TOR mediates cytokinin-driven development and defense cues

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Keywords: TOR, Cytokinin, Development, immunity, tomato

Dr. Maya Bar is responsible for distribution of materials integral to the findings presented in this article in accordance with the policy described in the Instructions for Authors (www.plantcell.org).

Abstract

Target of Rapamycin (TOR) kinase is a conserved energy sensor that regulates plant growth and development in response to nutritional and environmental inputs. TOR is also involved in the regulation of plant immunity. TOR downregulation, for example, results in enhanced plant defense responses and plant resistance to several pathogens in *Arabidopsis*, rice, and tomato. Similarly, the plant hormone cytokinin (CK) has also been demonstrated to mediate both development and defense processes. Although TOR is positioned at the interface between development and defense, little is known about the mechanisms in which TOR may potentially regulate the switch between these two modalities. Here, we investigated the interplay between TOR-mediated development and TOR-mediated defense. We show that *TOR*-silencing or inhibition led to enhanced defense responses and disease resistance in WT or CK-deficient backgrounds. However, in a high-CK background, which is already immuno-activated and disease resistant, TOR-inhibition reduced defense responses and disease resistance. *TOR*-silencing resulted in the normalization of developmental phenotypes associated with high or low CK levels, as well as of other classical developmental mutants, demonstrating that TOR is required for the execution of developmental cues. We found that CK represses TOR activity, suggesting the existence of a cross talk mechanism between the two pathways. Our results demonstrate that TOR likely acts downstream to CK signaling and hormonal signaling in general, executing signaling cues resulting from both high and low CK, in both defense and development. Thus, differential regulation of TOR or TOR-mediated processes could underlie a development-defense switch.

22 **Introduction**

23 To survive, plants have developed sophisticated strategies and molecular mechanisms to
24 protect them against attacks by pathogens (Jiang et al., 2020). When plants recognize that they
25 are being attacked by a pathogen, they activate an array of cellular and molecular processes
26 which include the production of defense proteins and metabolites. The activation of plant
27 defense responses is energetically costly, and as a result may be associated with growth arrest,
28 due to resource restrictions. Thus, plants must constantly regulate growth and defense
29 responses, and balance between them. To do so, plants coordinate inputs from the
30 environment with their metabolism, growth, and development, mostly by using hormonal
31 pathways (Huot et al., 2014).

32

33 The plant hormone Cytokinin (CK) regulates many aspects of the plant growth and development
34 including cell division, leaf senescence, apical dominance, vascular differentiation, chloroplast
35 biogenesis, root development and stress responses (Zürcher and Müller, 2016). CKs have been
36 previously shown to have a role in plant response to biotic stresses in tobacco (Großkinsky et
37 al., 2011), Rice (Jiang et al., 2013) and tomato (Gupta et al., 2020b). CKs were reported to
38 promote resistance through the SA signaling pathway (Choi et al., 2010; Naseem et al., 2012).
39 We have previously shown that CK-deficiency results in higher susceptibility to the fungi
40 *Botrytis cinerea* (*Bc*) and *Oidium neolycopersici* (*On*), while high endogenous CK content, as well
41 as external application of CK, confer increased resistance against these fungi, and against

42 bacterial pathogens, in a SA-defendant manner in tomato (Gupta et al., 2020b). Moreover, we
43 have also shown that CKs directly inhibit the growth, development, and virulence of fungal
44 pathogens (Gupta et al., 2021) and that CKs improve *Xanthomonas campestris pv. Vesicatoria*
45 (*Xcv*) and *Pseudomonas syringae* pv. *tomato Pst* disease outcome in tomato (Gupta et al.,
46 2020a).
47
48 The Target of Rapamycin (TOR) kinase is an energy sensor that was shown, in contrast to CK, to
49 act as a negative regulator of plant immunity. TOR is a conserved Ser/The protein kinase that
50 coordinates between environmental cues and nutritional information to metabolism, protein
51 synthesis, ribosome biogenesis, and development (Dobrenel et al., 2016). Generally, when
52 nutrients are abundant, TOR is active and promotes anabolism and developmental processes,
53 and when nutrients are limited, TOR is inactive and promotes catabolic processes (Saxton and
54 Sabatini, 2017). Previous studies have demonstrated that TOR plays a role in plant immunity. In
55 rice, for example, TOR was shown to act as a negative regulator of immunity by antagonizing
56 the defense hormones JA and SA (de Vleesschauwer et al., 2018). In agreement with this,
57 mutants impaired in TOR complex and TOR-inhibited *wt Arabidopsis* plants were more resistant
58 to *Fusarium* (Aznar et al., 2018). In citrus spp., TOR inhibition was found to attenuate the
59 growth of *Xanthomonas citri* (Soprano et al., 2018). In another study, *TOR* expression was
60 downregulated upon NB-LRR activation. Moreover, suppression of *TOR* expression enhanced
61 disease resistance, whereas *TOR* overexpression decreased it, suggesting that translational
62 regulation executed by TOR plays an important role in the switch from growth to defense.

63 (Meteignier et al., 2017). TOR inhibition was also found to block growth and to activate the SA
64 signaling pathway in *Arabidopsis* (Moreau et al., 2012; Dong et al., 2015).
65 In agreement with this, we have recently shown that TOR inhibition or *TOR*-silencing promotes
66 resistance against *Xcv*, *TMV, On* and *Bc* in tomato and *N. benthamiana*, through the activation
67 of plant defense responses in a SA-dependent manner (Marash et al., 2022), although the exact
68 mechanism by which the inhibition of TOR primes resistance, is still unclear. Some explanations
69 for the effect of TOR on immunity include selective translational control during plant immunity
70 (Meteignier et al., 2018), or negative regulation of autophagy in plants, as was reported in yeast
71 and mammals (Liu and Bassham, 2010).
72 In *Arabidopsis*, TOR inhibition was shown to alter the expression of hundreds of genes,
73 including genes that are linked to plant hormones signaling networks (Dong et al., 2015). The
74 TOR signaling pathway was later shown to interact with plant hormones. For example, the TOR
75 signaling pathway interacts with the brassinosteroid signaling pathway during hypocotyl
76 elongation through the BZR1 transcription factor (Zhang et al., 2016) and activates ABA
77 receptors by phosphorylation (Wang et al., 2018). Moreover, The Auxin efflux facilitator PIN2 is
78 phosphorylated and stabilized by TOR, which influences the gradient distribution of PIN2 in
79 *Arabidopsis* primary root (Yuan et al., 2020). TOR monitors the level of sugar in meristematic
80 regions and halts growth when the sugar level is low, blocking hormone signals that normally
81 promote growth (Xiong et al., 2013). Therefore, as plant growth rate is dictated by hormones, it
82 seems that energy status and growth are integrated through the activity of TOR (Monson et al.,
83 2022).

84 Considering that TOR and CK regulate growth and development, and since they were both
85 implicated in SA-dependent plant responses to pathogens, it appears possible that CK and TOR
86 may interact or share similar defense response pathways. To date, there is limited evidence of
87 the crosstalk between TOR and CK. For example, (Dong et al., 2015) showed that *TOR*
88 downregulated the expression of genes involved in the CK pathway. These findings
89 demonstrate the existence of a relationship between TOR and CK signaling, yet they did not
90 address the role of TOR in CK-mediated immunity.
91 Here, we assessed the involvement of TOR in CK-mediated immunity by testing whether *TOR*
92 downregulation affects CK signaling or CK-mediated disease resistance in tomato. We found
93 that defense responses and disease resistance are induced in the CK-deficient line *pFIL>>CKX*
94 upon *TOR* downregulation, whereas they are reduced in the high CK *pBLS>>IPT* line. We found a
95 similar relationship between TOR inhibition and CK-driven developmental cues, whereby leaf
96 patterning was dependent on TOR levels in both high and low CK transgenic lines, as well as in a
97 series of classical tomato developmental mutants.
98 Transcript levels of classical CK-signaling genes and developmental genes were altered in
99 response to TOR inhibition, and TOR activity was reduced in response to exogenous CK-
100 treatment, demonstrating a partially antagonistic relationship between the TOR and CK
101 signaling pathways. Collectively, our results suggest that CK-mediated immunity and
102 developmental processes likely function via TOR, and strengthen the notion that TOR functions
103 as a master switch, controlling plant growth and defense programs.
104
105

106 **Results**

107 ***TOR inhibition mediates CK-driven immunity***

108 To date, roles for TOR in CK-mediated immunity have not been reported. To determine whether
109 TOR is involved in CK-mediated immunity, we first tested the effect of *TOR*-silencing and
110 inhibition on pathogen resistance in tomato lines with altered CK levels. We used *pBLS>>IPT*
111 and *pFIL>>CKX* as lines with high and low CK levels, respectively, and performed *Bc*
112 pathogenicity assays as previously described in (Gupta et al., 2020b). As can be seen in **Figure 1**,
113 compared with the background line M82, we observed significantly enhanced *Bc* resistance in
114 plants with elevated CK levels, and reduced resistance in plant with low CK levels, which is in

115 agreement with our previous results (Gupta et al., 2020b). Silencing of the tomato *SlTOR* gene
116 by virus-induced gene silencing (VIGS) resulted in a reduction of *Bc* disease symptoms in the
117 M82 background, as we previously reported. This silencing methodology inhibits *TOR*
118 transcription by about 50% (Marash et al., 2022). Similar reduction was observed in the CK-
119 deficient plants CKX, as *TOR*-silencing reduced disease symptom by more than **50%**. However,
120 when *TOR* was silenced in IPT plants, we observed a small but significant increase in disease
121 levels **(Figure 1)**. Notably, disease levels following *TOR*-silencing were similar in all three

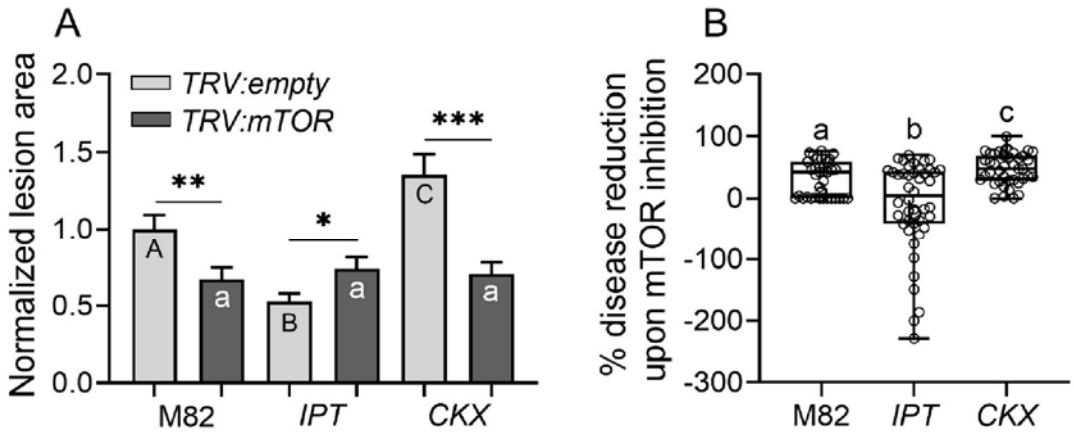

Figure 1: *TOR* inhibition mediates disease resistance downstream to CK

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were *TOR*- silenced using the VIGS system. Plants were challenged with *B. cinerea (Bc)* mycelia from a 72h old-culture 4 weeks after VIGS, on leaflets derived from leaves 5-6. **A**: *Bc* necrotic lesion size. **B**: percentage of disease reduction following *TOR* silencing in the different genotypes. Bars represent mean ±SEM; boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Experiments were repeated 4 independent times.

A: Asterisks indicate statistically significant disease reduction upon *TOR* silencing when compared with empty vector ("EV") silencing. Different letters indicate statistically significant differences among samples, upper case letters for Mock altered CK genotypes and lower case letters for samples with silenced TOR, in a one-way ANOVA with a Tukey post hoc test, N=12, $p<0.035$ (*$p<0.05$, **$p<0.01$, ***$p<0.001$). **B:** Different letters indicate statistically significant differences between samples in one-way ANOVA with a Tukey post-hoc test, N=36, $p<0.025$.

genotypes, irrespective of CK levels. These results were further confirmed by TOR inhibition using specific TOR inhibitors (**Figure S1**), where disease symptoms decreased in *pFIL>>CKX* and M82 in the presence of the TOR specific inhibitors Torin2 and WYE132. No significant increase was observed in the IPT line when using TOR inhibitors **(Figure S1)**. This difference could be related to different levels of TOR inhibition in the different methodologies used. Us and others have previously demonstrated the specificity of Torin2 and WYE132 (Li et al., 2017; Montané and Menand, 2013; Marash et al., 2022).

129 To further examine the relationship between TOR inhibition and CK in plant defense, we
130 assessed *Bc* sensitivity of M82 plants upon Torin2 and 6-BAP treatment. Plants were either
131 treated with Torin2 or with 6-BAP, or both. As expected, both 6-BAP and Torin2 treatments
132 promoted disease resistance, as lesion size was reduced by about 40% with either Torin2 or CK
133 respectively **(Figure S2A)**. Treatment with both Torin2 and 6-BAP, however, had no additive
134 effect on disease resistance. To assess the effect of 6-BAP and Torin2 on plant defense
135 responses, we analyzed ROS accumulation and ion leakage with or without Torin2 and 6-BAP
136 treatment **(Figure S2B,C).** ROS accumulation and ion leakage were increased by either 6-BAP or
137 Torin2 treatment. However, no additive effect on induction of defense responses upon
138 combined treatment with both Torin2 and 6-BAP was observed. Collectively, these results
139 suggest that TOR inhibition likely promotes plant defense and disease resistance downstream
140 to CK.
141
142 Both high endogenous CK levels and *TOR* downregulation were shown by us and others to
143 induce plant defense responses (Gupta et al., 2020b; Marash et al., 2022). Given that *TOR*
144 downregulation increased disease susceptibility in resistant high-CK plants, we hypothesized
145 that CK and TOR effects on plant defense responses might be dependent. To test this
146 hypothesis, we examined the effect of TOR inhibition in lines with different endogenous CK
147 levels on ROS accumulation. In the absence of Torin2, consistent with our previous report
148 characterizing CK-mediated immunity (Gupta et al., 2020b), flg-22 elicited ROS levels were
149 higher in the IPT line, and lower in CKX plants. TOR inhibition using Torin2 increased ROS
150 accumulation in both CKX and WT plants **(Figure 2)**. By contrast, ROS accumulation significantly
151 decreased in IPT plants upon Torin2 application. Similar results were obtained when quantifying

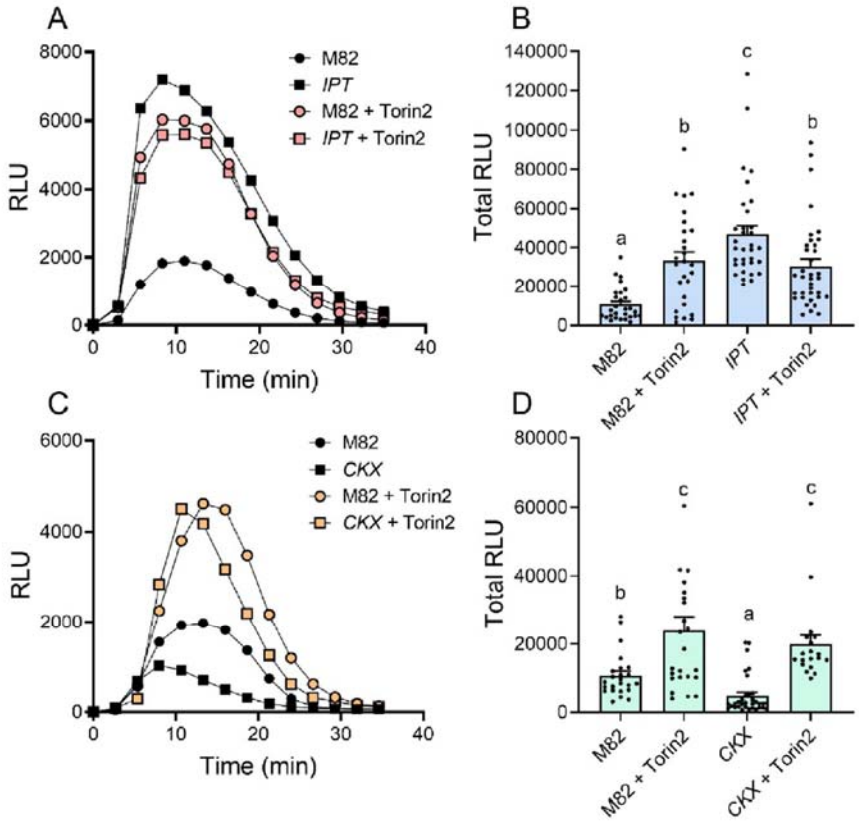

Figure 2: TOR inhibition mediates increased immunity downstream to CK

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*") (**A, B**), the decreased CK line *pFIL>>CKX3* ("*CKX*") (**C, D**), and their WT background M82, were treated with Mock (1:5000 DMSO in DDW), or 2 µM Torin2. Plants were challenged with the immunity elicitor flg-22 (1 µM) 24 h after Torin2 treatment. ROS production was measured immediately after flg-22 application every three minutes, using the HRP-luminol method, and expressed as Relative Luminescent Units (RLU). (**B, D**) Average total RLU per treatment. Bars represent mean ±SEM, all points shown. Experiments were repeated 3 independent times. Different letters indicate statistically significant differences between samples in Welch's ANOVA with a Dunnett post-hoc test, **B:** N=28, $p<0.0001$. **D:** N=20, $p<0.031$.

ion leakage, an -increase of 36% and 76% in M82 and CKX respectively, and a decrease by 46% in IPT, were observed **(Figure S3)**. These results further support the notion that TOR acts downstream to CK in promoting plant defense.

TOR mediates CK-driven developmental cues

157 Transgenic tomato lines with altered leaf CK content have altered developmental programs,
158 resulting in quantifiable phenotypic changes to leaf development. IPT has significantly more
159 complex leaves, while CKX has significantly simpler leaves, when compared with their M82
160 background (Shani et al., 2010). To investigate whether TOR plays a role in CK-mediated leaf
161 development, we compared the leaf complexity of lines with different CK levels upon *TOR*-
162 silencing. Interestingly, whereas the leaves in the WT M82 plants did not show any significant
163 phenotypical changes in response to *TOR*-silencing, we observed a reduction in leaf complexity
164 in the highly complex IPT plants, and an increase in leaf complexity in the simple-leaved CKX
165 plants **(Figure 3)**, suggesting that TOR is required to execute the developmental cues generated
166 by CK. We wondered whether TOR activity could account for other phenotypic changes
167 resulting from alterations to leaf developmental programs observed in "classical"
168 developmental mutants which have not been directly linked to CK levels. Interestingly, *TOR*
169 inhibition "normalized" the phenotypes observed in several mutants (**Figure 4**), suggesting that
170 the execution of developmental cues is mediated by TOR as a general mechanism.
171
172 ***TOR inhibition alters CK response***
173 A recently deposited BiorXiv paper has shown that TOR inhibition reduces CK levels by the
174 induction of the CK deactivating CKX enzyme genes in *Arabidopsis* (Janocha et al., 2021). In
175 agreement with this observation, we found that both CKX2 and CKX5 mRNA levels were
176 upregulated in response to Torin2 treatment, while the level of the CK-mediated response
177 regulator gene TRR3/4 was reduced, suggesting that TOR inhibition results in a corresponding
178 effect on CK signaling **(Figure 5)**. TOR Inhibition also induced expression of the KNOX2

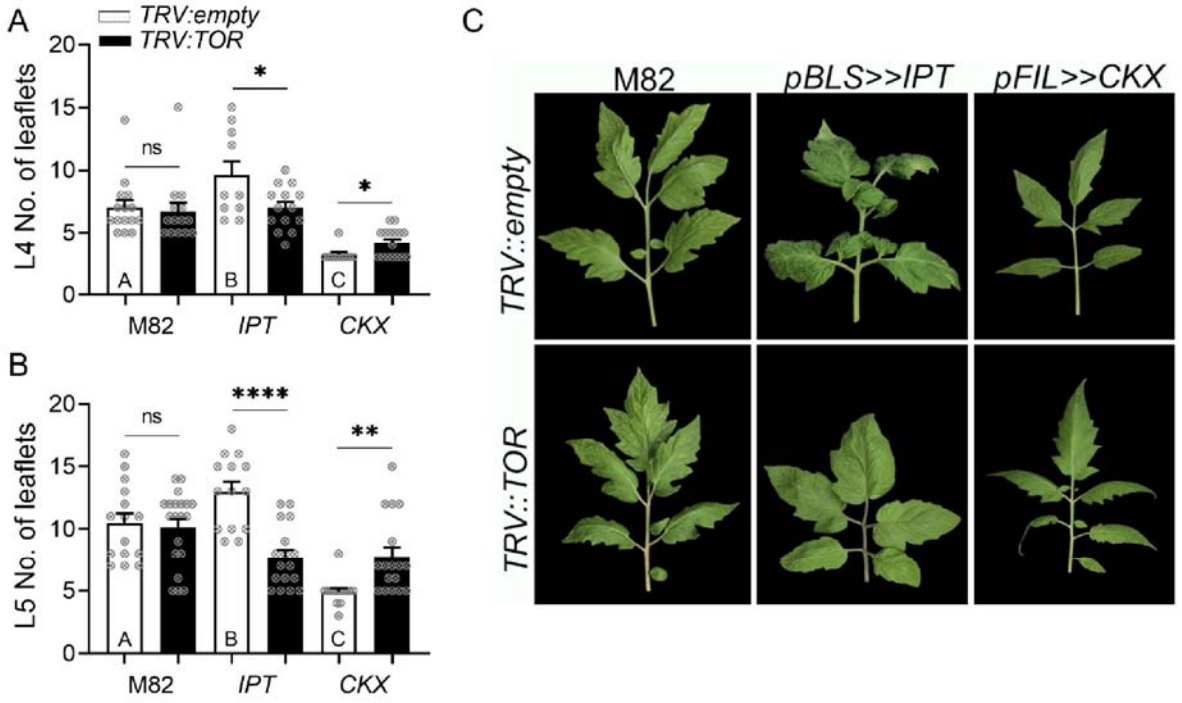

Figure 3: *TOR* silencing affects leaf development downstream to CK

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were *TOR*-silenced using VIGS. 4 weeks after silencing, leaf complexity was quantified by counting the leaflets on leaves 4 (**A, C**) and 5 (**B**). Experiment was conducted 3 times. Bars represent Mean ±SEM, all points shown. Asterisks indicate statistically significant changes in leaf complexity upon *TOR* silencing, and different letters indicate statistically significant differences among the control samples, in a one-way ANOVA with a Holm-Sidak post hoc test. **A:** N>10 individual plants, *p<0.05, ns- non significant. **B:** N>14 individual plants, **p<0.01, ****p<0.0001, ns- non significant.

179 homeobox transcription factor TKN2, that is responsible for meristem maintenance (Shani et
180 al., 2009), and reduced expression of the MYB transcription factor *clausa*, that promotes
181 differentiation (Bar et al., 2016), both of which could correspond with a more juvenile
182 developmental state (**Figure 5**).
183 Pathogen infection has been previously demonstrated to alter the expression of CK pathway
184 genes (Argueso et al., 2012; Gupta et al., 2020b, 2020a).

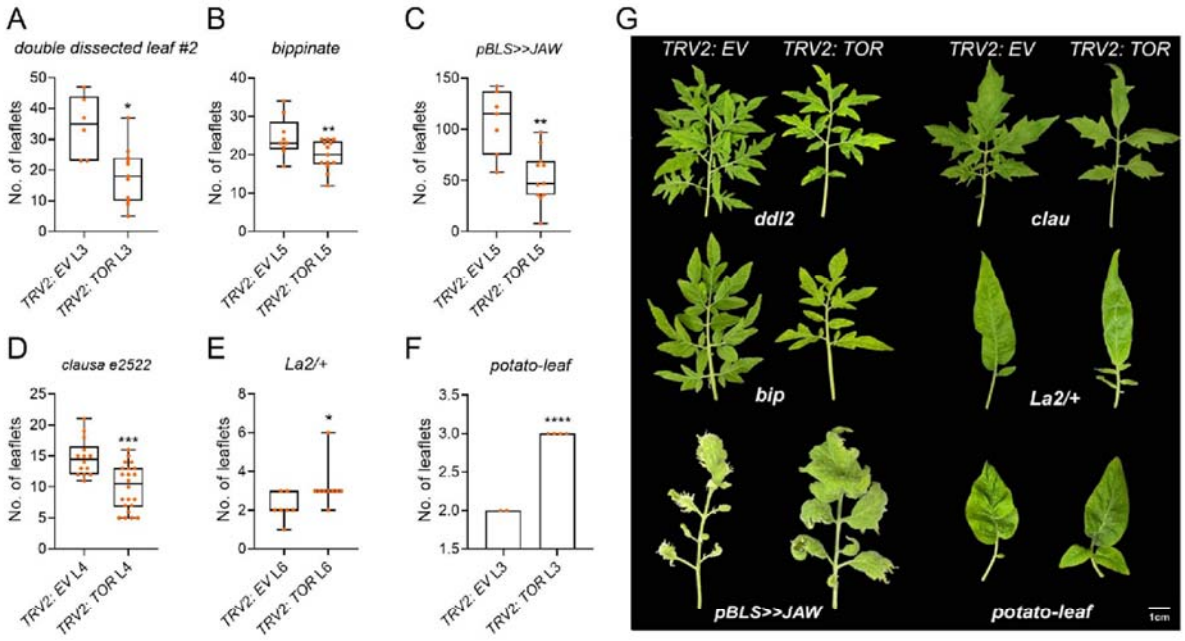

Figure 4: TOR is required for the execution of developmental cues in the leaf

S. lycopersicum plants mutated in the BELL transcription factors *Double Dissected Leaf*: *ddl2* (**A, G**), *Bippinate*: *bip* (**B, G**), the MYB transcription factors, *CLAU*: *clausa* (**D, G**), and *C: potato leaf* (**F, G**), the TCP transcription factor *Lanceolate*: *La2/+* (**E, G**), or overexpressing miR390 under the leaf specific promoter BLS: *pBLS>>JAW* (**C, G**), were *TOR*-silenced using VIGS. 4 weeks after silencing, leaf complexity was quantified by counting the leaflets on leaves 3, 4, 5 or 6- as indicated.

Experiment was conducted 3 times. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), (A-E), or, bars represent Mean ±SEM (F), all points shown. Asterisks indicate statistically significant changes in leaf complexity upon TOR silencing as compared with the same leaf in empty-vector VIGSed plants, in a two-tailed t-test or a Mann-Whitney U test. **A:** N=6-11 individual plants, *p<0.05. **B:** N=9-14 individual plants, **p<0.01. **C**: N=7-11 individual plants, **p<0.01. **D**: N=14-22 individual plants, ***p<0.001. **E**: N=7-9 individual plants, *p<0.05. **F**: N=3-4 individual plants, ****p<0.0001.

185 To investigate possible effects of TOR status on pathogen-driven alterations in CK pathway
186 genes, we examined gene expression following infection with *Botrytis cinerea* (Bc), with and
187 without Torin2 treatment (**Figure S4**). CK-mediated signaling (examined by assaying expression
188 of the response regulators TRR3/4 and TRR5/6/7) showed the expected increase following Bc
189 treatment (**Figure S4A,B**). TRR3/4 is reduced by Torin2 treatment (**Figure 5, S4B**), and following

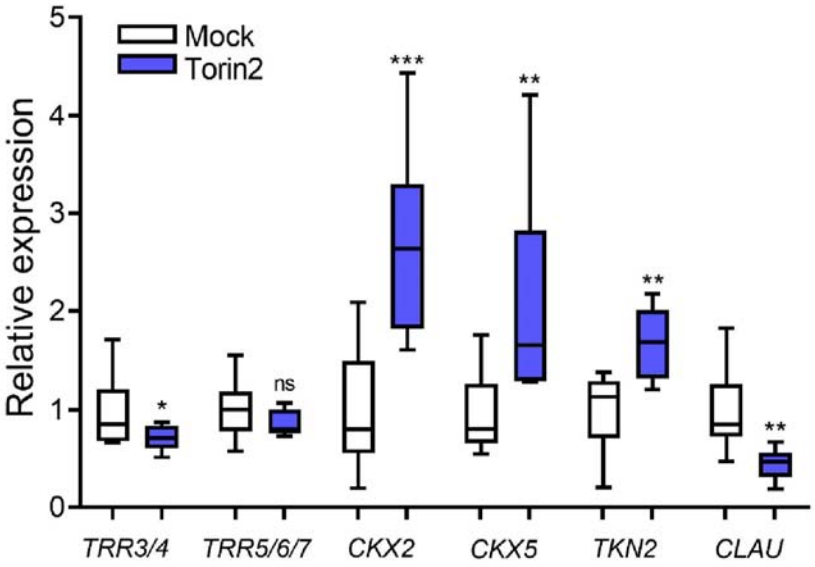

Figure 5: TOR inhibition alters CK pathway and developmental gene expression

Gene expression analysis of the indicated CK pathway and developmental genes, with and without Torin2 (2 µM) treatment, was measured by RT-qPCR. 1:5000 DMSO in DDW served as Mock. Relative expression was calculated using the mean between the gene copy number obtained for three reference genes: RPL8 (Solyc10g006580), EXP (Solyc07g025390), and CYP (Solyc01g111170), and normalized to Mock treatment. Analysis was conducted on 6 individual plants. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box). Asterisks indicate significant differential regulation upon Torin2 treatment in Welch's t-test comparing each gene, *p<0.05, **p<0.01, ***p<0.001, ns- non significant.

Bc and Torin2 co-treatment, returns to background levels (**Figure S4A**). TRR5/6/7 is not affected by Torin2 (**Figure 5, S4B**), however, upon combined treatment, it increases beyond the levels elicited by Bc alone, suggesting that TOR mediated effects on the CK pathway may be differential through interactions with different CK pathway genes. CKX gene expression is reduced in response to Bc infection (**Figure S4C,D**), as was observed following Torin2 treatment (**Figure 5**), and the combination of both Bc infection and Torin2 treatment does not further augment this reduction in CKX expression. The developmental meristem-maintenance KNOX gene TKN2 is induced by Torin2 and repressed by Bc infection, and in this case, the infection process has a dominant effect (**Figure S4E**), indicating that defense processes may take

199 precedence over meristem maintenance in this case. The effect of TOR inhibition on meristem
200 maintenance is likely also dependent on the developmental stage of the plant.
201 To assess the effect of TOR inhibition on CK signaling in young developing shoots, we next
202 examined the effect of TOR inhibition on CK signaling by using the CK-response transgenic
203 reporter line TCSv2::3XVENUS, that expresses VENUS under the control of the CK responsive
204 synthetic promoter TCS (Steiner et al., 2016; Zürcher et al., 2013; Steiner et al., 2020).
205 We found that in the presence of Torin2, there is a reduction in CK signaling in the meristem
206 zone, as treated TCSv2::3XVENUS meristems showed a significant reduction in signal relative to
207 untreated meristems **(Figure 6)**. This is consistent with the increase in CKX gene expression
208 upon Torin2 treatment (**Figure 5**). Similar results were achieved in TCS expressing plants in
209 which *TOR* was silenced by VIGS **(Figure S5)**. To further investigate whether TOR is required for
210 CK signaling, we used *pFIL>>CKX* plants expressing the CK responsive promotor TCSv2.
211 Similarly to disease reduction (**Figure 1**) and defense responses (**Figure 2,S2,S3**), we observed
212 an increase in TCS driven Venus signal in the meristem of Torin2 treated *pFIL>>CKX* plants, in
213 comparison with untreated plants **(Figure S6)**. These results suggest that TOR activity is
214 required for an intact CK signaling pathway.
215
216 ***CK antagonizes TOR***
217 To further probe the relationship between CK and TOR, we next examined the effect of CK
218 application on the phosphorylation of a downstream target of TOR. We hypothesized that if
219 TOR is indeed downstream to CK signal transduction, CK might affect TOR activity. We used an
220 antibody against the phosphorylated form of S6K1, one of the classical TOR targets that has

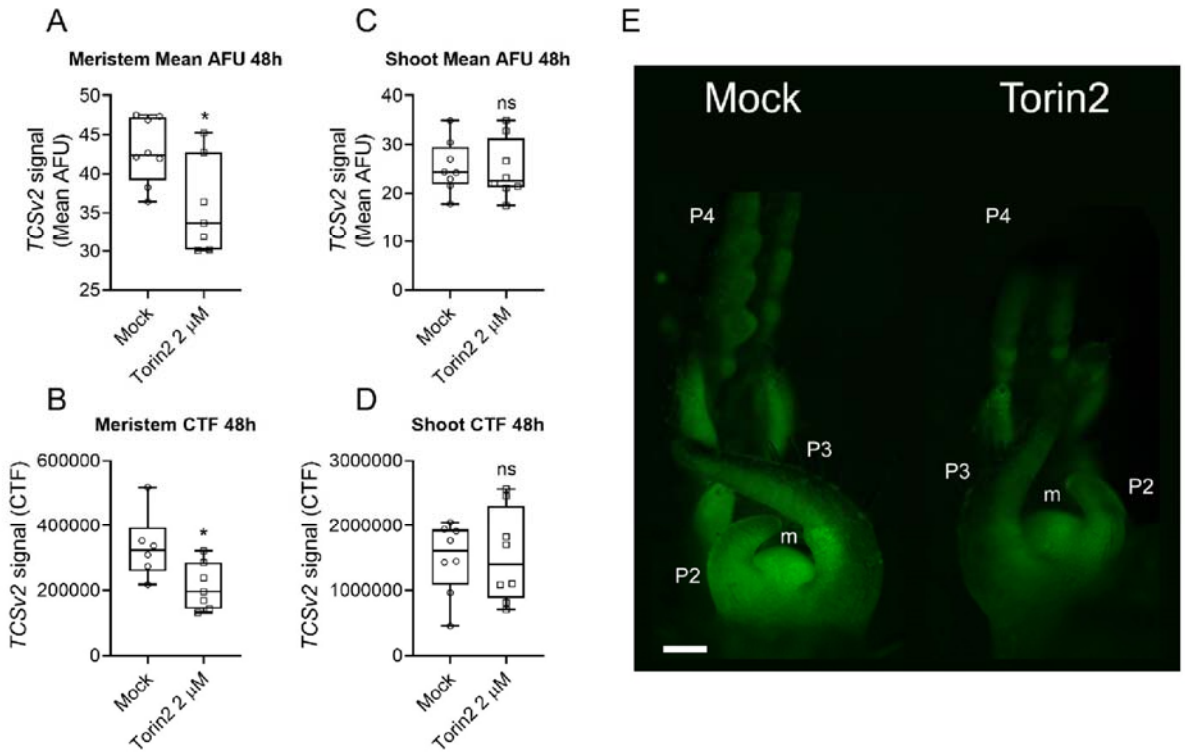

Figure 6: TOR inhibition reduces CK response in the meristem of young shoots

S. lycopersicum cv. M82 10 day-old seedlings expressing VENUS driven by the cytokinin responsive promoter TCSv2 were treated with Torin2 (2 µM) or Mock (1:5000 DMSO in DDW) for 48 h.

TCSv2 driven total Venus fluorescence in the meristem (**A,B**) or total shoot (**C, D**) was measured as mean arbitrary fluorescent units (AFU, the strength of the signal, **A, C**) or corrected total fluorescence (CTF, a quantification taking into account the fluorescent area, **B, D**), in images captured under identical conditions in shoots comprising the 4 youngest primordia. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Asterisks indicate significant TCSv2 signal reduction upon Torin2 treatment in an unpaired two-tailed *t*-test, N>7, *p<0.05, ns- non significant.

(**E**) Typical Mock treated and Torin2 treated shoots are depicted. Images captured under identical conditions. The meristem (m), second (P2) third (P3) and fourth (P4) youngest leaf primordia are indicated. Bar- 1000 µM.

221 been previously used as an indication of TOR activity in plants (Li et al., 2017). We found that CK

222 application reduces the phosphorylation of S6K1 by TOR, suggesting that CK negatively

223 regulates TOR activity **(Figure 7A,B)**. This was further verified in the *pBLS>>IPT* and *pFIL>>CKX*

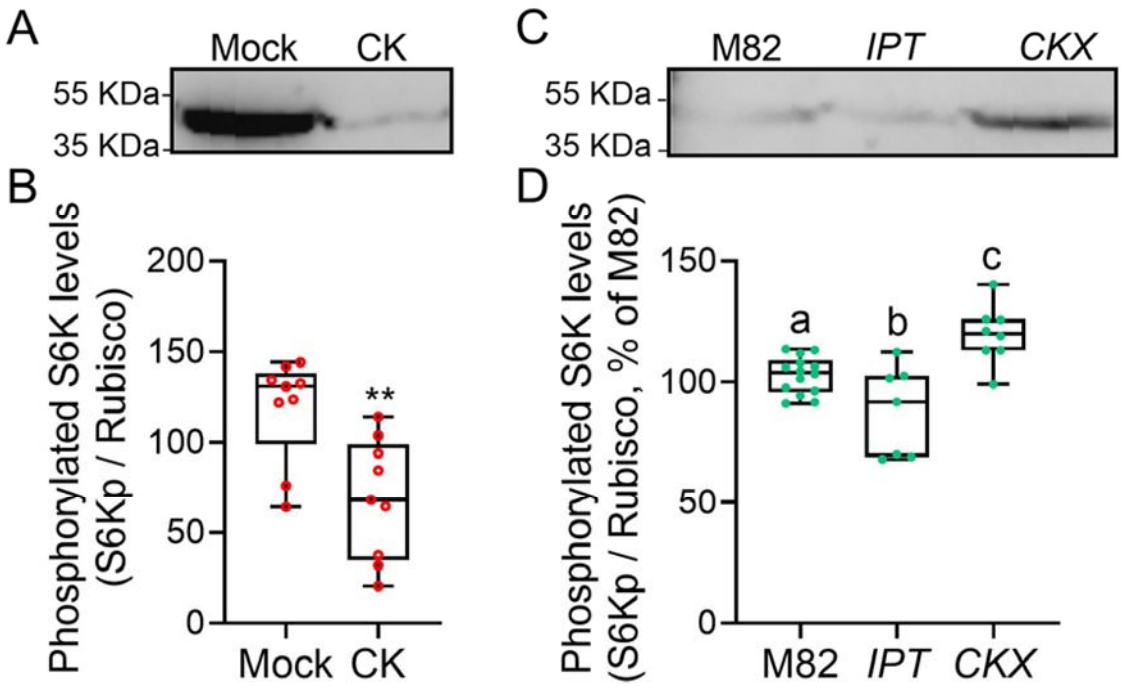

Figure 7: CK reduces TOR activation

A-B *S. lycopersicum* cv. M82 10 day-old seedlings were treated with Mock (10 µM NaOH) or 10 µM of the CK 6-benzylaminopurine (6-BAP). 24 h after treatment, total cellular proteins were preapared from 3 biological replicas of 10 plants each, and TOR activation was assessed by detection of phosphorylated S6K using specific antibodies.

C-D Total cellular proteins were prepared from *S. lycopersicum* cv. M82, and *pBLS>>IPT* or *pFIL>>CKX* transgenic lines in the M82 background (3 biological replicas of 10 plants each). TOR activation was assessed by detection of phosphorylated S6K using specific antibodies.

Experiment was repeated 3 times. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. **B** Asterisks indicates statistically significant reduction in phosphorylated S6K in a Mann Whitney U test, N=9, $p<0.01$. **D** Different letters indicate staistically significant differences between samples in a one-way ANOVA with a Tukey post hoc test, *$p<0.05$, N=7-14.

224 transgenic lines, as the phosphorylation of S6K1 was reduced in *pBLS>>IPT* and enhanced in

225 *pFIL>>CKX* in comparison to the background M82 **(Figure C,D)**.

226

227

228 **Discussion**

229 ***The role of TOR as a development-defense switch***

230 Plants constantly perceive and process environmental signals and balance between the
231 energetic demands of growth and defense. Generally, it is believed that the growth arrest upon
232 pathogen attack is the result of a redirection of the plants' metabolic resources towards the
233 activation of plant defense responses at the expense of growth (Campos et al., 2016). Indeed,
234 growth was found to be prioritized over defense in plants grown under light deprivation, and
235 they were reportedly more susceptible to attacks by *Pseudomonas syringae* and *Botrytis*
236 *cinerea* (Huot et al., 2014). It is still unclear, however, whether the shift in the metabolic
237 resources toward immunity is the sole factor of growth inhibition, or whether it is an adaptive
238 response regulated by growth and defense signaling networks (Guo et al. 2018). The ability of
239 TOR to sense many different inputs such as hormone levels, nutrients, energy, light, and abiotic
240 or biotic stress signals, enables concerted regulation of downstream anabolic and catabolic
241 processes, resulting in the optimization of plant growth (Dobrenel et al., 2016). TOR and has
242 been previously suggested to act at the intersection of growth and defense as a molecular
243 'switch' that activates cell proliferation and plant growth at the expense of defense (de
244 Vleesschauwer et al., 2018). Likewise, we have recently reported that TOR negatively regulates
245 plant immunity and defense responses in tomato (Marash et al., 2022). The main objective of
246 this study was to provide insights on the relationships between TOR and CK in the mediation of
247 immunity. We discovered that TOR executes signaling cues resulting from both high and low CK,
248 in both defense and development. We hypothesize that the crosstalk between TOR and CK

249 signaling is likely involved in the ability of plants to "turn off" growth and developmental
250 programs upon pathogen attack, and thus enable a faster activation of plant defense responses.
251 It was shown previously that TOR interacts with plant hormones (Wu et al., 2019; Dong et al.,
252 2015). For example, a link between the CK and TOR pathways was recently demonstrated by
253 Janocha et al., 2021, who provided evidence that TOR suppresses CK signaling in the shhot
254 apical meristem of Arabidopsis, by promoting the expression of CKXs genes. In addition,
255 because most of the evolutionarily conserved regulators of TOR are absent in land plants, it was
256 suggested that in plants, hormones play a more substantial role in the upstream regulation of
257 TOR (Schepetilnikov and Ryabova, 2018), and that plants, unlike other eukaryotic species, have
258 thus evolved a distinct regulatory mechanism (van Leene et al., 2019).
259
260 ***Involvement of TOR in CK-mediated defense and development***
261 We used plants with different CK levels to test the idea that TOR is required for CK-mediated
262 immunity. We found that *TOR*-silencing promotes *Bc* resistance in CK-deficient CKX
263 overexpressing plants. By contrast, plants with high CK levels showed an opposite trend as they
264 became more susceptible to *Bc* **(Figure 1)**, implying that CK-mediated immunity requires TOR
265 activity for execution. Another line of evidence supporting the role of TOR in CK-mediated
266 immunity comes from the observation that defense responses were induced upon TOR
267 inhibition in *pFIL>>CKX3* plants, whereas they were reduced in the high CK line *pBLS>>IPT*
268 **(Figures 2 and S2-S3)**. This could also explain why TOR inhibition did not further enhance
269 defense responses or *Bc* resistance when combined with CK application **(Figure S2)**.

270 Both TOR (Eltschinger and Loewith, 2016) and CK (Werner and Schmülling, 2009; Keshishian
271 and Rashotte, 2015) are growth regulators that were shown to play a role in plant immunity;
272 TOR inhibition (Marash et al., 2022) or high endogenous CK levels (Gupta et al., 2020b)
273 promote pathogen resistance in a SA-dependent manner in tomato. Thus, in addition to TOR
274 sensing being required for the achievement of developmental and defense phenotypes
275 determined by signals stemming from hormone levels, it is likely that TOR and CK signaling
276 pathways coordinately regulate plant defense responses through the modulation of SA.
277
278 TOR is required for the patterning of leaf organs programmed by CK. The increased leaf
279 complexity in the high-CK overexpressing IPT, and the diminished leaf complexity in the CKX
280 over-expressor which has low CK levels, were both tempered to WT M82 levels by the inhibition
281 of TOR **(Figure 3)**. This phenotypic change might suggest that CK distribution and/or signaling
282 are altered in response to *TOR*-silencing, or that factors which execute organ patterning
283 downstream of hormonal cues are dependent on TOR status. These changes in phenotypes
284 likely stem from the fact that TOR is a translation regulator that acts downstream of CK
285 mediated signals in both defense and development contexts. Interestingly, we found that TOR
286 inhibition decreases the severity of developmental phenotypes of several additional mutants
287 which have not necessarily classically been associated with CK levels **(Figure 4)**. This brings forth
288 the notion that TOR mediates signals from additional hormones, or rather, that TOR is
289 responsible for the reduction to practice of a variety of cues and signals generated by the
290 balance and crosstalk of several developmental hormones (Israeli et al., 2021; Greenboim-
291 Wainberg et al., 2005).

292

293 ***Possible mechanisms by which TOR mediates developmental and defense cues***

294 As previously reviewed in (Du et al., 2018) light and sugar, i.e. plant food, generate signals of a
295 positive energy status that are required to enable organ formation in the SAM. These signals
296 converge on TOR (Pfeiffer et al., 2016; Li et al., 2017). Auxin biosynthesis is activated by light in
297 the shoot apex, while auxin mediates light-dependent activation of TOR (Li et al., 2017). The
298 light signal is then relayed through cytokinin signaling pathways (Pfeiffer et al., 2016; Yoshida et
299 al., 2011). Thus, light regulates leaf initiation by activating cytokinin signaling and affecting
300 auxin gradients (Yoshida et al., 2011). As TOR functions in concert with light and positive
301 metabolic status to promote cell growth and division, it has been suggested that active growth
302 and cell-cycle progression are required for the formation of the hormonal axis, involving auxin
303 and cytokinin, that is required for organ formation and patterning during plant development
304 (Du et al., 2018).

305 Differences in leaf outgrowth are typically attributed to two processes: cell division and cell
306 expansion (reviewed in Kalve et al., 2014). Dividing cells grow by increasing their cytoplasmic
307 volume, which is an energy demanding process that requires the synthesis of macromolecules.
308 The TOR pathway plays a central role in ensuring an adequate supply of elementary building
309 blocks. TOR integrates growth related genes to glucose signaling and is thereby an important
310 regulatory hub in the development of organs. Several previous studies indicated that TOR plays
311 a role during leaf development in *Arabidopsis*. For example, *TOR* downregulation has been
312 shown to result in the production of smaller leaves with fewer cells (Caldana et al., 2013)
313 whereas *TOR* overexpression results in the production of bigger leaves with larger cells

314 (Deprost et al., 2007). Likewise, mutation in *LST8*, a member of the TOR complex, results in a
315 reduction in the number of leaves and in leaf size (Moreau et al., 2012), and mutation in
316 *AtRAPTOR1B*, another component of the TORC1 complex, stalls leaf initiation (Anderson et al.,
317 2005). By contrast, we did not observe any significant phenotypic lterations in the tomato WT
318 M82 cultivar upon *TOR*-silencing. This could be ascribed to the different inhibition methods
319 used, or the different plant species. We found that *TOR*-silencing caused tempering of the
320 phenotypes of several developmental mutants, with both simple-leaved and complex-leaved
321 mutants becoming closer to WT leaf phenotypes following *TOR*-silencing. We thus conclude
322 that TOR is required for the execution of a variety of cues that are integrated to form a cohesive
323 leaf developmental program.
324
325 TOR plays a key role as a regulator of translation and ribosome biogenesis in mammals and
326 plants, and therefore its activity is tightly regulated (Pereyra et al., 2020). Interestingly,
327 proteome analysis of cytokinin activity in *Arabidopsis* demonstrated extensive differential
328 regulation of ribosomal proteins in response to CK (Brenner and Schmülling, 2012). In another
329 proteomic study, the functional classification 'Ribosome biogenesis' was found to be strongly
330 differential in response to CK depletion or overproduction (Černý et al., 2013). CKs are known
331 to alter leaf development and morphology (Werner et al., 2003; Hay and Tsiantis, 2010; Shani
332 et al., 2010), and the differentially regulated ribosomal proteins are probably involved in the
333 underlying molecular mechanism. Horiguchi et al., 2011 demonstrated that ribosomal proteins
334 play a key role in *Arabidopsis* leaf development, supporting this notion. Thus, it is likely that
335 TOR is involved in the execution of CK-mediated signals, in both defense and development, by

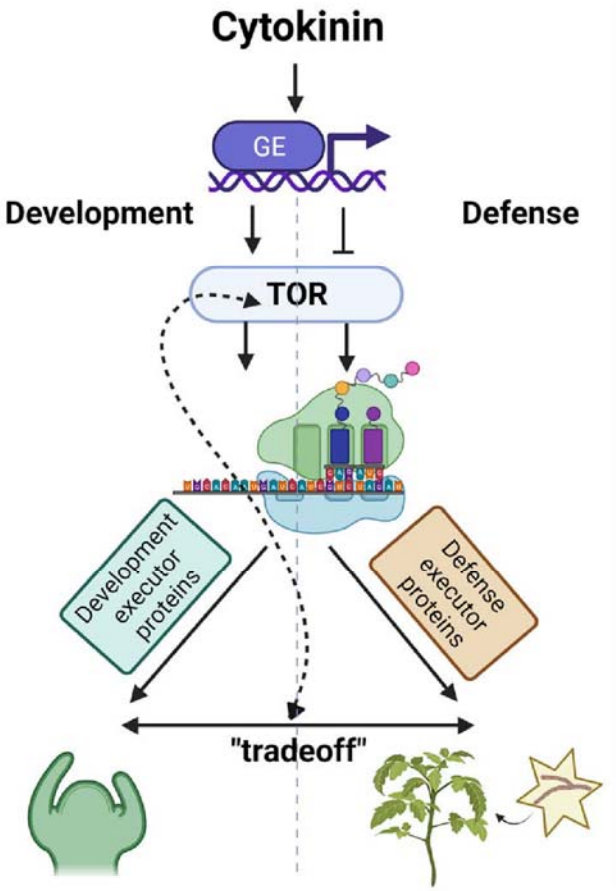

Figure 8: Model describing the role of TOR as a mediator of both development and defense cues, and the tradeoff between them.

Cytokinin promotes both development and defense. Balanced CK levels are required to achieve "normal" developmental patterning and disease resistance.
Under low CK, development and defense are inhibited, resulting in reduced patterning (Fig. 3), and increased disease susceptibitlity (Fig. 1). Under high CK, development and defense are promoted, resulting in increased patterning (Fig. 3) and disease resistance (Fig. 1).
Inhibition of TOR results in rescue of both low and high CK pehnotypes, resulting in return to baseline developmental patterning and disease resistance, and suggesting that TOR mediates these develpmental and defense cues originating from CK.
In the tradeoff between development and defense, high CK causes downregulation of TOR (Fig. 6), resulting in a shift towards defense. The switch between development and defense may be modulated by cross-talk between environmental sensing and TOR status.

its direct or indirect regulation of proteins required for the execution of these processes (**Figure 8**).

339 ***TOR activity is needed for normal CK signaling***

340 When plants are exposed to pathogens, the CK signaling pathway is activated (Argueso et al.,
341 2012; Gupta et al., 2020b) leading to down-regulation of TOR activity **(Figure 6)**. Our results
342 support the notion that down-regulation of TOR could be the mechanism executing CK-
343 mediated induced immunity and disease resistance, at least in part. Our results demonstrating
344 that TOR inhibition results in a decrease in CK signal intensity in the meristem of
345 *pTCSv2::VENUS* plants **(Figure 5)**, as was recently similarly found in *Arabidopsis* (Janocha et al.,
346 2021), indicate that TOR activity is required for a normal CK signaling pathway. The increase of
347 TCSv2 signal in *pFIL>>CKX* plants that were *TOR*-silenced **(Figure S6)**, also demonstrates that
348 TOR is responsible for CK signaling output, and that in its absence, a more "normal" CK signal is
349 generated in the otherwise CK-deficient CKX overexpressing plants, as was evident also by their
350 increase in leaf complexity (**Figure 3**). The observation that CK application results in a decrease
351 in TOR activation in the meristem might suggest the existence of a mechanism that balances
352 between TOR activity and CK signal. Interestingly, an opposite result was reported in
353 *Arabidopsis* cell suspensions, where kinetin and auxin both induced the phosphorylation of
354 AtS6k (Turck et al., 2004). Our data show that TOR is likely downstream to CK-signaling in
355 plants, and that the ability of CK to induce immunity is related to TOR status. Therefore,
356 increased CK leads to a reduction in TOR activity. The difference between our report and the
357 previous one likely relates to a cell suspension being used in the previous report, or to the
358 different plant hosts being examined.

359

360 We propose a model by which TOR modulates CK signaling and pathogen resistance. Under
361 standard growth conditions, CK and TOR work together to carry out developmental programs,
362 with TOR mediating the execution of CK-derived signals. Upon pathogen attack, metabolic
363 resources are redirected toward the activation of defense mechanisms at the cost of growth
364 (Campos et al., 2016). The decrease in available resources is sensed by TOR, and that leads to a
365 decrease in TOR activity in the meristem and to the subsequent upregulation in the expression
366 of CKX genes and decrease in CK levels. Thus, TOR, through CK, actively halts growth during
367 pathogen attack. The upregulation in CK degrading genes CKX2 and CKX5, as well as the
368 downregulation of the CK-responsive response regulator gene TRR3/4 upon TOR inhibition,
369 could also be associated with a transition from a "growth" to "defense" state. CK-mediated
370 differential phenotypic output is diminished upon TOR inhibition, indicating that TOR is
371 required for CK-mediated phenotypes in both defense and development. **Figure 8** provides a
372 model for the role of TOR as a mediator of both developmental and defense cues downstream
373 of CK. Inhibition of TOR results in rescue of both low and high CK phenotypes, resulting in
374 return to baseline developmental patterning and disease resistance, and suggesting that TOR
375 mediates these developmental and defense cues originating from CK. Its involvement in both
376 development and defense poises TOR as a prime regulator of tradeoffs between these two
377 important aspects of plant life. It will be interesting to investigate how different metabolic
378 states and biotic and abiotic stresses alter the cross talk between CK and TOR signaling in the
379 future.
380
381

382 **Acknowledgements**

383 We thank members of the Spiegelman group for technical assistance, Dr. Barak Rotblat for
384 helpful discussions, and members of the Bar group for continuous support.

385

386 **Author Contributions**

387 MB and IM conceived and designed the study. IM, ML-M, RG, and MB formulated the
388 methodology and carried out the experiments. IM, ML-M, RG, and MB analyzed the data. All
389 authors contributed to the writing of the manuscript.

390

391 **Competing Interests Statement**

392 The authors declare no competing interests.

393

394 **Materials and methods**

395 Plant material and growth conditions

396 *S. lycopersicum* tomato cultivar M82 plants were used in this study. Genotypes used, all in the
397 cv. M82 background, were as follows: M82 background line; *pBLS>>IPT7*, which contains
398 elevated endogenous levels of CK- referred to hereinafter as "*pBLS>>IPT* "or "*IPT*"; and the CK
399 depleted *pFIL>>CKX3*, referred to hereinafter as "*pFIL>>CKX*" or "*CKX*". The lines used in this
400 work overexpress Arabidopsis AtIPT7 or AtCKX3 from the leaf specific promoters pFIL and pBLS,
401 in tomato cv M82, and were previously characterized (Shani et al., 2010). The transgenic plants
402 have normal early development and are viable and fertile (Shani et al., 2010). TCSv2:3XVENUS
403 overexpressing plants were also previously described (Steiner et al., 2016; Steiner et al., 2020;

404 Zürcher et al., 2013). Plants were grown in soil (Green 443; Even-Ari Green, Ashdod, Israel) in a
405 growth chamber set to long-day conditions (16/8 light/dark) at 24°C, or in a greenhouse under
406 natural day length conditions.
407
408 Torin2 and WYE132 treatments
409 Torin2 (SML1224 Sigma-Aldrich) or WYE132 (PZ0321 Sigma-Aldrich), were applied to detached
410 tomato leaves through the petiole for 24 hours prior to pathogen inoculation (both inhibitors),
411 defense response quantification (only Torin2), or RNA preparation (only Torin2). For both
412 inhibitors, a 10 mM stock solution was prepared in concentrated DMSO (P0037 SIGMA-Aldrich)
413 and diluted to 2 µM in water. Mock leaves were treated with water containing 1:5000 of DMSO.
414
415 6-BAP treatment
416 Two weeks old M82 plants were sprayed with 100mM 6-benzyl purine (6-BAP) solution (Sigma-
417 Aldrich) or mock solution 24h prior to analysis. Stock solution was prepared in NaOH and
418 diluted with water.
419
420 Virus Induced Gene Silencing (VIGS)
421 VIGS was performed as previously described (Liu et al., 2002). The *SlTOR* silencing construct was
422 generated as previously described (Marash et al., 2022). The *TRV2:TOR* construct, as well as an
423 empty TRV RNA2 for control, were introduced into *A. tumefaciens* strain GV3101::pMP90. TRV
424 RNA1 was mixed in at a ratio of 1:1 with RNA2 (either empty or *TRV2:TOR*) in infiltration buffer,
425 and infiltrated into tomato cotyledons. Fifth leaves of six-week-old tomato plants were used for

426 pathogenicity assays, measurement of defense responses, complexity quantification and TCSv2
427 driven Venus quantification.
428
429 Pathogenesis assays
430 *Botrytis cinerea* pathogenicity assays were performed as previously described (Gupta et al.,
431 2020b). Briefly, *B. cinerea* isolate Bcl16 was maintained on potato dextrose agar (PDA; Difco)
432 plates in 22C. 0.4 cm diameter agar discs were pierced from colony margins and used to
433 inoculate detached leaves. Inoculated leaves were kept in a humid chamber at 22°C under long-
434 day conditions. Necrotic lesion size was measured 5 days post inoculation using ImageJ. For Bc
435 inoculation prior to RT-qPCR analysis, Bc spores were collected in 1 mg/ml glucose and 1 mg/ml
436 K_2HPO_4, filtered through cheesecloth, and tomato leaves were then spray inoculated with the
437 spore suspension. Mock plants were sprayed with similar concentrations of glucose and
438 K_2HPO_4. RNA was prepared 24 h after Bc inoculation.
439
440 ROS production measurement
441 ROS measurement was carried out as previously described by (Leibman-Markus et al., 2017).
442 0.5 cm diameter leaf discs were collected, and each disc was incubated in 250 ul distilled water
443 in a 96-well plate (SPL Life Science) at room temperature with agitation. After 4 hours, the
444 water was removed and 50 µL of distilled water were added. Right before measurement, 100
445 µL of distilled water with or without 1 µM flg22 (PhytoTechLabs #P6622) were added. Light
446 emission was measured using a luminometer (GloMax® Discover, Promega, United States).
447

448 Ion leakage (conductivity) measurement

449 Conductivity was measured according to (Leibman-Markus et al., 2017). 0.9 cm diameter leaf
450 discs were harvested and washed with distilled water for 3 hours in a 50 mL tube. For each
451 sample, five discs were placed in a 10-flask with 1 ml of distilled water, with 2 µM Torin2, 6-
452 BAP, or DMSO, for 48 hours with agitation. After incubation, 1.5 mL of distilled water were
453 added to each sample, and conductivity was measured using a conductivity meter (AZ®
454 Multiparameter pH/Mv/Cond./Temp Meter 86505, Taiwan).

455

456 RNA extraction and RT-qPCR

457 Isolation of total RNA was performed according to the TRI reagent (Sigma-Aldrich) procedure,
458 with application of DNAse (EN0521 ThermoFisher) to remove genomic DNA. 1 µg of RNA was
459 used for cDNA synthesis using Maxima reverse transcriptase (ThermoFisher). RT-qPCR was
460 conducted with Power SYBR Green Mix (Life Technologies), using specific primers
461 (Supplemental Table 1) in a Rotor-Gene Q machine (Qiagen). Standard curves were achieved by
462 dilutions of one cDNA sample. Relative expression was quantified by dividing the expression of
463 the relevant gene by the geometric mean of the expression of three normalizers: ribosomal
464 protein RPL8 (Solyc10g006580), Cyclophillin CYP (Solyc01g111170) and EXPRESSED EXP
465 (Solyc07g025390). All primer pairs had efficiencies in the range of 0.97-1.03 (see supplemental
466 Table 1).

467

468 Protein purification and Western Blotting

469 25 mg of tissue was collected from shoots of 4-week-old tomato plants and ground in liquid
470 nitrogen with 3 volumes of extraction buffer (100mM MOPS pH 7.6, 100mM NaCl, 40mM ß-
471 MeOH, 5% SDS, 10% Glycerol, 4mM EDTA, 2mM PMSF). The samples were boiled for 5 minutes
472 and centrifuged at 10,000 rpm for 10 minutes, to remove cell debris. Protein concentration in
473 each sample was determined using the Bradford assay with BSA calibration curves. Samples
474 with Equal amounts of protein were then separated on 15% SDS acrylamide gels, transferred to
475 nitrocellulose membranes (Protran, #10401380), and blocked with 3% skimmed milk in Tris
476 buffer saline (TBS)- Tween.
477 Membranes were probed overnight with Anti-S6K1 p-Thr449 polyclonal antibody (AB-
478 ab207399, Abcam) (dilution 1:1000) at 4°C. A goat-anti-rabbit IgG HRP antibody (AB-ab205718,
479 Abcam) was used as secondary antibody (dilution 1:10,000). Chemiluminescence was observed
480 using Elistar Supernova as substrate (Cyanagen, #XLSE2) and images of protein bands were
481 acquired and quantified using the Alliance UVITEC software.
482
483 Statistical analysis
484 All data are presented as average ±SEM, or as boxplots showing minimum to maximum values,
485 with the box representing inner quartile ranges and the whiskers representing outer quartile
486 ranges. Data sets were analyzed for normality using the Shapiro-Wilk test. For non-Gausian
487 distributed samples, differences between two groups were analyzed for statistical significance
488 using a Mann-Whitney U test, and differences between three groups or more were analyzed
489 using Kruskal-Wallis ANOVA with Dunn's post hoc test. For normally distributed samples,
490 differences between two groups were analyzed for statistical significance using a two tailed t-

491 test, with Welch's correction for samples with unequal variances, where appropriate.
492 Differences among three groups or more were analyzed for statistical significance using one-
493 way ANOVA. Regular ANOVA was used for groups with equal variances, and Welch's ANOVA for
494 groups with unequal variances. When a significant result for a group in an ANOVA was
495 returned, significance in differences between the means of different samples in the group were
496 assessed using a post-hoc test. Tukey or Holm-Sidak tests were employed for samples with
497 equal variances, and Dunnett's test was employed for samples with unequal variances. All
498 statistical analyses were conducted using Prism8.
499
500 Data availability Statement
501 The authors declare that the data supporting the findings of this study are available within the
502 paper and its Supplementary information files. Raw data is available from the corresponding
503 author upon reasonable request.
504
505 **Supplemental data files**
506 **Supplemental Figures S1-S7**
507 Supplemental Figure S1: TOR inhibition with drugs mediates disease resistance downstream to
508 CK.
509 Supplemental Figure S2: TOR inhibition mediates disease resistance downstream to CK: co-
510 application of CK and Torin2.
511 Supplemental Figure S3: TOR inhibition mediates increased immunity downstream to CK- ion
512 leakage.

513 Supplemental Figure S4: TOR inhibition and Bc infection have differential effects on CK pathway

514 genes.

515 Supplemental Figure S5: TOR inhibition by VIGS reduces CK response in the meristem of young

516 shoots.

517 Supplemental Figure S6: TOR inhibition increases CK response in the meristem of cytokinin

518 deficient *pFIL>>CKX* shoots.

519 Supplemental Figure S7: Original uncropped blots used in Figure 7.

520 Supplemental Table 1: RT-qPCR primers used in this work.

Figure Legends

Figure 1: *TOR* inhibition mediates disease resistance downstream to CK
S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were *TOR*- silenced using the VIGS system. Plants were challenged with *B. cinerea (Bc)* mycelia from a 72h old-culture 4 weeks after VIGS, on leaflets derived from leaves 5-6. **A**: *Bc* necrotic lesion size. **B**: percentage of disease reduction following *TOR* silencing in the different genotypes. Bars represent mean ±SEM; boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Experiments were repeated 4 independent times.
A: Asterisks indicate statistically significant disease reduction upon *TOR* silencing when compared with empty vector ("EV") silencing. Different letters indicate statistically significant differences among samples, upper case letters for Mock altered CK genotypes and lower case letters for samples with silenced TOR, in a one-way ANOVA with a Tukey post hoc test, N=12, $p<0.035$ (*$p<0.05$, **$p<0.01$, ***$p<0.001$). **B:** Different letters indicate statistically significant differences between samples in one-way ANOVA with a Tukey post-hoc test, N=36, $p<0.025$.

Figure 2: TOR inhibition mediates increased immunity downstream to CK
S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*") (**A, B**), the decreased CK line *pFIL>>CKX3* ("*CKX*") (**C, D**), and their WT background M82, were treated with Mock (1:5000 DMSO in DDW), or 2 µM Torin2. Plants were challenged with the immunity elicitor flg-22 (1 µM) 24 h after Torin2 treatment. ROS production was measured immediately after flg-22 application every three minutes, using the HRP-luminol method, and expressed as Relative Luminescent Units (RLU). (**B, D**) Average total RLU per treatment. Bars represent mean ±SEM, all points shown. Experiments were repeated 3 independent times. Different letters indicate statistically

significant differences between samples in Welch's ANOVA with a Dunnett post-hoc test, **B:** N=28, p<0.0001. **D:** N=20, p<0.031.

Figure 3: *TOR* silencing affects leaf development downstream to CK

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were *TOR*-silenced using VIGS. 4 weeks after silencing, leaf complexity was quantified by counting the leaflets on leaves 4 (**A, C**) and 5 (**B**). Experiment was conducted 3 times. Bars represent Mean ±SEM, all points shown. Asterisks indicate statistically significant changes in leaf complexity upon *TOR* silencing, and different letters indicate statistically significant differences among the control samples, in a one-way ANOVA with a Holm-Sidak post hoc test. **A:** N>10 individual plants, *p<0.05, ns- non significant. **B:** N>14 individual plants, **p<0.01, ****p<0.0001, ns- non significant.

Figure 4: TOR is required for the execution of developmental cues in the leaf

S. lycopersicum plants mutated in the BELL transcription factors *Double Dissected Leaf*: *ddl2* (**A, G**), *Bippinate*: *bip* (**B, G**), the MYB transcription factors, *CLAU*: *clausa* (**D, G**), and *C: potato leaf* (**F, G**), the TCP transcription factor *Lanceolate*: *La2/+* (**E, G**), or overexpressing miR390 under the leaf specific promoter BLS: *pBLS>>JAW* (**C, G**), were *TOR*-silenced using VIGS. 4 weeks after silencing, leaf complexity was quantified by counting the leaflets on leaves 3, 4, 5 or 6- as indicated.

Experiment was conducted 3 times. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), (A-E), or, bars represent Mean ±SEM (F), all points shown. Asterisks indicate statistically significant changes in leaf complexity upon TOR silencing as compared with the same leaf in empty-vector VIGSed plants, in a two-tailed t-test or a Mann-Whitney U test. **A:** N=6-11 individual plants, *p<0.05. **B:** N=9-14 individual plants, **p<0.01. **C**: N=7-11 individual plants, **p<0.01. **D**: N=14-22 individual plants, ***p<0.001. **E**: N=7-9 individual plants, *p<0.05. **F**: N=3-4 individual plants, ****p<0.0001.

Figure 5: TOR inhibition alters CK pathway and developmental gene expression

Gene expression analysis of the indicated CK pathway and developmental genes, with and without Torin2 (2 µM) treatment, was measured by RT-qPCR. 1:5000 DMSO in DDW served as Mock. Relative expression was calculated using the mean between the gene copy number obtained for three reference genes: RPL8 (Solyc10g006580), EXP (Solyc07g025390), and CYP (Solyc01g111170), and normalized to Mock treatment. Analysis was conducted on 6 individual plants. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box). Asterisks indicate significant differential regulation upon Torin2 treatment in Welch's t-test comparing each gene, *p<0.05, **p<0.01, ***p<0.001, ns- non significant.

Figure 6: TOR inhibition reduces CK response in the meristem of young shoots

S. lycopersicum cv. M82 10 day-old seedlings expressing VENUS driven by the cytokinin responsive promoter TCSv2 were treated with Torin2 (2 µM) or Mock (1:5000 DMSO in DDW) for 48 h.

TCSv2 driven total Venus fluorescence in the meristem (**A,B**) or total shoot (**C, D**) was measured as mean arbitrary fluorescent units (AFU, the strength of the signal, **A, C**) or corrected total fluorescence (CTF, a quantification taking into account the fluorescent area, **B, D**), in images captured under identical conditions in shoots comprising the 4 youngest primordia. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Asterisks indicate significant TCSv2 signal reduction upon Torin2 treatment in an unpaired two-tailed *t*-test, N>7, *p<0.05, ns- non significant.

(**E**) Typical Mock treated and Torin2 treated shoots are depicted. Images captured under identical conditions. The meristem (m), second (P2) third (P3) and fourth (P4) youngest leaf primordia are indicated. Bar- 1000 µM.

Figure 7: CK reduces TOR activation

A-B *S. lycopersicum* cv. M82 10 day-old seedlings were treated with Mock (10 µM NaOH) or 10 µM of the CK 6-benzylaminopurine (6-BAP). 24 h after treatment, total cellular proteins were preapared from 3 biological replicas of 10 plants each, and TOR activation was assessed by detection of phosphorylated S6K using specific antibodies.

C-D Total cellular proteins were prepared from *S. lycopersicum* cv. M82, and *pBLS>>IPT* or *pFIL>>CKX* transgenic lines in the M82 background (3 biological replicas of 10 plants each). TOR activation was assessed by detection of phosphorylated S6K using specific antibodies.

Experiment was repeated 3 times. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. **B** Asterisks indicates statistically significant reduction in phosphorylated S6K in a Mann Whitney U test, N=9, p<0.01. **D** Different letters indicate staistically significant differences between samples in a one-way ANOVA with a Tukey post hoc test, *p<0.05, N=7-14.

Figure 8: Model describing the role of TOR as a mediator of both development and defense cues, and the tradeoff between them.

Cytokinin promotes both development and defense. Balanced CK levels are required to achieve "normal" developmental patterning and disease resistance.

Under low CK, development and defense are inhibited, resulting in reduced patterning (Fig. 3), and increased disease susceptibitlity (Fig. 1). Under high CK, development and defense are promoted, resulting in increased patterning (Fig. 3) and disease resistance (Fig. 1).

Inhibition of TOR results in rescue of both low and high CK pehnotypes, resulting in return to baseline developmental patterning and disease resistance, and suggesting that TOR mediates these develpmental and defense cues originating from CK.

In the tradeoff between development and defense, high CK causes downregulation of TOR (Fig. 6), resulting in a shift towards defense. The switch between development and defense may be modulated by cross-talk between environmental sensing and TOR status.

Supplemental materials

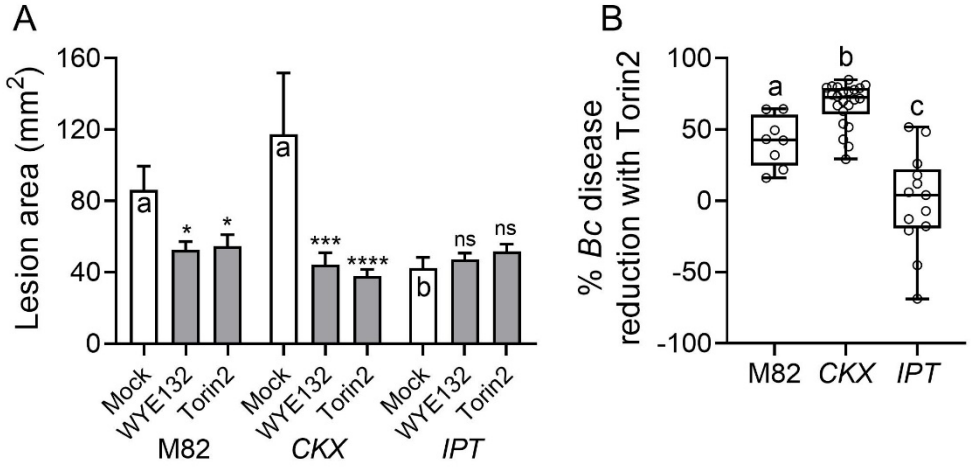

Figure S1: TOR inhibition with drugs mediates disease resistance downstream to CK

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were treated with Mock (1:5000 DMSO in DDW) or 2 µM of the TOR inhibitors Torin2 (**A, B**) or WYE132 (**A**). Plants were challenged with *B. cinerea (Bc)* mycelia from a 72h old-culture, 24 h after drug treatment. **A**: *Bc* necrotic lesion size. **B**: percentage of disease reduction following TOR inhibition in the different genotypes. Bars represent mean ±SEM; boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Experiments were repeated 3 independent times.

A: Asterisks indicate statistically significant disease reduction with Torin2 or WYE132 treatment, and different letters indicate statistically significant differences among samples, in a one-way ANOVA with a Tukey post hoc test, N=9, $p<0.05$ (****$p<.0001$, ***$p<0.001$, *$p<0.05$, ns- not significant). **B:** Different letters indicate statistically significant differences between samples in ANOVA with a Tukey post-hoc test, N=9, $p<0.047$.

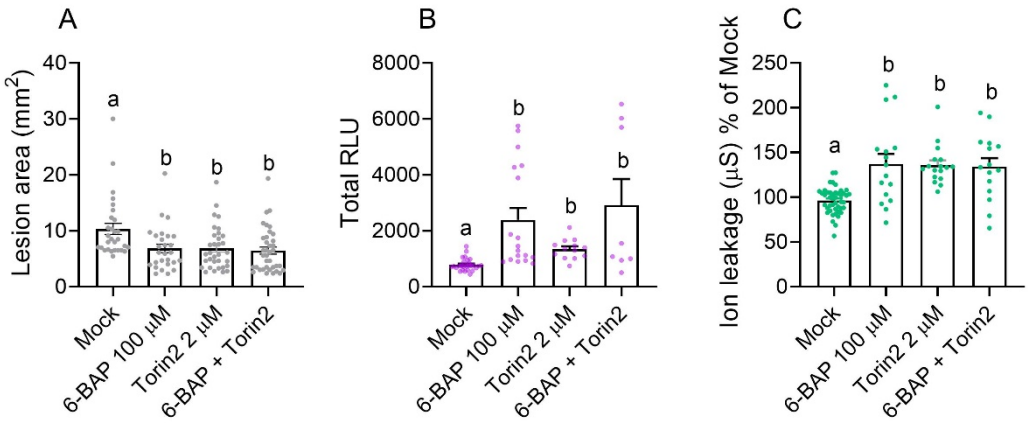

Figure S2: TOR inhibition mediates disease resistance downstream to CK: co-application of CK and Torin2.

S. lycopersicum cv M82 plants were treated with 100 µM of the CK 6-benzylaminopurine (6-BAP), 2 µM Torin2, or a combination of both. Plants were challenged with *B. cinerea (Bc)* mycelia from a 72h old-culture (**A**), or with the immunity elicitors flg-22 (1 µM) (**B**) or Xylanase (1 µg mL^{-1})(**C**), 24 h after CK and Torin2 treatments. **A** Lesion area was quantified 72 h after *Bc* inocculation. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Different letters indicate statistically significant differences in a one-way ANOVA with a Tukey post hoc test, N>25, p<0.017. **B** ROS production was measured immediately after flg-22 application every three minutes, using the HRP-luminol method, and expressed as the total Relative Luminescent Units (RLU) generated. Floating bars represent minimum to maximum values, line indicates median. Different letters indicate statistically significant differences in a one-way ANOVA with a Holm-Sidak post hoc test, N>8, p<0.01. **C** Conductivity of samples immersed in water for 40 h was measured. Mock average conductivity was defined as 100%. Bars represent mean ±SEM, all points shown. Different letters indicate statistically significant differences among samples in Welch's ANOVA with a Dunnett post hoc test, N>15, p<0.02.

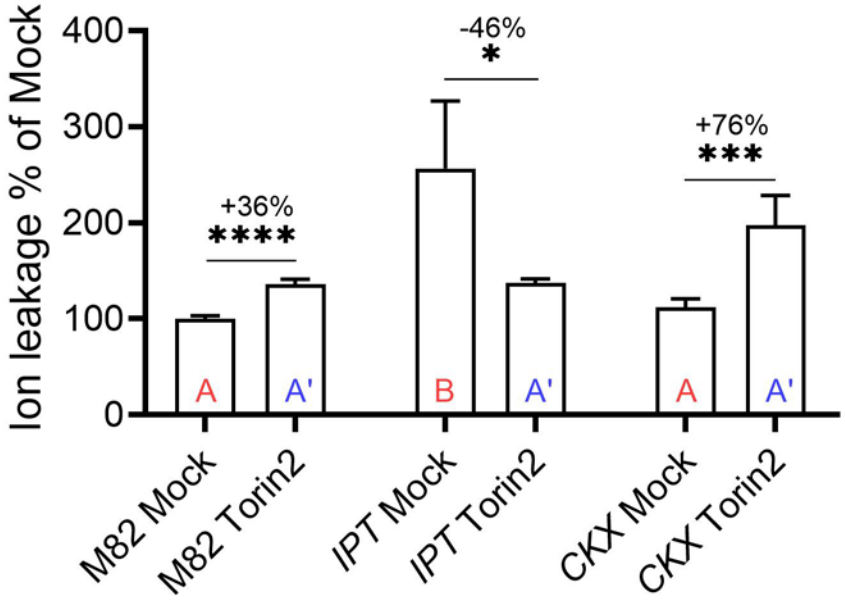

Figure S3: TOR inhibition mediates increased immunity downstream to CK- ion leakage

S. lycopersicum plants of the increased CK line *pBLS>>IPT7* ("*IPT*"), the decreased CK line *pFIL>>CKX3* ("*CKX*"), and their WT background M82, were treated with Mock (1:5000 DMSO in DDW) or 2 µM Torin2. Leaf discs were prepared 24 h after Torin2 treatment, and ion leakage sue to wounding, measured as conductivity of samples immersed in water for 40 h, was quantified. Mock average conductivity was defined as 100%. Bars represent mean ±SEM. Experiments were repeated 3 independent times, on at least 5 plants per experiment per treatment. Asterisks indicate significant differences in conductivity within each genotype following Torin2 treatment, and different letters indicate statistically significant differences between samples in Welch's ANOVA with a Dunnett post-hoc test, red letters for baseline differences in the wounding-response of the different Mock-treated genotypes, N=10, $p<0.0058$, and blue letters for the wounding response following Torin2 treatment, N=10, no significant differences. The percent change in the conductivity of each genotype following Torin2 treatment is indicated above the relevant bar.

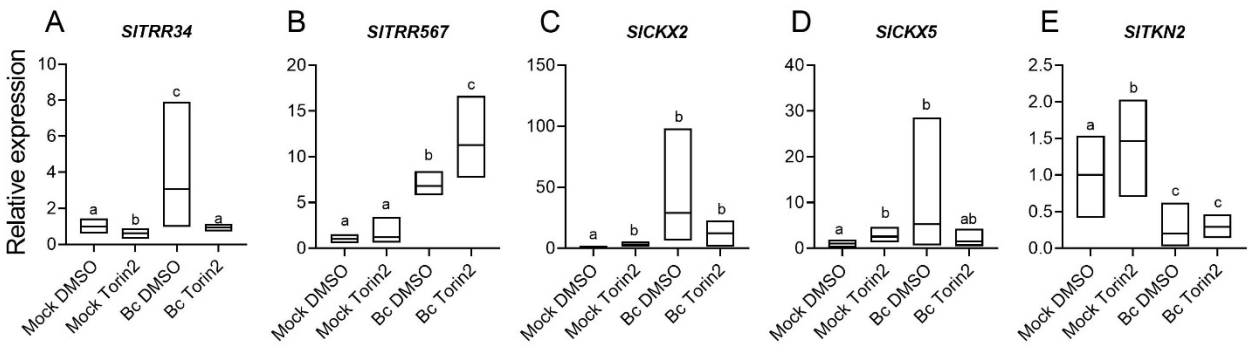

Figure S4: TOR inhibition and Bc infection have differential effects on CK pathway genes

Gene expression analysis of the indicated CK pathway and developmental genes, with and without Torin2 (2 µM) treatment, Bc infection, or combined Bc infection and Torin 2 treatment, was measured by RT-qPCR. Relative expression was calculated using the mean between the gene copy number obtained for three reference genes: RPL8 (Solyc10g006580), EXP (Solyc07g025390), and CYP (Solyc01g111170), and normalized to Mock treatment. Analysis was conducted on 6 biological samples comprised of 10 plants each, and repeated twice, N=12. Floating bars represent minimum to maximum values, line in bar represents the median. Different letters indicate statistically significant differences among samples in Welch's ANOVA (A, B), one-way ANOVA (E), or Kruskal Wallis ANOVA (C, D) tests comparing each gene, A: $p<0.013$; B: $p<0.047$; C: $p<0.001$; D: $p<0.008$; E: $p<0.05$.

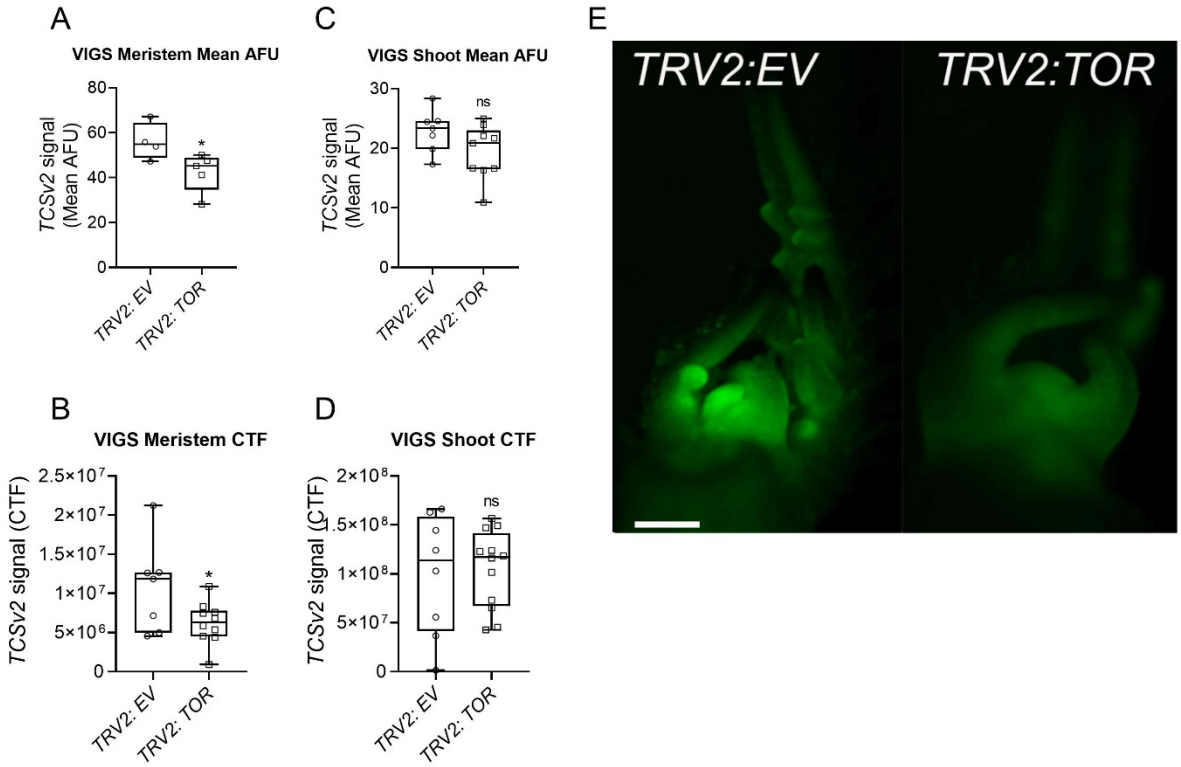

Figure S5: *TOR* silencing by VIGS reduces CK response in the meristem of young shoots

S. lycopersicum cv. M82 seedlings expressing VENUS driven by the cytokinin responsive promoter TCSv2 were *TOR*-silenced using VIGS. 2 weeks after silencing, TCSv2 driven total Venus fluorescence in the meristem (**A,B**) or total shoot (**C, D**) was measured as mean arbitrary fluorescent units (AFU, the strength of the signal, **A, C**) or corrected total fluorescence (CTF, quantification taking into account the fluorescent area, **B, D**), in images captured under identical conditions in shoots comprising the 4 youngest primordia. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Asterisks indicate significant TCSv2 signal reduction upon TOR silencing in a t-test, N>4, *p<0.05, ns- non significant. Typical Mock silenced (**E**) and TOR silenced (**F**) shoots are depicted. Bar- 1000 µM.

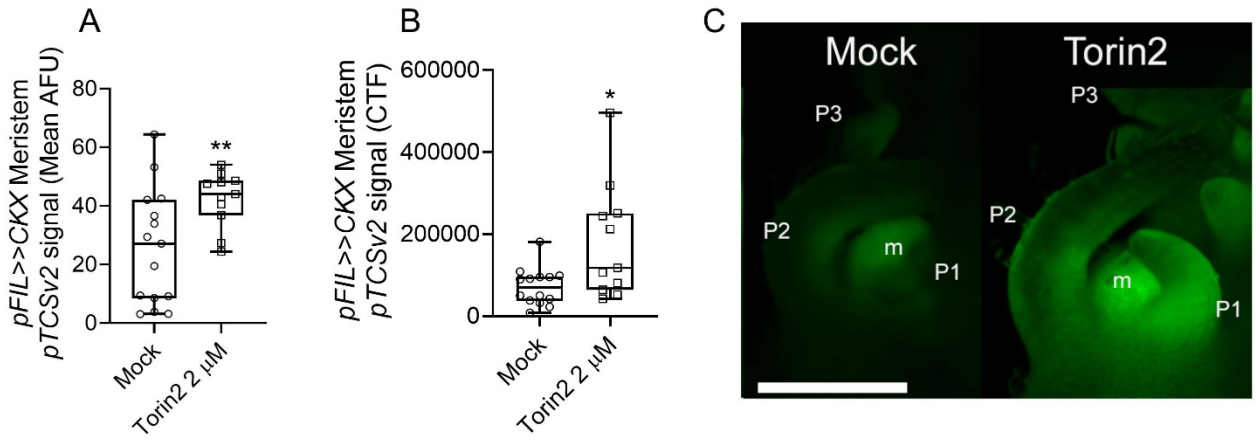

Figure S6: TOR inhibition increases CK response in the meristem of cytokinin deficient *pFIL>>CKX* shoots

S. lycopersicum pFIL>>CKX 10 day-old seedlings expressing VENUS driven by the cytokinin responsive promoter TCSv2 were treated with Torin2 (2 µM) or Mock (1:5000 DMSO in DDW) for 48 h.

TCSv2 driven total Venus fluorescence in the meristem was measured as mean arbitrary fluorescent units (AFU, the strength of the signal, **A**) or corrected total fluorescence (CTF, quantification taking into account the fluorescent area, **B**), in images captured under identical conditions in shoots comprising the 3 youngest primordia. Boxplots represent inner quartile ranges (box), outer quartile ranges (whiskers), median (line in box), all points shown. Asterisks indicate significant TCSv2 signal increase upon Torin2 treatment in a t-test with Welch's correction, N>11, **p<0.01, *p<0.05.

Typical Mock treated and Torin2 treated shoots are depicted in **C**. Images captured under identical conditions. The meristem (m), first (P1), second (P2) and third (P3) youngest leaf primordia are indicated. Bar= 100 µM.

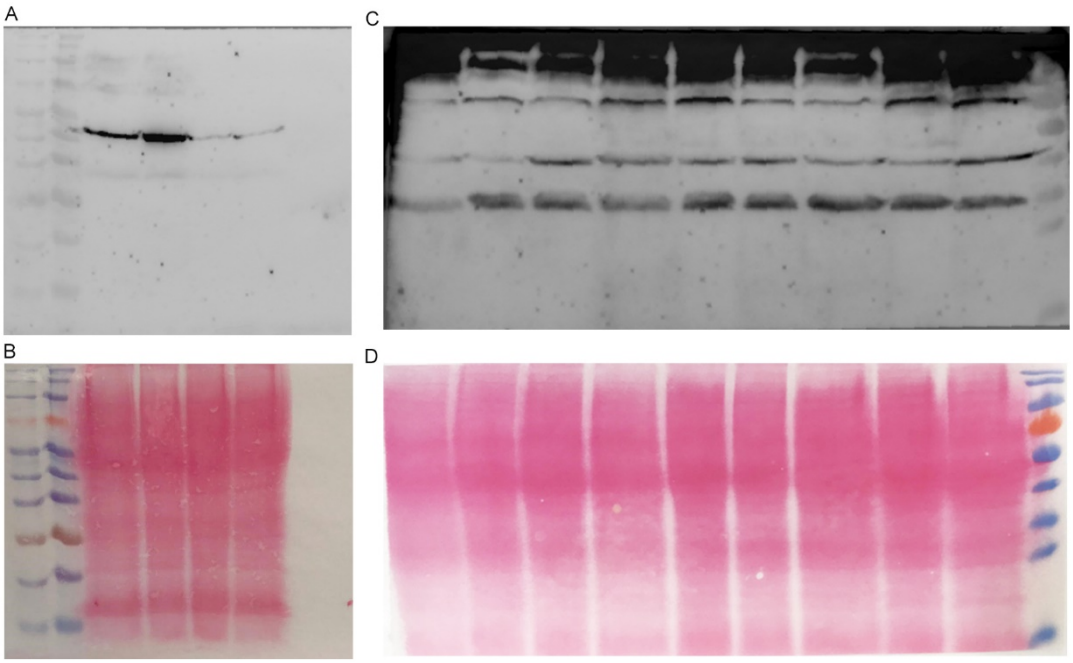

Figure S7: Original uncropped blots used in Figure 7.

A, C Anti-S6K1 p-Thr449 polyclonal antibody (AB-ab207399, Abcam).

B, D PonceauS staining.

Table S1: Primer pairs used for RT-qPCR

Locus	Name	Forward	Reverse
Solyc05g006420	TRR3/4	CGTCCCCTAAAGCATTCTCA	CGTCTTGTTGGTGATGTTGG
Solyc03g113720	TRR5/6/7	GGGATTGATGGTTTGAAGGT	ATCTTGCTCAACACCGATGA
Solyc01g088160	CKX2	CCCCGAAAATGGTGAAATG	CAAAGTGGCTTGCTTGAACA
Solyc04g016430	CKX5	TGTCACTGGTAAAGGAGAGGTG	GAGCAATCCTAGCCCTTGTG
Solyc10g006580	RPL8	TGGAGGGCGTACTGAGAAAC	TCATAGCAACACCACGAACC
Solyc01g111170	*CYP*	TGAGTGGCTCAACGGAAAGC	CCAACAGCCTCTGCCTTCTTA
Solyc07g025390	*EXP*	TGGGTGTGCCTTTCTGAATG	GCTAAGAACGCTGGACCTAATG
Solyc01g106770	*TOR* (VIGS)	GGTCTAGAATGGCTGCCACCGTTCAGGCGATCCG	GGGGATCCTTCGCTGATGGTGACATCTAT
Solyc02g081120	*TKN2*	CCATATCCATCGGAATCTCAG	TGGTTTCCAATGCCTCTTTC
Solyc04g008480	*CLAUSA*	CCTCTCACAACAAGCAATGAACTT	AGGACGATGCAATGAGAGAGAC

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