Ultraviolet-B Activates Components of the Systemin Signaling Pathway in Lycopersicon peruvianum Suspension-cultured Cells

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Among the early responses of Lycopersicon peruvianum suspension-cultured cells to the polypeptide wound signal systemin are the alkalinization of the culture medium and the activation of a 48-kDa mitogen-activated protein kinase (MAPK). Here, we report that both responses are induced in the cells by exposure to ultraviolet-B (UV-B) radiation. Suramin, an inhibitor of systemin receptor function, strongly inhibited the UV-B-induced medium alkalinization and MAPK activity. The UV-B response was also reduced when cells were initially treated with systemin or systemin antagonist Ala-17-systemin, which competitively inhibits binding of systemin to the systemin receptor. Cells that were initially treated with either UV-B or systemin exhibited a strongly reduced response to a subsequent elicitation with systemin. The desensitization was transient, reaching a maximum at 30–60 min after the initial treatment. Several hours later, depending on the initial UV-B dose or systemin concentration, the cells regained their initial responsiveness. When cells were irradiated with low doses of UV-B and subsequently treated with systemin, the UV-B response reached levels higher than the response without UV-B treatment. The data provide evidence for an involvement of the systemin receptor and/or systemin-responsive signaling elements in the UV-B response.

Depletion of the stratospheric ozone layer is causally linked to increases in ultraviolet B (UV-B) fluxes at ground levels and has raised concerns about large scale effects of UV-B on ecosystems and agriculture. Plant cells are frequently exposed to high energy UV-B radiation, which has the potential to damage essential macromolecules including DNA, lipids, and proteins. Much of the UV-B radiation is absorbed by protective pigments such as flavonoids. Genes coding for enzymes functioning in biosynthetic pathways for pigment synthesis are expressed in response to UV-B exposure. Phytochromes are known to perceive light in the red/ far red light range, and cryptochromes and phototropins perceive light in the UV-A/blue light range. For the UV-B range of the solar spectrum (280–320 nm), light perception is not well understood. No specific UV-B photoreceptor has been identified so far, although certain photomorphogenic UV-B responses are indicative of the presence of such photoreceptors (1).

Animal cells lack specific UV-B photoreceptors, but they have sophisticated mechanisms to protect themselves against UV-induced damage. During the UV response, prostaglandin synthesis increases, and a range of genes is activated eventually leading to inflammatory symptoms like erythema or apoptosis (2, 3). The underlying signal transduction involves ligand-independent activation of cell surface receptor tyrosine kinases for polypeptide growth factors and cytokines. This results in the Ras/Raf-mediated activation of a mitogen-activated protein kinase (MAPK) cascade, which in turn activates transcription factor complexes like AP-1. Accordingly, many genes are activated by both UV-B and growth factors/cytokines (3–6). Moreover, UV irradiation was shown to result in autophosphorylation of the epidermal growth factor receptor (EGFR), and a dominant negative EGFR mutant showed a decreased UV-C response (5). The receptor tyrosine kinases are most likely not the primary targets of UV radiation. There is evidence showing that these receptors are activated as a consequence of UV-induced inhibition of tyrosine phosphatases (7–9).

The difficulties in identifying a specific UV-B photoreceptor in plants may be in part due to the multiple and diverse UV-B effects that comprise photomorphogenic, protective, and defense responses. Some UV-B-responsive gene products function in protection against harmful UV-B effects as well as pathogen defense. For example, biosynthetic pathway enzymes such as phenylalanine ammonia lyase and chalcone synthase are involved in the synthesis of protective UV-absorbing pigments like flavonoids and defensive phytoalexins. Other UV-B-responsive genes like PR, defensin, or proteinase inhibitor genes have no obvious function for UV protection (10–16).

In the leaves of tomato plants, the herbivore/wounding-induced defense signaling pathway is regulated by the polypeptide signal systemin. The systemin signaling pathway exhibits several analogies to the animal inflammatory response such as systemin perception by a membrane-bound receptor and activation of a MAPK and a phospholipase A2 (17–22). UV-C radiation (<280 nm) affects the wound response in tomato plants by inducing the synthesis of protease inhibitors (23). Proteinase inhibitors play a role in resistance of plants to herbivorous insects. In contrast to UV-C, UV-B radiation did not induce proteinase inhibitor synthesis in leaves of 14-day or older tomato plants. However, UV-B caused a strong potentiation of proteinase inhibitor synthesis in response to wounding (15). Moreover, in field studies plants exposed to solar UV-B are more resistant to herbivorous insects than plants exposed to solar radiation without UV-B (24). The synergistic effects of UV-B and wounding suggest that the UV-B response pathway and the wounding/systemin-induced signaling pathway overlap in a yet unknown way.

Furthermore, some signaling events induced by wounding/
systemin show striking similarities to UV-B signaling, including proton and potassium fluxes (25–27), increases in intracellular Ca\(^{2+}\) concentrations (28–30), activation of calmodulin genes (28, 31, 32), activation of MAPKs (15, 22, 33, 34), activation of an NADPH-dependent oxidase (35–37), generation of reactive oxygen species (11, 25, 35, 38), and increases in levels of ethylene (27, 39, 40), and jasmonic acid (39, 41, 42). However, it is still largely unknown how these signaling events are initiated by UV-B, what their precise cellular function is, and whether wounding/systemin-induced pathways and UV-B-induced pathways utilize some common signaling components. Here we provide evidence for the involvement of the systemin receptor and/or systemin-responsive signaling elements in the UV-B response in tomato (*Lycopersicon peruvianum*) suspension-cultured cells.

**EXPERIMENTAL PROCEDURES**

**Suspension-cultured Cells—** *L. peruvianum* suspension-cultured cells (kindly provided by A. Schaller) were cultivated under constant light as described previously (21). Cells were subcultured weekly and used for experiments 4–7 days after subculturing. For the experiments, cells were transferred to multiwell plates (1.5 ml/well) that were vigorously shaken on an orbital shaker under ambient room light and temperature conditions. After a 6-h equilibration period, the pH of the medium reached a starting pH of 4.8 ± 0.2. 

**UV Irradiation—** UV-B lamps, the UV filter (Melinex®651/1000 gauge; 0.25 mm; DuPont), and the UV meter were described previously (15). The distance between lamps and the surface of the medium was adjusted for a UV-B irradiance of 5.4 ± 0.6 mW/cm\(^2\) at the surface of the medium. The exact irradiance and, thus, the dose at the cell surface cannot be determined because UV light is strongly absorbed by the growth medium (75% at 310 nm), and the distance between the cell or medium surface and UV lamps varies while cultures are vigorously shaken.

**Medium Alkalization Response (AR) Assay—** Systemin was supplied to 1.5 ml of suspension-cultured cells at the times and concentrations indicated in the text (see “Results”). Suramin in water, fuscocin (Sigma) in 10% (v/v) ethanol, and 10% ethanol (control), no effect on the pH of the medium) were supplied to the cells at the times and concentrations indicated in the text (see “Results”). For the UV-B time course experiment (see Fig. 1) untreated samples were assayed over the course of the experiment. The pH of the medium was measured with a pH meter as described previously (22).

To determine the UV-B-induced AR and the inhibition of UV-B-induced AR by systemin, the pH increase in untreated control and in response to UV-B irradiation was measured at the times indicated after the start of irradiation, and the difference was referred to as ΔpH or 0% inhibition of UV-B-induced AR. Another set of cells was pretreated for 5 min with suramin at various concentrations and then irradiated for 10 min with UV-B or left untreated. The pH was measured 20 min after the start of irradiation. The UV-B-induced response in the presence of suramin was expressed as the percentage of the response to UV-B alone (% inhibition of UV-B-induced AR). In each case, the increase in medium pH was corrected for a weak change in the baseline (∼0.3 pH units) of untreated cells or cells that had been treated with suramin alone.

**Kinase Assays—** In-gel myelin basic protein kinase assays, and immunocomplex assays were performed as described previously (22). Radioactive signals corresponding to phosphorylation of myelin basic protein by a myelin basic protein kinase were quantified using a Storm PhosphorImager (Molecular Dynamics).

**Desensitization Assays—** To determine the pH increase in response to a second stimulation after an initial treatment at time 0 (t = 0), cells were either supplied with systemin, Ala-17-systemin, or a random 18-amino acid peptide, irradiated with UV-B as described above, or left untreated. At the times indicated in the text (t = x), the conditioned medium of all samples was quantitatively exchanged replaced with fresh medium (pH 5.0). Immediately thereafter a subset of pre-treated and untreated cells was supplied with systemin or irradiated with UV-B (treatment 2). The increase in medium pH was measured 15 min later (t = x + 15 min). The series of treatments was as indicated in Table I.

The difference between 2 and 1 in Table I is referred to as 100%, or the full response. The effect of the initial treatment (treatment 1) on treatment 2 was expressed as the percentage of the full response using the equation (4 − 3)/2 × 100 = % of full response.

**RESULTS**

**UV-B Radiation Induces MAPK-like Activity and Alkalization of the Medium of Suspension-cultured *L. peruvianum* Cells—** Suspension-cultured *L. peruvianum* cells respond to the polypeptide signal systemin with a rapid and transient increase in the activity of a 48-kDa MAPK and the alkalization of the culture medium (18, 22, 27). We have found that a 5-min UV-B irradiation of *L. peruvianum* cells caused a rapid increase of the AR (Fig. 1A) and in 48-kDa MAPK-like activity (Fig. 1B), similar to systemin. Both the kinase activity and the AR exhibited rapid increases within 10 min after irradiation. The lag phase for the AR was about 30 s (Fig. 1A, inset). The rapid increase was followed by a decrease and a second increase that maximized at about 60–90 min for the kinase activity and at 90 min for the AR.

Cells were exposed to UV-B irradiation for increasing time periods and to white light for 10 min. They were then assayed for kinase activities and AR at 30 and 20 min after the start of irradiation, respectively. The two responses were UV-B dose-dependent (Fig. 1C). The UV-B-induced AR and the kinase activity reached a maximum after an irradiation period of 10–15 min. A longer irradiation period of 30 min led to profound decreases in both responses (data not shown), perhaps due to UV-induced damage to essential signaling components. White light was inactive. The lamps used have a peak emission at 310 nm. They do not emit UV-C radiation, but 41% of the emitted light is in the UV-A range (15). When the cells were

| Time (min) | pH Measurement | Treatment |
|-----------|----------------|-----------|
| 0         | Medium exchange | No treatment |
| 10        | Measure pH      | Treatment 2 |
| 20        | Measure pH      | Quick freeze |

**Table II**

**Series of treatments for MAPK desensitization assays**

| Time (min) | Treatment |
|-----------|-----------|
| 0         | No treatment |
| 10        | Treatment 2 |
| 30        | Quick freeze |

**Table I**

**Series of treatments for AR desensitization assays**

| Time (min) | Treatment | pH Measurement |
|-----------|-----------|----------------|
| 0         | Medium exchange | No treatment |
| 10        | Measure pH      | Treatment 2 |
| 20        | Measure pH      | Quick freeze |

**Table III**

**Series of treatments for MAPK desensitization assays**

| Time (min) | Treatment |
|-----------|-----------|
| 0         | No treatment |
| 10        | Treatment 2 |
| 30        | Quick freeze |
irradiated through a UV filter that totally cut off UV-B radiation and partially short wavelength UV-A radiation, both responses were almost completely abolished (Fig. 1C). This demonstrated that the active wavelength range is largely in the UV-B region of the spectrum.

**Activation of AR and MAPK by UV-B Is Inhibited by Suramin**—Suramin was previously shown to interfere with the perception of systemin by the 160-kDa membrane-bound systemin receptor in suspension-cultured *L. peruvianum* cells, resulting in the inhibition of systemin-induced AR and MAPK activation (22). When *L. peruvianum* cells were pretreated for 5 min with increasing suramin concentrations and subsequently irradiated with UV-B for 10 min, the AR was inhibited in a concentration-dependent manner (Fig. 2A). The IC_{50} for suramin was about 300 μg·ml^{-1} (210 μM). However, the UV-B-induced AR could not be completely inhibited by suramin, even at higher concentrations than shown. At 1500 μg·ml^{-1}, suramin inhibited the AR by about 70%. At this concentration, the induction of MAPK-like activity by UV-B was nearly abolished (Fig. 2B). These data indicate that suramin-sensitive cell surface components such as the systemin receptor may participate in the UV-B response.

The activation of the kinase was associated with tyrosine phosphorylation, demonstrated by immuno-complexing of the active kinase with a monoclonal antibody that is specific for phosphotyrosine (15). This is a distinguishing feature of members of the MAPK family of protein kinases. In the presence of suramin, no tyrosine phosphorylation of the kinase was detected (Fig. 2C).

**Systemin Transiently Desensitizes *L. peruvianum* Cells to a Second Treatment with Systemin**—To test a possible interaction of the systemin and UV-B signaling pathways, a typical feature of signaling pathways was analyzed, the transient down-regulation of signaling components after an initial activation. This results in a reduced responsiveness of cells to a subsequent treatment with the same or a related stimulus (43, 44). The ability of the *L. peruvianum* cells to respond to a second systemin treatment after an initial activation by systemin was assayed for the AR and MAPK. Fig. 3 shows that the initial activation of both AR and MAPK by systemin leads to a
Procedures

is indicated as 100% at time 0 (for details see the percentage of the full response to systemin treatment alone, which MAPK activity after the second systemin treatment was expressed as for MAPK activity. The systemin-induced increase in medium pH and supplied with 10.0 nM systemin or not treated, and 15 min later, the pH of the growth medium was measured. B, another set of cells was supplied with 3.3 nM systemin or left untreated. At the times indicated, systemin-treated and untreated cells were either left untreated or supplied with 3.3 nM systemin. 10 min thereafter, cells were frozen and assayed for MAPK activity. The systemin-induced increase in medium pH and MAPK activity after the second systemin treatment was expressed as the percentage of the full response to systemin treatment alone, which is indicated as 100% at time 0 (for details see “Experimental Procedures”).

...transient reduced responsiveness of the cells to a second treatment with a saturating concentration of systemin. The magnitude of the desensitizing effect was dependent on the initial systemin concentration. A concentration of 10 or 3.3 nM led to an almost complete loss of responsiveness to the second treatment at 30 min. This effect was transient, and at 3.5 h, the responsiveness of the cells was almost completely restored. This indicates that the initial activation results in a desensitization of a component or components of the systemin signaling pathway.

UV-B Treatment Desensitizes L. peruvianum Cells to Subsequent Systemin Treatments—To determine whether UV-B treatments would desensitize L. peruvianum suspension-cultured cells to a subsequent systemin treatment, cells were initially irradiated for increasing times with UV-B, and 1, 2, 4, and 8 h later they were treated with systemin. One hour after a 5-min UV-B irradiation period, the systemin-induced AR was reduced by 80% compared with the response without initial UV-B treatment (Fig. 4A). At 30 min after a 10-min UV-B treatment, the systemin-induced MAPK activity was also reduced by 80% compared with the response without initial UV-B treatment (Fig. 4B). The desensitizing effects of UV-B on both AR and MAPK activity were dose-dependent and transitory. The MAPK recovery occurred sooner than the AR. At 8 h after the initial irradiation of the cells with lower UV-B doses, the systemin induction of both responses was 135% (p < 0.05) that of the response without initial UV-B treatment (Fig. 4, A and B). After a 10-min UV-B exposure, systemin-induced MAPK activity did not return to pre-exposure levels, perhaps due to UV-B damage that did not occur at lower doses. These results suggest that UV-B activates components of the systemin signaling pathway.

UV-B and Systemin Signaling
DISCUSSION

We have investigated the effects of UV-B radiation on two rapidly occurring defense signaling responses that are activated by systemin in suspension-cultured cells. These responses are the acidification of the cell culture medium due to an enhanced pumping of protons out of the cell and a 48-kDa MAPK. These are among the earliest known signaling events induced by systemin (27, 34), which is perceived by a 160-kDa membrane-bound receptor (18, 21). We found that the AR and MAPK activity were induced when suspension-cultured cells were exposed to UV-B irradiation (Fig. 1). The initial kinetics of AR and MAPK inductions were similar to the responses induced by systemin (22, 27). After a short lag phase, the pH increased rapidly within the next 10 min and then decreased. Unlike systemin, UV-B induced a second increase in AR and MAPK activity at 60–90 min, indicating that UV-B and systemin were either activating different signaling pathways or affecting the same signaling pathway differently. The kinetics and dose dependence of the UV-B-induced AR and MAPK response and AR differed slightly. The MAPK was maximally activated after a 10–15-min irradiation period, similar to the AR, but lower doses induced a stronger AR than MAPK response, and MAPK activity was more prolonged than the AR (Fig. 1C). This indicated that the two responses may not have a tightly coordinated cause-effect relationship.

Whether the systemin-inducible and UV-B-inducible MAPK activity resides in the same or different MAPK isoforms has not been established. Several MAPKs have been identified that are involved in plant defense responses (49). Like animals, Arabidopsis has been shown to possess MAPK cascades that function downstream from receptor kinases as part of the innate defense against pathogens (50). Among the known MAPKs, the tomato SIPK responds to both biotic and abiotic forms of stress (51), and the tomato ortholog may be the systemin-inducible enzyme. Isolation of the systemin-activated MAPK should help establish the identity of the UV-B-inducible enzyme and determine whether more than one MAPK is involved in the UV response.

In animal cells, UV responses are mediated through receptor tyrosine kinases and can be blocked by suramin, a hydrophilic polycyclic compound that acts as an inhibitor of growth factor/cytokine interactions with the corresponding cell surface receptors (5). Suramin had previously been shown to interfere with the binding of systemin to its cell surface receptor in L. peruvianum cells (22). Several lines of evidence suggest that both responses are inhibited by the highly hydrophilic suramin in a solely extracellular manner (22). Suramin also inhibited UV-B responses in a concentration-dependent manner (Fig. 2). The IC(50) of 210 μM for the inhibition of the UV-B-induced AR was
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2–3 times higher than the IC₅₀ for inhibition of the systemin-induced AR (90 μM) and for inhibition of animal receptor function (22, 52). This and the incomplete inhibition of UV-B-induced medium alkalization and MAPK activation suggested the presence of additional suramin-insensitive mechanisms participating in UV-B activation of AR and MAPK. The activation of a MAPK by both systemin and UV-B involves the phosphorylation of tyrosine residues on the kinase, a distinguishing feature of MAPKs. Tyrosine phosphorylation induced by both systemin and UV-B was inhibited by suramin (Fig. 2C) (22). This confirmed that suramin acts upstream of MAPK activation, most likely inhibiting a component of the signaling pathway that mediates both systemin and UV-B effects. Because the systemin receptor is a known target for suramin and suramin does not act intracellularly, it appeared that the systemin receptor may be involved in UV-B signaling. Appropriate controls using a compound with the same UV absorption spectrum as suramin, N-(1-naphthyl)ethylene-diamine dihydrochloride, excluded the possibility that UV absorption by suramin can account for the inhibition of AR and MAPK by suramin (data not shown). Recently it was shown in tobacco suspension-cultured cells that suramin also blocks the UV-C activation of SIPK, a MAPK from tobacco. UV-C radiation is not part of solar radiation and known to cause different effects than UV-B radiation. However, both UV-C and UV-B cause oxidative stress, and it was speculated that suramin may interfere with oxidative activation of cell surface receptors (33).

The initiation of signaling pathways by ligand-receptor interactions in animals and plants is known to result in a transiently decreased responsiveness of the signaling pathway to further challenges by its ligand. In HeLa cells for example, application of epidermal growth factor, basic fibroblast growth factor, or interleukin-1α desensitized the cells to subsequent treatment with the same ligand. Similarly, pretreatment with a growth factor partially desensitized the cells to the effects of a subsequent UV-C irradiation and vice versa (5). We used this behavior of signaling pathways to test if UV-B and systemin would activate the same signaling pathway. If systemin and UV-B share common signaling elements, their activation by UV-B might affect the response of L. peruvianum cells to systemin. This hypothesis was tested employing the AR and MAPK activation as marker responses. When cells were irradiated and subsequently treated with systemin, UV-B irradiation caused a dose-dependent loss in the AR and MAPK activity in response to systemin (Fig. 4). This desensitization was transient, and within 8 h the response was 135% that of the systemin response without a previous UV-B irradiation. The effect of UV-B in reducing the responsiveness of the cells to systemin within an hour and the subsequent time-dependent recovery and synergistic action of UV-B and systemin are both consistent with the presence of signaling components responsive to both systemin and UV-B.

We also attempted to determine if the down-regulation of signaling elements by systemin might affect the response of L. peruvianum cells to UV-B. A measurable effect of systemin on UV-B responses was expected only if the systemin signaling pathway contributed significantly to the UV-B response. We found that an initial systemin treatment reduced the UV-B-induced AR and MAPK activity by ~35 and 25%, respectively (Fig. 5). This confirmed that UV-B and systemin signaling pathways at least partly overlapped. Moreover, the data indicated that additional components beside systemin-responsive components participate in the UV-B response. Multiple effects of UV on animal signaling components had been shown previously. A treatment of cells with one growth factor caused a partial loss, but a combination of three different growth factors caused an almost complete loss of the UV response (5). This indicated that the UV response in animals may be a consequence of a UV interaction with multiple cell surface receptors. Our results indicated that a similar situation may occur in plants.

To further address the possibility that UV-B activates the systemin receptor, Ala-17-systemin, a systemin analog that competitively inhibits the binding of systemin to its receptor (18, 21) was assayed for its ability to inhibit the UV response. When Ala-17-systemin was applied to suspension-cultured cells and the cells were subsequently irradiated with UV-B, the UV-induced AR and MAPK activity in response to UV-B were reduced by 25 and 40%, respectively (Fig. 5). The reduced responsiveness to UV-B after initial treatment with systemin or Ala-17-systemin was very brief and could only be observed at significant levels at 30 min after initial systemin or Ala-17 treatment. These results suggested that binding of Ala-17-systemin to the systemin receptor reduces the ability of UV-B to activate the AR and MAPK activity and are consistent with the suramin experiments shown in Fig. 2.

The reciprocal transient loss of responsiveness to either UV-B or systemin in the experiments involving two consecutive treatments indicate that the systemin receptor and/or other systemin-responsive signaling components are involved in the UV-B response. In animal cells, receptor clustering and internalization upon ligand binding and UV irradiation are well documented phenomena (4, 6), causing a transient loss of receptor function in the membranes until new receptors are synthesized. UV-B irradiation could be interacting with the receptors either directly or indirectly to induce a degradation process. The systemin receptor is known to have a rapid turnover rate (21), and the scenario suggested here would provide a mechanistic explanation for the reciprocal transient desensitization of UV-B and systemin signaling. The inhibition of AR and MAPK activity by suramin and Ala-17-systemin, both competitive inhibitors of systemin-receptor interactions, is also consistent with a participation of the systemin receptor in the UV-B response.

Another possibility is that UV-B and systemin initiate intracellular signaling events that contribute to the AR and MAPK activation. Oxidative stress leading to generation of reactive oxygen species is a well known effect of UV-B radiation in plants. Reactive oxygen species are also generated in response to systemin via receptor-mediated induction of a NADPH oxidase activity (36, 38). Moreover, activation of MAPK cascades by some forms of oxidative stress have been shown to depend on generation of reactive oxygen species (33, 53). In animal cells, oxidative processes appear to be the mechanism by which growth factor receptors are activated in response to UV light (7–9).

The data presented here show that the systemin and the UV-B signaling pathway at least partly overlap. They do not show that both pathways are identical. The participation of additional signaling components in the UV-B response such as specific UV-B photoreceptors cannot be excluded, and the evidence suggests that the systemin signaling pathway is likely not the only signaling pathway engaged by UV-B. In summary, several lines of evidence support the involvement of the systemin receptor and/or systemin-responsive signaling elements in the UV-B response; (i) UV-B and systemin both induce the AR and activate a 48-kDa MAPK; (ii) UV-B effects could be inhibited by suramin, an inhibitor of systemin receptor function, and by Ala-17-systemin, a systemin antagonist; (iii) UV-B and systemin caused a reciprocal transient desensitization of UV-B and systemin responses; and (iv) over longer periods of time, UV-B and systemin acted synergistically.
The evidence associating the UV-B response with a cell surface receptor and other early signaling components provides a foundation for further investigations aimed at elucidating the mechanisms of UV-B interactions with other forms of plant stress.

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