and first instar
568 caterpillars were collected soon after hatching in a climate controlled insect rearing room
569 with a temperature of 25 ± 2°C, photoperiod of 16 h light / 8 h darkness, light intensity of
570 300 µmoles $m^{-2}s^{-1}$ and RH of ca. 60%. For the herbivore treatment, a total of 30 first
571 instar *P. brassicae* caterpillars were mounted on the three highest fully expanded leaves
572 of each plant (ten caterpillars per leaf) and left to feed for 24 hours. After 24 hours (day

573 six), VOCs were collected and plant samples were harvested for metabolomics and
574 transcriptomics analyses.
575
576 **Physiological Measurements of Photosystem and Gas Exchange**
577 Chlorophyll relative content in leaf tissues was determined by optical absorbance at 653
578 nm (CCM-200 plus; Opti-science®) for the three youngest fully expanded leaves (L5-L7).
579 Photosynthetic and gas exchange parameters – i.e. carbon assimilation rate (μmol CO_2
580 m^{-2} s^{-1}), intracellular CO_2, stomatal conductance and leaf transpiration (μmol H_2O m^{-2} s^{-1})
581 – were measured for a period of ca. 1 hour, on one fully expanded leaf (L6) per plant (n
582 = 10) using a LI-COR® gas analyzer (LI-6400). The leaf chamber parameters were set
583 to mimic the ambient growth conditions, with block temperature at 24°C, RH at 60%,
584 CO_2 at 400 μL L^{-1}, and saturating light at 1000 μmol m^{-2} s^{-1}. In addition, leaf (L6)
585 stomatal conductance was determined via steady-state porometry (SC-1, Decagon
586 Devices®), which measured the actual water vapor flux (μmol H_2O m^{-2} s^{-1}) from the leaf
587 through the stomata and out to the environment.
588
589 **Sampling for Metabolomics and Transcriptomics**
590 At the time of sampling, the plants were four weeks + six days old. Counting from the
591 apex, the three youngest fully expanded leaves (L5-L7) of each of the three plants
592 (altogether 9 leaves from 3 plants per treatment) were cut at the petiole with a sharp
593 knife and pooled together. The detached leaves were then immediately wrapped in tin
594 foil and flash frozen in liquid nitrogen. The leaves were stored at -80^0 C and later ground
595 with mortar and pestle together with liquid nitrogen into a fine powder. Equal amounts of
596 powder from each sample were sent express on dry ice to the laboratories in Umeå, (SE)

597 and Lausanne, (CH), for metabolomics and transcriptomics analyses, respectively.
598 Exactly the same samples were thus shared between the laboratories.
599
600 **Metabolomics Analyses**
601 All metabolomics analyses were performed at Umeå Plant Science Center - Swedish
602 Metabolomics Center (UPSC-SMC), Umeå (Sweden). For the preparation of LC-MS and
603 GC-MS leaf tissue analysis, 10-12 mg of frozen sample were extracted using 1 ml of
604 cold chloroform:methanol:H2O (20:60:20), containing 7.5 ng/µl of labeled salicylic acid-
605 D4 (m/z [M-H-] 141.046) as internal standard (IS). A 3 mm tungsten carbide bead was
606 added in each vial, and samples were agitated for 3 min at 30 Hz in a MM 301 Vibration
607 Mill (Retsch GmbH and Co. KG, Haan, Germany). In order to separate the mixture from
608 tissue debris and avoid contamination, extracts were centrifuged at 20.800 × g for 10
609 min at 4°C. 200 µl of the supernatant was evaporated to dryness using a SpeedVac™.
610 For GC-MS analysis samples were derivatized using 30 µl of methoxyamine (15 ug/uL in
611 pyridine) and shaked for 10 min and thereafter letting it react for 16 hours at 25°C.
612 Sylilation was achived using 30 µl of MSTFA reacting for 1 hour at 25°C. Finally,
613 samples were diluted with 30 µl of heptane containing 15ng/µl of methyl stearate
614 (internal standard), and injected into the system. For LC-MS analysis, dried samples
615 were then re-dissolved in 10 µl cold methanol and diluted with 10 µl cold water, and
616 injected into the system.
617
618 **GC-MS**
619 One µL of the derivatized sample was injected splitless by a CTC Combi Pal
620 autosampler (CTC Analytics AG, Switzerland) into an Agilent 6890 gas chromatograph

621 equipped with a 10 m x 0.18 mm i.d. fused silica capillary column with a chemically
622 bonded 0.18 μm DB 5-MS UI stationary phase (J&W Scientific). The injector
623 temperature was 270 °C, the purge flow rate was set to 20 ml min-1 and the purge
624 turned on after 60 s. The gas flow rate through the column ws 1 ml min-1, the column
625 temperature held at 70 °C for 2 minutes, then increased by 40 °C min-1 to 320 °C, and
626 held for 2 min. The column effluent was introduced into the ion source of a Pegasus III
627 time-of-flight mass spectrometer, GC/TOFMS (Leco Corp., St Joseph, MI, USA). The
628 transfer line and the ion source temperatures were set to 250 °C and 200°C,
629 respectively. Ions were generated by a 70 eV electron beam at an ionization current of
630 2.0 mA, and 30 spectra s-1 were recorded in the mass range 50 - 800 m/z. The
631 acceleration voltage was turned on after a solvent delay of 150 s. The detector voltage
632 was set to 1700 V.
633
634 **LC-MS**
635 For analysis of secondary metabolites, samples were analyzed by ultra-high
636 performance liquid chromatography -electrospray ionization/ time of flight mass
637 spectrometry (UHPLC-ESI/TOF-MS, Waters, Milford, MA USA). The Acquity™ system
638 was equipped with a 2.1×100 mm, 1.7 μm C18 UPLC™ column (reversed phase column
639 /non-polar stationary phase) held at 40°C. The LC system was coupled to an LCT
640 Premier TOFMS. 2 μl of each sample were injected and separated throughout the
641 mobile phase containing a mix of solvents A (H2O + 0.1% formic acid) and B
642 (acetonitrile + 0.1% formic acid). The elution gradient between over time of solvent B
643 over A was: 0–4 min 1–20%, 4–6 min 20–40%, 6–9 min 40–95%, 9–13.5 min 95%. The
644 total running time for each sample was 19 min, with a flow rate of 500μl/min. The source

645 temperature was 120°C, cone gas flow 10 L/h, desolvation temperature 320°C,
646 nebulization gas flow 600 L/h, and the capillary and cone voltages were set at 2.5 kV
647 (negative ionization mode) and 35 V , respectively. Data were acquired in dynamic
648 range enhancement (DRE) mode every 0.1 s, with a 0.01 s inter-scan delay. The lock
649 mass compound for accurate mass measurements (leucine enkephalin) was infused
650 directly at 400 pg/µl in 50:50 acetonitrile:H2O at 20 µl/min. The normal lock mass in
651 DRE mode was the negative 13C ion of leucine enkephalin (m/z 555.265), and the
652 extended lock mass was the normal negative ion (m/z 554.262). Mass spectra were
653 acquired in centroid mode with m/z range 100–1000 and data threshold value set to 3.
654

655 **Orbitrap MSMS**

656 In order to verify the data acquired by the UHPLC-ESI/TOF-MS, samples were re-
657 analyzed for determination of selected peaks of interest by UHPLC-MS-MS using linear
658 ion trap (LTQ-Orbitrap). Separation was performed on a Thermo Accela LC system,
659 equipped with a column oven (held at 40°C) and a Hypersil C18 GOLD™ column
660 (2.1×50 mm, 1.9 µm; mobile phase as for the UHPLC-ESI/TOFMS) and analyzed by
661 tandem mass spectrometry using a LTQ/Orbitrap mass spectrometer (Thermo Fisher
662 Scientific, Bremen, Germany). External mass calibration was performed according to the
663 manufacturer's guidelines.
664

665 **Data Processing and Identification**

666 GC-MS was operated with the LECO ChromaTOF® software (optimized for Pegasus HT;
667 Leco Corp., St Joseph, MI, USA). Retention time indexes (RIs) were calculated relative
668 to an alkane series C8-C40. From the raw data, feature extraction and peak integration

669 were all performed with Matlab®, combining target analysis (a predefined list of retention
670 time windows and m/z values) and automated peak deconvolution. Compounds were
671 identified comparing RIs and mass spectra to UPSC-SMC in-house database, and to the
672 public Golm Metabolome Database of the Max Planck Institute (GMD-MPI). For the
673 comparison with the GMD, RIs measured on the 5%-phenyl-95%-dimethylpolysiloxane
674 capillary column - VAR5 (GMD) were transfered to the DB-5 (10m) system of UPSC-
675 SMC (**Strehmel et al., 2008; Hummel et al., 2010**). Samples were normalized on the
676 UVN scores of integrated areas for IS (methyl stearate and salicylic acid-D4).
677 The UHPLC-ESI/TOFMS instruments were operated with MassLynx™ v. 4.1 software
678 (Waters, Milford, MA, USA). Compounds from LC-MS analysis were compared to
679 standards of glucosinolates (sinigrin, glucobrassicin, gluconapin, glucotropaeolin,
680 gluconasturtiin, sinalbin - Phytoplan, Diehm & Neuberger GmbH, Heidelberg, Germany),
681 METLIN mass spectra depository, and additional literature references for glucosinolates
682 (**Clarke, 2010**) and for flavonol glucosides and hydroxycinnamic acid derivates (**Lin et**
683 **al., 2011**). Tandem mass data analysis by Orbitrap was used to compare the MSn
684 profiles and further confirm the identifications. Raw data were processed using Sieve®
685 and Matlab® software for peak alignment and integration. The peak areas were
686 normalized against that of the labaled internal standard of salicylic acid-D4 (m/z [M-H-]
687 141.046).
688

689 **VOCs Collection and Analyses**

690 All VOC collection and analyses were performed at the University of Eastern Finland,
691 Kuopio (Finland). The plants were first enclosed in glass jars. Filtered air was fed into
692 the glass jars at a rate of 250 ml min^{-1} and pulled out at a rate of 200 ml min^{-1} through

693 stainless steel tubes filled with Tenax TA and Carbopack B adsorbents (150 mg each;
694 mesh 60/80; Markes International. Llantrisant, RCT, UK). The samples were collected
695 for 60 minutes. The plant volatiles were analyzed by gas chromatography–mass
696 spectrometry (GC–MS; Agilent 7890A GC and 5975C VL MSD; New York, USA).
697 Trapped compounds were desorbed with an automated thermal desorber (TD-100;
698 Markes International Ltd, Llantrisant, UK) at 250 °C for 10 min, cryofocused at −10 °C,
699 and then injected in a split mode onto an HP-5 capillary column (50 m×0.2 mm; film
700 thickness 0.33 μm) with helium as a carrier gas. The oven temperature program was
701 held at 40 °C for 1 min, then raised to 210 °C at a rate of 5 °C min^{-1} and then further to
702 250 °C at 20 °C min^{-1} . The column flow was maintained at a rate of 1.2 ml min^{-1}. The
703 compounds were identified by comparing the mass spectrum of an individual compound
704 to the spectra of compounds in an external authentic standard and to compounds in the
705 Wiley Library. Relative emissions were measured by peak integration (absolute rates
706 expressed as nmol $m^{-2}hr^{-1}$ are reported in the **Supplemental Dataset S2**.
707

708 **Transcriptomic Analyses**

709 Transcriptomics analyses were performed at University of Lausanne, Lausanne
710 (Switzerland). *Brassica nigra* leaves (3-6 g) were ground in liquid N_2 and total RNA was
711 extracted, reverse-transcribed, and processed according to a previously published
712 procedure (**Bodenhausen and Reymond, 2007**). Labeled probes were hybridized onto
713 CATMA v4 microarrays containing 32,998 A. thaliana gene-specific tags and gene family
714 tags (**Sclep et al., 2007**). Hybridization and scanning have been described previously
715 (**Reymond et al., 2004**). Data analysis was carried out using an interface developed at
716 the University of Lausanne (Gene Expression Data Analysis Interface) (**Liechti et al.,**

717 **2010**). Differentially expressed genes were identified by fitting a linear model for each
718 gene and evaluating the fold change and moderated t statistic *P*-values (**Smyth, 2004**).
719 To address the issue of multiple comparisons we used the false discovery rate method
720 of **Storey and Tibshirani** and computed a *q* value (**2003**). Because we employed
721 Arabidopsis whole-genome microarrays to probe expression of *Brassica nigra* genes,
722 the number of genes that produced hybridizaton signals was clearly low and overall
723 hybridization signal intensity was also weaker than with Arabidopsis samples. Hence, we
724 noticed that high FDR values are estimated when the number of induced genes is
725 relatively small. However, by comparing gene expression between experiments, genes
726 with small *P*-values in response to one treatment often had a small *P*-value in another
727 treatment. Thus interexperiment comparison adds to data interpretation, and FDR
728 calculations might be too conservative in some cases. For data analysis, we thus used
729 an unadjusted *P*-value of 0.05. FDR values are indicated in **Supplemental Dataset S1**.
730

731 **Statistical Analyses**

732 Matrixes for gene expression and metabolites were created in Excel®. All steps of basic
733 statistic (i.e. Pearson´s correlation, Student t-test, ANOVA and post-hoc Tuckey test)
734 were performed with Excel and with Minitab 17 Statistical Software® (2010) State
735 College, PA: Minitab, Inc. (www.minitab.com). Other more specific analyses have been
736 performed with the open-source software R (https://www.r-project.org/) and RStudio
737 (https://www.rstudio.com/) or with other software as mentioned below.
738
739
740

741 **Multivariate Analyses**

742 Gene expression and metabolite profiles were subjected to multivariate analysis using
743 SIMCA® 14 software package (Umetrics, Umeå, Sweden). Supervised regression
744 models such as partial least square (PLS) an orthogonal projection of latent structures
745 (OPLS) discriminant analysis (DA) were used to investigate the variation in X-variables
746 (gene or metabolites) which was modeled for the Y-explanatory variables, corresponding
747 to O_3 and *P. brassicae* treatments. The cumulative (c) variation in X and in Y explained
748 by the models is reported by the terms R2X(c) and R2Y(c) respectively. Models were fit
749 to the minimum number of latent variables (LVs) corresponding to the highest value of
750 predicted variation - Q2(c). Selection of important variables was based on the Variable
751 Importance for Projection (VIP) score, considered significant if above the threshold of
752 1.00.

753

754 **Gene Expression Data Evaluation and Pathway Analyses**

755 Gene selection for student t-test cut-off of *P*-value ≤ 0.05 was executed in Excel. The
756 open-source software R (and RStudio) was used to create heat-maps, hierarchical
757 clustering, and correlation of gene expression profiles using the CRAN library packages
758 and functions *heatmap* (gplots), *hclust* and *corrgram* respectively. More specifically,
759 gene expression values for each sample (up- or down- regulation) were represented
760 graphically using the *heatmap* function, while rows (genes) and columns (samples) of
761 the matrix were reorder in dendograms following hierarchical clustering. The default
762 function *hclust* was used with its method of complete linkage which agglomerates
763 clusters computing the largest distance between any object in one cluster and the other
764 objects in the other clusters. Similarity between each sample group was further tested

765 using the *corrgram* function (default method Pearsons´s correlation). Thus, a correlation
766 matrix was produced as a graphical display (i.e. the correlogram) with cells colored
767 according to the respective correlation coefficient (ρ) for each of the paired sample
768 comparison.
769 Gene onthology (GO) enrichment analysis of the gene clusters was performed with the
770 web-based tool Functional Classification SuperViewer of the University of Toronto
771 (Canada) (http://bar.utoronto.ca/ntools/cgi-bin/ntools_classification_superviewer.cgi)
772 where GO categories for genes in a given cluster are normalized for the frequency in
773 Arabidopsis, while bootstraps and standard deviation provide confidence intervals for the
774 accuracy of the output (**Provart and Zhu, 2003**). *P*-values of the hypergeometric
775 distribution were used to select the significant functional classes. Only enrichments with
776 significant *P*-values ≤ 0.05 were considered and reported in the graph. The MapMan
777 tool (**Thimm et al., 2004**); http://mapman.gabipd.org/web/guest) was used for
778 visualization of the gene expression dataset in the context of metabolic pathways or
779 other processes represented in modules ("bins"), and in order to build the Venn
780 diagrams for up- and down- regulated genes. Beside MapMan, other resources used for
781 pathway analysis and interpretation of "omics" data included the free databases KaPPA
782 View4 (**Tokimatsu et al., 2005; Sakurai et al., 2011**); http://kpv.kazusa.or.jp/) and
783 Kyoto Encyclopedia of Genes and Genomes (KEGG) database (**Kanehisa and Goto,**
784 **2000**; http://www.genome.jp/kegg/). Gene sub-cellular localizations and expressions
785 were searched with the ePlant server of the University of Toronto
786 (Canada)(https://bar.utoronto.ca/eplant/).
787
788

789

790 **Integrative Omics Network Analyses**

791 The open source platform Cytoscape (version 3.2.1) was used for visualization and
792 analysis of the omics networks. The correlation matrix between genes and metabolites
793 was computed into a similarity network using the *ExpressionCorrelation* app
794 (http://apps.cytoscape.org/apps/expressioncorrelation). The network was built setting the
795 edge (links) parameters to Pearson´s coefficient $\rho \geq 0.85$ for both positive and negative
796 correlations. For network visualization, the graphic layout was set to (yFile) "organic".
797 Network topological features were evaluated with *Network Analyzer* (Max Planck Institut
798 Informatik; **Assenov et al., 2008**). For comparative correlation analysis, the network
799 between glycerol and the five genes components – *GPDHc1* (At2g41540), *SDP6*
800 (At3g10370), *NOGC1* (At1g62580), *FMO* (At1g12200) and *SDH1-1* (At5g66760) – was
801 produced with the open-source software R using the CRAN library package *qgraph*
802 (**Epskamp et al., 2012**). Correlation significance was tested with Minitab 17.

803

804 **GO Network Analyses**

805 AraNet (http://www.inetbio.org/aranet) is a free database of co-functional gene networks
806 based on *Arabidopsis thaliana* TAIR10 annotations (**Lee et al., 2015**), which can be
807 used for computational identification of new candidate genes in functional pathways and
808 for the integration of high-throughput omics datasets (**Lee et al., 2010**). Closely
809 connected genes are listed and ranked in a guilt-by-association network on the basis of
810 previous experimental datasets and Gene Ontology evidence codes, such as IDA
811 (inferred from direct assay), IPI (inferred from protein interaction), ISS (inferred from
812 sequence or structural similarity) and TAS (traceable author statement). Model accuracy

813 and coverage are assessed with the “receiver operating characteristic” (ROC) which
814 calculates the probability rate of true-positives versus false-positives, between the inter-
815 connectivity of the entry genes and a selection of random genes. The receiver operating
816 characteristic (ROC) calculates the model fitness for the connected genes, as true-
817 positives and false-positives rate between the entry genes (red curve) and a randomly
818 generated gene-set (green curve). The corresponding score of the “area under the ROC
819 curve” (AUC) ranges from ~0.5 to 1, respectively indicating random and perfect
820 performance. New candidate genes were searched with the function “*new members of a*
821 *pathway*”. The predictive power of the new network is automatically estimated from the
822 initial inter-connectivity of its genes, on the basis of the connection to the entry genes
823 (ranked by connectivity scores). The AraNet function “GeneSet analysis / GO” was used
824 to evaluate enrichment of the network. The same GO analysis function was also used to
825 confirm the network enrichment in glycerol and glycerolipid metabolic processes of the
826 gene-set selection (by enzyme substrate annotation; 76 genes) later used for
827 multivariate effects of the treatments. Results from the AraNet analysis were imported
828 into Cytoscape and colored according to statistically overrepresented GO categories
829 using the plugin GOlorize by (**Garcia et al., 2007**)
830 (http://apps.cytoscape.org/apps/golorize).
831 Another public web server was used for prediction of biological interaction namely
832 GeneMANIA (http://www.genemania.org/), which can also be used as a Cytoscape
833 plugin (**Warde-Farley et al., 2010**). The initial entry list consisted of the five genes
834 *GPDHc1* (At2g41540), *SDP6* (At3g10370), *NOGC1* (At1g62580), *FMO* (At1g12200)
835 constituting the core region of the glycerol network in analysis, and the predicted
836 interaction with *SDH1-1* (At5g66760). GeneMANIA extended this list to create a network

837 of genes identified as having similar functions. The predicted gene interactions and their
838 weights were estimated on the basis of *Arabidopsis* knowledge through genomics and
839 proteomics data (e.g. co-expression and protein interaction) which are retrieved from
840 GEO, BioGRID, Pathway Commons and I2D, as well as organism-specific functional
841 genomics data sets (Warde-Farley et al., 2010).
842
843 **Figure Layout and Editing**
844 Photoshop CS5.1© (Adobe) was used for editing the final graphic layouts of the figures.
845
846 **Accession Numbers**
847 Microarray data from the transcriptomics analysis were deposited in the ArrayExpress
848 database (www.ebi.ac.uk/arrayexpress) under accession number E-MTAB-5030.
849 Sequence data from this article can be found in the Arabidopsis Genome Initiative or
850 GenBank/EMBL databases under the following accession numbers: At2g30570 (*PSBW*),
851 At3g54890 (*LHCA1*), At1g19150 (*LHCA6*), At2g34420 (*LHB1B2*), At2g40100 (*LHCB4.3*),
852 At4g10340 (*LHCB5*), At1g15820 (*LHCB6*), At1g60950 (*FED A*), At1g08550 (*NPQ1*),
853 At1g07110 (*F2KP*), At2g21330 (*FBA1*), At4g38970 (*FBA2*), At3g54050 (*CFBP1/HCEF1*),
854 At2g25540 (*CESA10*), At4g16590 (CSLA01), At2g22900 (*MUCI10*), At3g46970 (*PHS2)*,
855 At5g37600 (*ATGSR1*), At2g29110 (*GLR2.8*), At2g29100 (*GLR2.9*), At3g01120 (*MTO*1),
856 At5g09220 (*AAP2*), At4g39660 (*AGT2*), At1g17290 (*ALAAT1*), At1g05940 (*CAT9*),
857 At1g20020 (*LFNR2*), At5g11670 (*ATNADP-ME2*), At5g09660 (*PMDH2*), At3g14420
858 (*GOX1*), At3g21070 (*NADK1*), At5g66760 (*SDH1-1*), At3g10920 (*MSD1*), At4g31800
859 (*WRKY18*), At1g80840 (*WRKY40*), At2g46400 (*WRKY46*), At3g45140 (*LOX2*),
860 At1g17420 (*LOX3*), At1g32640 (*MYC2*), At5g67300 (*MYB44*), At2g37630 (*MYB91*),

861 At1g72290 (*WSCP*), At3g45640 (*MPK3*), At5g45340 (*CYP707A3*), At5g47220 (*ERF2*),
862 At3g20770 (*EIN3*), AT2G02990 (*RNS1*), At2g38940 (*PT2*), At2g38170 (*CAX1*),
863 At1g68100 (*IAR1*), At1g62580 (*NOGC1*), At1g12200 (*FMO*), At1g29740 (*LRR-RK*),
864 At1g29310 (SecY protein/sec61), At2g15230 (*LIP1*), At2g41540 (*GPDHc1*), At3g10370
865 (*SDP6*), At3g18830 (*PLT5*), At5g13640 (*PDAT*), At3g11670 (*DGD1*), At5g01220 (*SQD2*),
866 At3g52430 (*PAD4*), At1g54100 (*ALDH7B4*), At2g37790 (*AKR4C10*), At2g10940 (*LTPc1*;
867 lipid-transfer protein; chloroplast), At2g45180 (*LTPc2;* lipid-transfer protein; chloroplast).
868

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881 Papazian et al., 2016
882
883 *Tables:*
884 **Table I** Major hubs in the integrative network correlation analysis

885 **Table II** Biological processes relative to glycerol metabolic responses
886 **Table III** Photosynthetic and gas exchange measurements
887

Table I Major gene hubs in *Brassica nigra* network for multiple stress response to O_3 and herbivory (Fig. 4)

AGI		Gene name	GO Process[a]	Cellular location[b]
At4g27740	-	Yippee family putative zinc-binding	Unknown	Nucleus
At4g16590	*CSLA1*	Cellulose synthase-like A01	Glycosyl transferase	Golgi, Cytosol
At5g04440	-	Unknown function (DUF1997)	Unknown	Chloroplast
At1g12390	-	Cornichon protein (Guard cells)	Signal transduction	Plasma membrane
At2g29100	*GLR2.9*	Glutamate receptor 2.9	Ca^{++} homeostasis	Plasma membrane, Golgi, ER
At3g50830	*COR413*	Cold acclimation WCOR413-like	Unknown	Plasma membrane
At1g29910	*LHCB1.2*	Light harvest chlorophyll binding 1.2	Photosynthesis	Chloroplast
At2g22900	*MUCI10*	Mucilage-related 10	Galactosyltransferase	Golgi, trans-Golgi
At2g32990	*GH9B8*	Glycosyl hydrolase 9B8	Cellulose biosynthesis	Extracellular (Cell wall)
At3g09360	-	TBP-binding protein	RNA polymerase II (TF)	Nucleus
At1g62580	*NOGC1*	NO-dependent guanylate cyclase 1	Stomatal closure	Chloroplast, cytosol
At3g50770	*CML41*	Calmodulin-like 41	Signaling, Ca^{++} binding	Chloroplast
At5g58270	*M3*	ABC transporter mitochondrion 3	Mo-cofactor biosynthesis	Mitochondria, chloroplast
At3g24100	-	SERF (uncharacterized)	Unknown	Nucleus
At1g07040	-	Unknown protein	Unknown	Chloroplast
At2g02390	*GST18*	Glutathione S-transferase 18	Amino acid biosynthesis	Cytoplasm, cytosol

[a]GO biological processes and/or molecular functions as reported by the TAIR database (https://www.arabidopsis.org).
[b]Cellular localization confirmed with ePlant visualization tool (BAR – University Toronto, http://bar.utoronto.ca/~dev/eplant).

888

889

Table II Biological processes relative to *Brassica nigra* glycerol metabolic network responsive to O_3 and herbivory

Rank	GO ID	Biological Process	*P*-value[a]	Genes
1	GO:0006636	Unsaturated fatty acid biosynthesis	0.0001632	*SQD2, LIP1, PDAT*
2	GO:0006127	Glycerol phosphate shuttle	0.0002918	*GPDHc1, SDP6*
3	GO:0016117	Carotenoid biosynthesis	0.0003421	*SQD2, LIP1, PDAT*
4	GO:0019375	Galactolipid biosynthesis	0.0003564	*DGD1, SQD2*
5	GO:0015995	Chlorophyll biosynthesis	0.0004397	*DGD1, SQD2, LIP1*
6	GO:0046506	Sulfolipid biosynthesis	0.0005835	*DGD1, SQD2*
7	GO:0016036	Phosphate starvation	0.0006321	*DGD1, SQD2*
8	GO:0019563	Glycerol catabolism	0.0008752	*GPDHc1, SDP6, LIP1*
9	GO:0042550	Photosystem I stabilization	0.0008752	*DGD1*
10	GO:0019761	Glucosinolate biosynthesis	0.0009609	*SQD2*
11	GO:0006072	Glycerol-3-phosphate metabolism	0.001167	*GPDHc1, SDP6*
12	GO:0009247	Glycolipid biosynthesis	0.001458	*DGD1, SQD2*
13	GO:0019288	Isopentenyl diphosphate biosynthesis (MEP pathway)	0.001849	*DGD1, SQD2*
14	GO:0090332	Stomatal closure	0.002915	*NOGC1*
15	GO:0006071	Glycerol metabolism	0.00466	*GPDHc1, SDP6*

[a]GO terms *P*-value < 0.01 calculated in AraNet as hypergeometric test on all 27416 gene entries in the Arabidopsis database.

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Table III Photosynthetic and gas exchange measurements of 5 weeks old *Brassica nigra,* under stress of O_3 and herbivory.

Treatment effect:	O_3 (5 days, 70 ppb)		*P. brassicae* herbivory (24 hours)		O_3 (16 days, 70 ppb)
	C	**O** (vs. C)	**P** (vs. C)	**OP** (vs. O)	**OL** (vs. C)
Photosynthesis (µmol CO_2 m^{-2} s^{-1})	11.72 ± 0.8	8.63 ± 0.63 **	11.5 ± 0.58 n.s.	11.24 ± 0.85 *	3.29 ± 0.26 ***
Stomatal conductance (mol H_2O m^{-2} s^{-1})	0.31 ± 0.02	0.15 ± 0.04 **	0.25 ± 0.10 n.s.	0.24 ± 0.03 *	0.12 ± 0.01 **
Leaf transpiration (mol H_2O m^{-2} s^{-1})	3.45 ± 0.22	1.84 ± 0.22 ***	2.97 ± 0.90 n.s.	2.66 ± 0.26 *	1.55 ± 0.19 ***
Intracellular CO_2 concentration (ppm)	300 ± 3.87	264 ± 4.93 *	291 ± 9.35 n.s.	288 ± 9.81 n.s.	333 ± 10.19 ***

Means ± SE (n = 6-10) and significant variation calculated via student t-test, *P*-values > 0.05 (*), > 0.01 (**), > 0.001 (***). Relative group comparisons as in brackets. Treatments abbreviations: controls (C), exposure to O_3 70 ppb / 5 days (O), exposure to O_3 70 ppb / 16 days (OL), *P. brassicae* herbivory for 24 hours (P), sequential O_3 70 ppb and herbivory (OP).

895 **Footnotes**

896 The authors responsible for distribution of materials integral to the findings presented in
897 this article in accordance with the policy described in the Instructions for Authors
898 (www.plantcell.org) are: Stefano Papazian (stefano.papazian@umu.se) and Benedicte
899 Albrectsen (benedicte.albrectsen@umu.se).
900
901 J.B. conceived the project; E.K., P.R, C.B., S.P. and B.A assisted in design the research;
902 J.B., S.P. and E.K. performed the experiments; S.P. C.B. and E.K. performed the
903 analyses; S.L. provided technical assistance to C.B; J.B., P.R., and T.M. supervised the
904 analyses; S.P. analyzed the data. B.A., C.B., and P.R. contributed statistical analyses.
905 S.P., J.B. and B.A. wrote the article with contributions of all the authors; P.R. and T.M
906 supervised and complemented the writing.

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