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ABA says NO to UV-B: a universal response?

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Abscisic acid (ABA) signaling pathways have been widely characterized in plants, whereas the function of ABA in animals is less well understood. However, recent advances show ABA production by a wide range of lower animals and higher mammals. This enables a new evaluation of ABA signaling pathways in different organisms in response to common environmental stress, such as ultraviolet (UV)-B. In this opinion article, we propose that the induction of common signaling components, such as ABA, nitric oxide (NO) and Ca^{2+}, in plant and animal cells in response to high doses of UV-B, suggests that the evolution of a general mechanism activated by UV-B is conserved in divergent multicellular organisms challenged by a changing common environment.

Universal UV-B stress responses in plants and animals?

Many life forms on the Earth's surface are inevitably exposed to UV radiation at potentially harmful levels; therefore, it is reasonable to assume that they share some basic molecular responses to this environmental stress. UV radiation (200–400 nm) represents almost 7% of the electromagnetic radiation emitted from the sun. The vast majority of UV-C (200–280 nm) and UV-A (320–400 nm) is absorbed by atmospheric gases. UV-B radiation (280–320 nm) is mostly absorbed by stratospheric ozone and only a very small proportion is transmitted to the Earth's surface [1]. Nevertheless, UV-B levels at the Earth's surface are increasing as a consequence of anthropogenic thinning of the stratospheric ozone layer. Cells exposed to high doses of UV-B increase reactive oxygen species (ROS) production, which causes damage to proteins and DNA, affecting the integrity, morphology, and physiology of the cell. It has been reported that NO may alleviate the oxidative stress originating from UV-B in bacteria, plants, and animals [2–4]. NO is a small, highly diffusible atmospheric gas and a ubiquitous bioactive molecule, which has been proposed to function as a broad-spectrum anti-stress compound [5]. The enzyme NO synthase (NOS) generates NO from arginine and its occurrence has been demonstrated in animals, bacteria, and plants [6–9].

Two articles have reported the key function of ABA in the induction of NO production in UV-B-stressed plants [4] and in proinflammatory responses during granulocyte activation in mammals [10]. More recently, granulocytes and keratinocytes (skin cells) were shown to respond to UV-B with increased ABA production and release, and induction of an autocrine signal (see Glossary) that is responsible for NO generation and activation of inflammatory responses associated with UV-B irradiation [11]. This and further experimental evidence accumulated over the past decade together support the conclusion that ABA is a hormone that also drives stress responses in animal cells [10,12]. In this opinion article we highlight the interplay between ABA and NO and analyze the molecular mechanisms underlying this common plant and animal cell response to UV-B.

Glossary

Autocrine signaling: a signaling form in which a cell secretes a hormone or chemical messenger that binds to receptors on the same cell, leading to a response.
Cytokines: small cell-signaling protein molecules secreted by the glial cells of the nervous system and by numerous cells of the immune system; these are signaling molecules used extensively in intercellular communication.
Granulocyte: white blood cells characterized by the presence of granules in their cytoplasm.
Hemopoietic progenitors: cells responsible for permanent formation of blood cells.
Inflammatory response: a nonspecific defensive reaction of the body to invasion by a foreign substance or organism.
Keratinocyte: the predominant cell type in the epidermis, the outermost layer of the skin.
Mesenchymal stem cells (MSC): multipotent stem cells that can differentiate into a variety of cell types, including adipocytes, myocytes, chondrocytes, and osteoctyes.
Microglia: glial cells that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of active immune defense in the central nervous system.
Monocyte: phagocytic white blood cell having a single well-defined nucleus and very fine granulation in the cytoplasm.
Nuclear factor-kappa B (NF-κB): a transcription factor that has a key role in regulating a large number of normal cellular and organismal processes, such as immune and inflammatory responses, developmental processes, cellular growth, apoptosis, and the immune response to infection. NF-κB is also implicated in the processes of synaptic plasticity and memory.
Paracrine signalling: cell signaling in which the target cell is near the signal-releasing cell. Whereas autocrine signaling occurs among the same types of cell, paracrine signalling may affect other types of (adjacent) cells.
Phagocytes: large white blood cells that contribute to the immune defenses by ingesting microbes, other cells, and foreign particles. The two principal phagocytes are neutrophils and monocytes. They can migrate from the blood into tissues in which an infection has developed.
Phagocytosis: the engulfing of microorganisms or other cells and foreign particles by phagocytes.
Prostaglandin E2 (PGE2): a primary proinflammatory product of arachidonic metabolism, synthesized by cyclooxygenase.
Tumor necrosis factor alfa (TNF-α): a proinflammatory cytokine mainly produced by activated macrophages and stimulating the acute phase reaction.

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ABA is synthesized by plant and animal cells and is ubiquitous in all kingdoms

Similar to NO, ABA is also a ubiquitous molecule synthesized by fungi [13] and bacteria [14], in addition to plant and animals cells.

A family of carotenoid cleavage dioxygenases (CCDs) is responsible for the oxidative cleavage of carotenoids to apocarotenoid precursors for signaling molecules in plants and animals. ABA and retinoic acid (RA) are two important biologically active molecules generated by CCDs. ABA is synthesized by direct or indirect mechanisms and the best characterized pathway is the indirect mechanism used by terrestrial plants (for a detailed review, see [15]).

In the indirect pathway, the 9-*cis*-epoxy-carotenoid dioxygenase (NCED) catalyzes the oxidative cleavage of 9-*cis*-neo/violaxanthin to xanthoxin, which is a rate-limiting step in ABA biosynthesis. Figure 1a shows the consensus tree derived from the phylogenetic analysis carried out to evaluate the occurrence of NCED in all kingdoms. The clustering pattern indicates the presence of NCED representatives in the many organisms, from bacteria to vertebrates, in which ABA has been detected. One of these enzymes, β-carotene 15,15′-oxygenase (BCO-I), is phylogenetically linked to NCED and is a key component of the RA biosynthetic pathway [16]. Figure 1b shows the structural similarity between the corresponding substrates and products of NCED and BCO-I. Figure 1c shows the alignment between NCED and BCO-I. The similarity between the proteins is 42% and the four histidines involved in enzyme activity are conserved in NCED and BCO-I. In dioxygenases, conserved histidines are ligands of a non-heme iron cofactor [17]. In the final step of plant ABA biosynthesis, xanthoxin is exported to the cytosol, converted to abscisic aldehyde by a short-chain dehydrogenase/reductase (ABA2) and finally oxidized to ABA by aldehyde oxidase (AAO3). Interestingly, it has been shown that the AAO3 enzyme from *Arabidopsis* (*Arabidopsis thaliana*) presents high homology with rat and human retinaldehyde dehydrogenase 1 (RALDH1), the enzyme that oxidates retinaldehyde to RA [18].

Given that the enzymes catalyzing the oxidative reactions of carotenoids and apocarotenoids are closely related and transform a whole range of substrates [18], it can be hypothesized that the metabolic pathway leading to the formation of RA is able to generate ABA. Alternatively, or additionally, an indirect ABA biosynthetic pathway may be active in animals, as occurs in plants and fungi. A similarity heat map of proteins involved in ABA metabolism and signaling was recently reported [19]. The authors suggested that humans synthesize ABA via the direct cytosolic pathway through the common intermediate of the isoprenoid pathway farnesyl diphosphate [19]. In this scenario, new approaches are likely to help elucidate the differences between the direct and indirect pathway/s of ABA synthesis among organisms from all kingdoms of life.

ABA and NO as stress signaling molecules in plants

ABA regulates many developmental and growth processes in plants, as well as signaling mechanisms associated with responses to environmental stresses. Concentrations of ABA increase rapidly in the shoot when plants dry out or sense low temperatures. ABA continues to spread throughout the plant, leading to ABA-responsive gene expression responsible for developing an adaptive metabolic response.

Over the past 30 years, pharmacological, biochemical, and genetic studies have identified more than 100 loci and a high number of second messengers acting downstream of ABA perception in plants. ABA activates ROS production and ROS-mediated signaling through the activation NADPH oxidase (NOX) activity. Cyclic nucleotides, such as cGMP, cAMP, and cADPR, are also involved in the ABA signaling cascades [20–23]. Table 1 summarizes the main plant physiological processes in which ABA regulates, as a central player, adaptive responses to stress situations.

During the past decade, many ABA-mediated events have been described to rely on a transient rise in NO levels, which is absolutely required for a successful downstream signaling (for a review, see [24]). Furthermore, the ABA–NO system was demonstrated to be functional and at the core of plant responses to UV-B [4]. ABA and NO concentrations increase rapidly and significantly in leaves of maize (*Zea mays*) irradiated with UV-B [4]. In mutant maize defective in ABA synthesis (*viviparous, vp14*), UV-B does not induce an increase of ABA and NO, and the plant is more susceptible to irradiation than is the wild type (WT). Interestingly, supplementation of *vp14* maize mutants with ABA restores NO production and a similar capacity to tolerate UV-B irradiation as WT maize.

ABA functions as a stress signal in animal cells through the same second messengers that occur in plants

In 1986, two papers presented evidence supporting the role of ABA as a universal effector of calcium signaling [25,26]. In the first paper, the identification of (+)-*cis*-ABA in pig and rat brain [25] resulted in many questions concerning the biological functions of the phytohormone in animal cell physiology. ABA purified from the brain was capable of inducing stomatal closure in epidermal peels from leaf tissues and glucose conjugates of ABA were found in the brain, similarly to what is observed in plants. Although several studies addressed the task of deciphering the role of ABA in brain tissue [27,28], this issue is still open to investigation. The second paper [26] presented interesting results showing striking similarities between ABA functionality in plants and animals. In mammalian smooth muscle, ABA mediated the increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), which was dependent on extracellular Ca^{2+} availability, supporting an ABA-mediated effect on calcium influx. It was postulated that ABA might be acting as a plasma membrane Ca^{2+} channel agonist [26].

More recently, evidence has been found for a role of ABA in lower animals. Sponges (Porifera) and hydroids (Hydrozoa) are positioned at the very beginning of animal evolution and they provide an opportunity to study the metazoan evolutionary tree from its roots. Heat and mechanical stress increase the ABA concentration in sponges, and ABA stimulates the sponge filtration and respiration rates via a cADPR/Ca^{2+}-dependent signaling cascade [29,30]. Tissue regeneration in hydroids is mediated by endogenous ABA production stimulated by light and

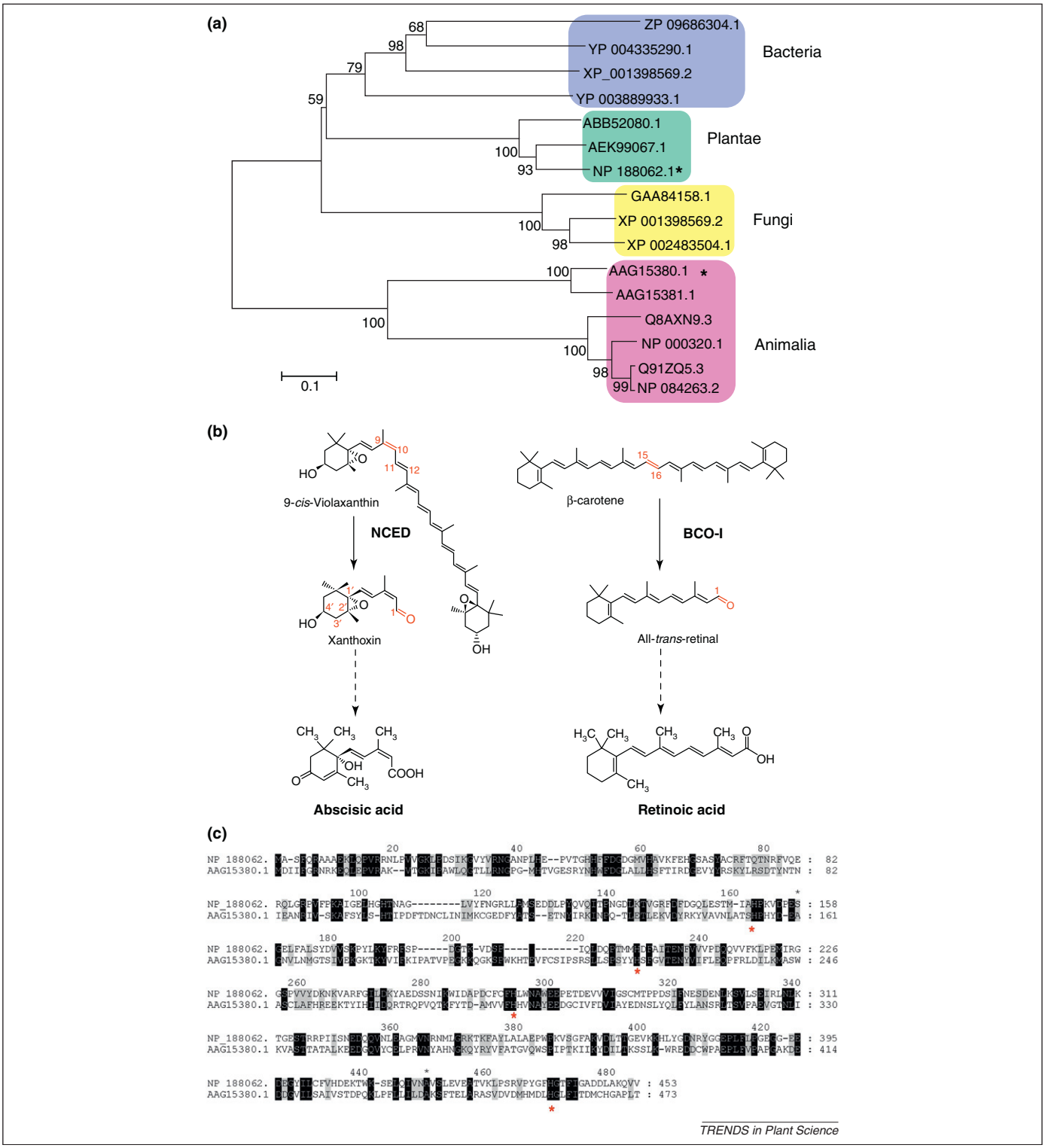

Figure 1. Phylogenetic analysis and comparison of enzymes involved in abscisic acid (ABA) and retinoic acid (RA) biosynthesis. **(a)** Unrooted neighbor-joining tree of 9-*cis*-epoxy-carotenoid dioxygenase (NCED) from plants. Sequences retrieved from databases were aligned using the CLUSTAL W algorithm [55] and protein sequence similarity searches were performed by using GeneDoc alignment editor version 2.6.002 [56]. Phylogenetic analysis was conducted using MEGA version 4.0 [57]. The phylogenetic tree was inferred using the neighbor-joining method [58] and the robustness of each node was assessed by bootstrap resampling (10 000 replicates) [59]. The amino acid sequences were obtained from previously reported sequences at the NCBI. The number access shown in the tree corresponds to the NCBI Reference Sequence. Scale bar = 0.1 substitutions per site. Asterisks highlight the sequences used in the alignment (c). **(b)** Substrates and products of the NCED and β-carotene 15,15′-oxygenase (BCO-I), key enzymes in the synthesis of ABA and RA, respectively. Cleavage of β-carotene to retinal is performed by the BCO-I and it is the first step of retinoid metabolism in vertebrates. Xanthoxin is produced by cleavage of 9-*cis*-violaxanthin or 9-*cis*-neoxanthin at the 11–12 position by NCED in ABA biosynthesis in plants. **(c)** Alignment of NCED (NP_188062.1) with BCO-I (AGG15380.1). Four conserved histidine residues are marked with red asterisks. Black boxes denote identical residues; light-gray boxes denote conservative residue substitution and broken lines are gaps.

Table 1. ABA in plant stress responses

Species	Stress	ABA function and mechanisms of action	[ABA]		Refs
Zea mays (*Zm*), *Commelina communis* (*Cc*), *Vicia faba* (*Vf*). *Arabidopsis thaliana* (*At*)	Drought	ABA synthesis is stimulated in roots and in leaf cells. ABA acts as a long-distance signal from root to leaf through the xylem. In the leaf, ABA induces an internal signal transduction cascade leading to the increase of $[Ca^{2+}]_{cyt}$, reduction of guard cell osmotic potential via loss of K^+ and Cl^- and stomatal closure. ABA regulates gene expression whose products protect vegetative tissues from dehydration and deleterious consequences.	(ng/gDW)		[60] [61] [62]
			Control	100 (*Vf*)	
			Drought	200 (*Vf*)	
Arabidopsis thaliana	Pathogens	ABA promotes the plant resistance to pathogens by: (i) Inducing the stomatal closure which prevents pathogen entry. (ii) Regulating one-third of the plant genes induced by pathogens. (iii) Inducing the priming of callose biosynthesis after pathogen recognition and inhibiting pathogen penetration of the cell.	(ng/gFW)		[63,64]
			Control	0	
			Infected	32	
Zea mays (*Zm*) *Vitis vinifera* (*Vv*)	UV-B	UV-B perception triggers an increase in ABA concentration, which activates pNOX, H_2O_2 generation and NO production to attenuate UV-B-derived cell damage. ABA induces biosynthesis of phenols that fllter the harmful radiation and act as antioxidants	(ng/gFW)		[4,65] [3]
			Control	52 (*Zm*)	
			UV-B	104 (*Zm*)	
			(ug/gFW)		
			Control	0.8 (*Vv*)	
			UV-B	2.2 (*Vv*)	
Solanum lycopersicum	Salt	ABA is synthesized by the root and transported by xylem to the aerial part. ABA induces both local changes (hydraulic conductivity) and long distance effects (stomatal closure).	(ng/gDW)		[66]
			Control	2	
			Salt	16	
Triticum durum (*Td*) *Vitis vinifera* (*Vv*)	Temperature	Genetic analysis indicates that *COR* gene expression is mediated by both ABA-dependent and -independent pathways. In the ABA-dependent pathway, endogenous ABA activates transcription factors. High and low temperatures during ripening affect the endogenous ABA level inducing anthocyanin biosynthesis through the regulation of genes coding for the involved enzymes.	(nmol/gFW)		[67] [68]
			Control (15 °C)	12 (*Td*)	
			Cold (5 °C)	22 (*Td*)	
			30 °C	– (*Vv*)	
			20 °C	up 1.6 fold (*Vv*)	
Pinus cembra	Ozone	ABA contributes with the defense against oxidative damage. (i) Increasing the antioxidant activity. (ii) Regulating stomatal closure which reduces de O_3 ingress. (iii) Inducing NO production.	(ng/gFW)		[69]
			Control (filtered air)	335 ± 34	
			Air + Ozone	528 ± 50	

is similarly dependent on a cADPR-mediated $[Ca^{2+}]_{cyt}$ increase [31].

Subsequent studies have unveiled tissue-specific effects of ABA in mammals, such as the cADPR/Ca^{2+}-dependent stimulation of hemopoietic progenitor (HP) and mesenchymal stem cell (MSC) proliferation, through the increased transcription of genes encoding growth factors and/or regulators, and cytokines [32,33]. ABA is also involved in the activation of the innate immune cells granulocytes, monocytes and/or macrophages, and microglia [10,34,35]. Granulocytes are the first line of animal defence against pathogens and environmental challenges. Granulocytes migrate to the site of injury where they kill pathogens via phagocytosis and the production of ROS and reactive nitrogen species (RNS) [10]. Monocytes are important actors in inflammation and immunity that are responsible for antigen presentation, phagocytosis and immunomodulation through the release of cytokines and growth factors. Activated monocytes release ABA, which autocrinally stimulates nuclear factor-kappa B (NF-κB) translocation and release of PGE-2 and TNF-α through a signaling pathway involving activation of NOX and ROS production [34]. ABA is also produced and released from human pancreatic islets and rodent insulinoma cell lines stimulated in response to high glucose concentrations and, interestingly, ABA stimulates insulin secretion from pancreatic β-cells through the same signaling cascade described in granulocytes [36,37]. Table 2 compiles the most relevant findings concerning ABA actions in animal cells, highlighting the key role played by ABA in the regulation of animal cell responses to environmental stimuli, including temperature, light, inflammatory stimuli, and nutrients.

ABA perception and signaling in plant and animal cells: similarities and differences

In plant cells, ABA perception has been proposed to occur on plasma membrane and cytosolic receptors. However, the plasma membrane ABA receptors proposed so far have failed to demonstrate the hormone binding unambiguously [38]. By contrast, the identification of the soluble pyrabactin resistance (PYR)/pyrabactin-like (PYL)/regulatory component of ABA receptor (RCAR) protein family [39,40] represented a breakthrough in deciphering ABA signaling in plants. Crystal structures show that PYR/PYL/RCAR proteins are *bona fide* ABA receptors. PYR/PYL/RCAR proteins are the only steroidogenic acute regulatory protein (StAR)-related lipid transfer (START)-domain containing proteins shown directly to function as receptors

Table 2. ABA functions in animal tissues and cells

Organism	Tissues/cells	ABA function and mechanism of action	[ABA]		Refs
Pigs and rats	Hearts, lungs, kidneys, livers, brains	ND	(ng/100 g FW)		[25]
			Heart	13 ± 5	
			Lung	27 ± 10	
			Kidney	37 ± 7	
			Liver	57 ± 16	
			Brain	180 ± 37	
Sponge (*Axinella polypoides*)		ABA mediates the sponge response to heat stress via the Ca^{2+}-releasing second messenger cADPR	(pmol/g wet tissue)		[29] [30]
			Control (14 °C)	4.1 ± 1.5	
			Heat stress (26 °C)	104.2	
Hydroid (*Eudendrium racemosum*)		ABA mediates light-induced tissue regeneration	(pmol/g wet tissue)		[70]
			(a) After sampling	22	
			(b) Dark, 24 h	18	
			(c) Fluridone	16	
			(d) Light 1 h	105	
			(e) (d) + fluridone	15	
Parasite (*Toxoplasma gondii*)		ABA-mediated calcium signaling controls the transition between lytic and chronic stage of infection that is central to pathogenesis and transmission.	(pmol/g wet tissue)		[71]
			Control	230 nM	
			Fluridone	40 nM	
			36 h after infection	1.3 mM	
Human	Granulocytes	ABA stimulates phagocytosis, ROS and NO production, and chemotaxis through a cADPR-induced $[Ca^{2+}]_i$ increase.	*Temperature stress* (pmol/mg protein)		[10,11]
			Control	0.23 ± 0.09	
			39 °C	Up 3 ± 0.5-fold	
		ABA released into the medium is a proinflammatory endogenous cytokine that stimulates granulocyte functions.	*UV-B stress* (total pmol)		
			Control	0.15	
			UV-B	0.38	
			Chemical or mechanical stimuli (pmol/5 x 10^7 cells)		
			Control	0.2	
			Zymosan	1.6	
			Latex bead	2.8	
Human	Monocytes/ macrophages	Autocrine ABA stimulates cell migration and the release of proinflammatory mediators via a Ca^{2+}–NF-κB-mediated signaling pathway.	(pmol/mg protein)		[34,72]
			Control (37 °C)	4.11 ± 0.82	
			39 °C (60 min)	Up 3.6-fold	
			Thrombin (1 h)	Up 9.2-fold	
			MCP-1 (1 h)	Up 2.8-fold	
			Quartz	Up to 10-fold	
Human	Mesenchymal stem cells (MSCs)	Autocrine ABA stimulates the trophic and immunomodulatory functions of MSC through the cADPR/$[Ca^{2+}]_i$ signaling pathway.	(pmol/mg protein)		[32,33]
			Control	2.17 ± 0.4	
			BMP-7	Up 6.0-fold	
			PBMNC	NC	
			M-CSF	NC	
Human	Keratinocytes	ABA plays a central role as an autocrine signal mediating responses to UV-B irradiation, such as the release of ROS, NO, PGE_2 and TNF-α. ABA released from UV-B irradiated keratinocytes behaves as a chemoattractant for granulocytes.	(total pmol)		[11]
			Control	0.5	
			UV-B (30 min)	2	
Human and rat	Pancreatic β cells	Glucose stimulates ABA release, which in turn increases insulin secretion that prolongs and enhances insulin release in response to glucose.	pmol/mg proteins		[36]
			Low glucose	5	
			High glucose	10	
Murine	Microglia	ABA stimulates NO and TNF-α production and cell migration through a cADPR-induced Ca^{2+} increase.	(pmol/mg protein)		[35]
			Control	0.31 ± 0.07	
			LPS	Up to 4.1-fold	
			β-amyloid	Up to 3.7-fold	
			fMLP	Up to 5.7-fold	
Murine	Adipocytes	ABA stimulates glucose uptake by enhancing GLUT-4 translocation to the plasma membrane.	ND	ND	[37]

ND, none determined. Based on data published by Li *et al.* (2010), with permission from Elsevier [53].

involved in ABA signal transduction and the only protein inhibitors of cytosolic type 2C protein phosphatase (PP2C) enzymatic activity. ABA-mediated PP2C inhibition results in the activation of sucrose nonfermenting (SNF)-1-related protein kinase 2 (SnRK2) and the downstream signals [40,41]. The presence of intracellular ABA sensors highlights the importance of ABA uptake into the cell for ensuring the intracellular signaling processes.

In human cells, no PYR/PYL/RCAR homolog and no cytosolic receptors for ABA have been described yet. On the contrary, it has been demonstrated that ABA acts through a pathway involving a pertussis toxin (PTX)-sensitive G protein/receptor complex located at the plasma membrane [10,36]. The lanthionine synthetase C-like protein, LANCL2, has been shown to be required for ABA binding to the membrane of human granulocytes and for the transduction of the ABA signal into cell-specific functional responses [42]; *in silico* analysis of LANCL2 predicted that this protein could be a target for ABA binding [43]. Furthermore, direct ABA binding to human recombinant LANCL2 has been recently demonstrated using different experimental approaches (saturation binding, scintillation proximity assays, dot blot experiments, and affinity chromatography), providing the first identification of a mammalian ABA receptor [44]. In summary, although the ABA membrane receptor LANCL2 seems to be present and functionally active in animal cells, the soluble cytosolic ABA receptor PYR/PYL/RCAR has been proved to be the link between the hormone perception and cell responses in plants. However, it cannot be discarded that multiple ABA receptors exist, in plants and animals alike, possibly with different cellular localizations and interconnected signaling pathways.

A recent revision of the molecular basis of ABA sensing, signaling, and transport in plants proposes that the ABC transporters ABCG25 and ABCG40 are responsible for ABA efflux and influx, respectively, in *Arabidopsis* cells, thereby mediating the paracrine signaling between ABA-synthesizing and -responsive cells [45]. Similarly to what has been observed in plants, intercellular trafficking of ABA also occurs in animal cell systems, where the paracrine delivery of the hormone from ABA-releasing cells has been shown to affect functional activities in bystander cells [32,34]. A phylogenetic analysis demonstrated that the ABA signaling components (PYR/PYL/RCAR-PP2C-SnRK2) are absent in *Chlamydomonas* but are conserved from Bryophytes through to all higher terrestrial plants [45].

Given that the divergence of the Plantae and Metazoa occurred 1.5–2.0 billion years ago, before the appearance of algae, it can be supposed that the evolution of the signaling components responding to UV-B and triggered by ABA has been independent in plants and animals. Therefore, the fact that the general mechanism of cell response to UV-B consisting of ABA, NOX, ROS, Ca^{2+}, and NO is common to both plants and animals suggests a convergent evolution of function.

ABA says NO to UV-B in plant and animal cells

UV-B is a strong abiotic stimulus for cells and several lines of evidence indicate that it generates similar responses in plants and animals. UV-B irradiation doubles the ABA concentration and enhances NOS-like-derived NO production in maize (*Zea mays*) [4]; UV-B also induces ABA synthesis and secretion, NO production, cytokine release, and granulocyte migration to the skin in humans [2,11,46,47]. Furthermore, ABA-induced NO production in both granulocytes [10] and plant cells is mediated by Ca^{2+}. Based on the available evidence, a broad general mechanism for the signaling pathway operating in response to UV-B appears to function in Metaphyta and Metazoa, with the common components being ABA, NOX, ROS, Ca^{2+}, and NO. We propose that UV-B perception in plant and animal cells triggers the increase of ABA, leading to the elevation of cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), which stimulates NO production through the increase in NOS activity. This NO contributes to the adaptive response and antioxidant defence (Figure 2). Even if the core of responses to UV-B (ABA-NO-Ca^{2+}) is conserved in plant and animals, different receptors and enzyme proteins may be involved in ABA perception and downstream signal transduction in plant and animals. Ultimately, in both types of organism, the ABA-induced enhancement of NO production may contribute to preserve cell redox homeostasis from UV-B-triggered uncontrolled ROS generation. Indeed, *in vivo* inhibition of NOX activity (and ROS production) by NO-mediated *S*-nitrosylation has been recently demonstrated in both plants and animals [48].

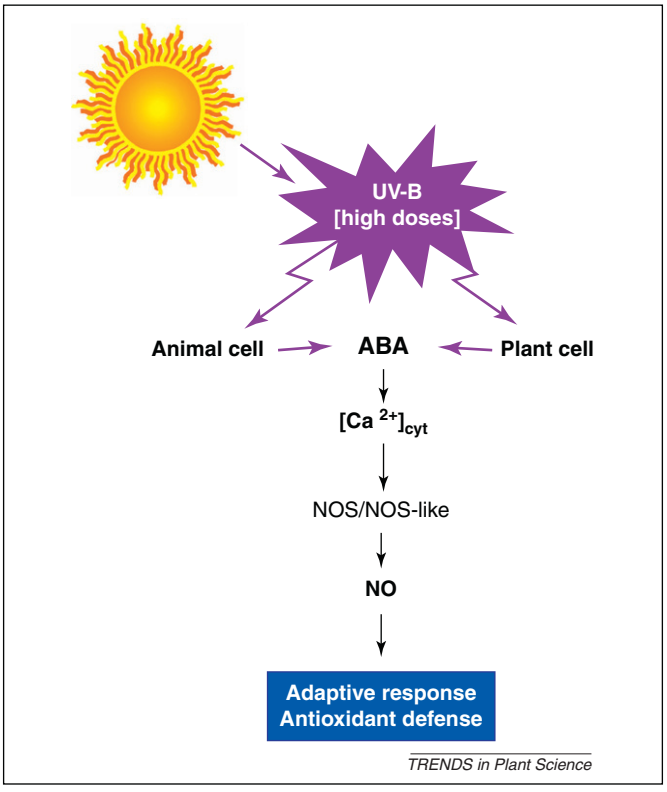

Figure 2. Common responses to ultraviolet (UV-B) irradiation in plant and animal cells. Simplified model showing the steps shared by plant and animal cells in the response to UV-B irradiation. UV-B perception in plant and animal cells triggers the increase of abscisic acid (ABA), leading to the elevation of the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), which stimulates nitric oxide (NO) production through the induction of NO synthase (NOS) and/or NOS-like activities. This enhancement of NO production contributes to preserving cell redox homeostasis from uncontrolled reactive oxygen species (ROS) generation and associated deleterious effects provoked by UV-B radiation.

These remarkable similarities at the core of signaling events occurring in UV-B-irradiated plant and animal cells should spur research on two main topics: (i) the evolution of molecular mechanisms and signaling pathways at the cellular and intercellular levels that enable the perception and decoding of the UV-B stimulus; and (ii) the genetic basis underlying UV-B adaptive responses in human cells, which could be studied by taking advantage of the knowledge and genetic tools available in *Arabidopsis*. This model plant is well suited for studying genotype–environment interactions and was recently proposed as an important organism in medical research for some human diseases [49].

Concluding remarks and outlook

ABA seems to trigger signaling pathways involving Ca^{2+} and NO that respond to UV-B stress and are conserved between plants and animals, from uni- to multicellular organisms. In plants, in addition to its role in abiotic and biotic stress responses, ABA has been involved in growth and developmental processes, such as embryo and seed formation, seed dormancy and germination, vegetative establishment, and reproduction. In animals, ABA stimulates cell-specific functions in pancreatic, immune, and vascular cells. Thus, a new and increasing body of evidence indicates that ABA plays a fundamental role in regulating many human cell responses to diverse stimuli. Therefore, ABA could be proposed as a therapeutic agent and experimental tool to modulate human cellular activities *in vivo*. However, to develop clinical uses of ABA, more experimental data on its pharmacological effects in mammalian organisms are needed. For instance, the pharmacokinetics of ABA in animal cells and the biological activities of ABA-derived metabolites, as well as the molecular mechanisms involved in ABA transport between cells, need to be investigated.

Fundamental studies on ABA functions in plant biology could contribute substantially to the development of original strategies and approaches in animal research systems [50]. For instance, ABA has been successfully assayed as a promising molecule to regulate chemically induced proximity (CIP) to control key processes in mammals [51]. In plants, ABA has been shown to regulate protein phosphatase 2 (PP2A) activity [39,40]. Interestingly, PP2A is a family of phosphatases involved in cell cycle regulatory functions and control of cell proliferation [52] and ABA has been proposed to be an effective and potent inducer of apoptosis in certain mammalian cancer cells without affecting normal cells [53]. Therefore, it would be interesting to take advantage of the CIP system based on ABA as an inducer to target cancer cells exclusively with specific drugs potentiating the previously characterized therapeutics effects of ABA. Thus, ABA appears to be a versatile and ubiquitous molecule that can modulate diverse physiological functions in many different organisms across the kingdoms of life.

As stated above, NO is key component of the downstream signals and molecular mechanisms regulated by ABA in many physiological processes in plants and animals. However, neither ABA nor NO would be working without the assistance of the cellular signals and hormones that constitute the fine-tuned network controlling the cell physiology.

It must be noteworthy that ABA-regulated mechanisms at the physiological and molecular levels are conserved in the basal members of extant plants, such as liverworts [54] and lower metazoa [29–31]. Therefore, it appears that the role of ABA as a stress hormone dates back to the early stages of the evolution of life on Earth, in ancestral organisms living before the divergence of the plant and animal lineages. Adaptability is necessary to overcome the challenges imposed by a changing environment to multicellular life, and ABA is still here to teach us about it.

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