Plant Signaling & Behavior 7:5, 1–5; May 2012; © 2012 Landes Bioscience

Damaged-self recognition as a general strategy for injury detection

Martin Heil[1,*]

[1]Departamento de Ingeniería Genética; CINVESTAV – Irapuato; Km. 9.6 Libramiento Norte; CP 36821; Irapuato, Guanajuato México

Keywords: alarmins, damage-associated molecular patterns, DAMPs, damaged-self recognition, jasmonic acid, octadecanoid signalling, sterile inflammation, wound response

Plants perceive endogenous molecules or their fragments as signals of danger when these appear at increased concentrations in the extracellular space and respond with increased endogenous levels of jasmonic acid. The wound hormone jasmonic acid represents a central player in the induced resistance of plants to herbivore feeding and infection by necrotrophic pathogens. This 'damaged self recognition' mechanism of plants exhibits astonishing similarities to the perception of 'damage-associated molecular patterns' (DAMPs) by the human immune system: endogenous cell constituents, or their fragments, that can be released into the extracellular milieu during states of cellular stress or damage function as 'stress signals' and trigger inflammatory and other immunity-related responses. Multicellular organisms use endogenous molecules as danger signals to mount adequate healing and resistance-related responses without depending on exogenous signals and to place exogenous, enemy-derived molecular signals into the adequate functional context.

Multicellular organisms rely on tissue integrity for multiple vital processes such as maintaining homeostastis, cell-cell communication, and to avoid desiccation and infection. Many critical resistance-related traits are localized in the outermost parts of the body (which usually form a skin, shell, or cuticle). Multicellular organisms thus require mechanisms to detect physical desintegrity in a rapid and reliable manner, in order to mount adequate counter-responses such as sealing the wound, healing of the damaged tissue, and a local or systemic resistance induction to prevent infection of the temporarily unprotected tissues.[1] We have recently reported that defense-related traits and the synthesis of the wound hormone, jasmonic acid (JA), in plants can be elicited by several endogenous molecules when these are applied exogenously. We applied aqueous solutions of ATP, sucrose or leaf extract to slightly wounded leaves of lima bean (*Phaseolus lunatus*) and observed significant increases in the secretion of extrafloral nectar, an indirect defense mechanism, and in endogenous levels of JA.[2]

We suggested that leaf extract contains multiple cell-derived molecules or their fragments, whose appearance or increased concentration in the extracellular space indicate tissue disruption, making the subsequent induction of a general resistance response highly adaptive. Because the response is quantitative (i.e., a higher dose of extract applied caused stronger responses),[2] damaged-self recognition might even allow to distinguish among different types of damage. Accidental mechanical damage by wind or trampling is usually a unique event that ruptures only few cells (that is, releases relatively few damaged-self signals). By contrast, damage inflicted by herbivores represent a continuous event that destructs large tissue areas bite by bite, releasing consecutively all the cell contents into the extracellular space. In lima bean, mechanical damage inflicted in a spatiotemporal pattern that mimicked caterpillar feeding elicited the same volatile profiles as feeding caterpillars.[3] In fact, many JA-inducing elicitors are, release, or contain, fragments of plant molecules (in particular fragments of proteins) that do not occur in the extracellular space of an intact plant tissue.[4] Prominent examples are hydrolytic enzymes,[5] fragments of endogenous proteins such as systemin and other peptide signals that are processed from a larger precursor upon damage, as well as cell wall-derived glyco-peptides.[6-9] Other resistance-inducing fragments of larger plant molecules that are formed upon damage are cell wall-derived pectines,[10] oligogalacturonide fragments and oligosaccharides.[11,12]

The recently published manuscript has been rejected by six scientific journals and its publication took more two years from the first submission to final acceptance by the seventh journal. Why do plant scientists have problems with the concept of damaged-self recognition? The most commonly raised criticism was "why should plants rely on the unspecific signals that cause damaged-self recognition, although they possess mechanisms to perceive specific, herbivore-derived elicitors?" In fact, most studies observed the full JA-mediated wound response only after the application of insect-derived elicitors (herbivore-associated molecular patterns, HAMPs), such as fatty acid-amino acid conjugates from caterpillar regurgitate.[13,14] With the exception of compounds from insect oviposition fluids,[15-18] however, seemingly no study applied HAMPs without some basic wounding treatment. According to my best knowledge, no published study to date has used non-damaging techniques to apply the elicitors to an intact leaf. If wounding is indeed the primary signal to induce a generic stress response, does it not appear plausible that insect-derived elicitors merely function to shape the response, because they provide further information about the detailed nature of the

*Correspondence to: Martin Heil; Email: mheil@ira.cinvestav.mx
Submitted: 02/29/12; Revised: 03/06/12;
http://dx.doi.org/10.4161/psb.19921

attacking enemy? How important is damaged-self recognition in comparison with HAMP-driven resistance responses? In lima bean leaves, the transcriptomice response to the application of leaf extract was almost identical to that induced by JA, indicating that insect-derived elicitors are not required to mount a full JA-dependent response in this species.[2] This raises the obvious question whether lima bean represents a common case or an exception in the plant kingdom?

Similar experiments with other plant species indicated that Arabidopsis, sesame and tomato also respond with strong increases in their endogenous JA content to mechanical damage or extract application, whereas maize and lima bean exhibited strong responses to extracellular sucrose.[2] Earlier studies reported resistance induction upon the exogenous application of leaf extract for cabbage (*Brassica oleracea*) and corn (*Zea mays*).[5,19] Extracellular ATP is also involved in coordinating the wound response in macro-algae.[20] Why do some researchers find damaged-self recognition, whereas others report that insect-derived elicitors are required for a full wound response in plants? What are the benefits of one or the other strategy, or their combination? In the following essay, I propose that the similarities among plant damaged-self recognition and certain aspects of the human immune system can help to address these questions. These similarities may also prove helpful in the design of future experiments that aim at understanding the role of damaged-self recognition in the overall response of plants to damage by herbivores.

Alarmins and 'Damage-associated Molecular Patterns' (DAMPs) in Humans

Humans are continuously exposed to pathogens and possess a sophisticated immune system to control infections. A central component of the immune system is therefore the recognition of invariable microbial molecules such as flagellin, chitin or microbial DNA, via the interaction of these molecules with Toll-like receptors or other pattern recognition receptors (PRRs).[21] This strategy is subject to a surprisingly high homology with the mechanisms by which plants recognize pathogen-associated molecular patterns (PAMPs) via PRRs.[22,23]

However, two common phenomena are seemingly inconsistent with the image of a highly coordinated human immune system that is triggered by the specific perception of PAMPs. On the one hand, humans are also colonized by myriads of commensalistic and mutualistic microorganisms without responding to their presence with a continuously accelerated immune response. On the other hand, humans suffer from sterile inflammation,[24] that is the development of inflammation-like symptoms in the absence of any infection by microbes. Why does the human immune system respond only to the pathogenic ones among all microorganisms to which it is exposed, and which molecular processes cause inflammation in the absence of infection? Inflammation after sterile injury or graft-vs.-host disease (GvHD) represent significant problems in contemporary medicine[25] and the advantages of the underlying responses appear difficult to understand.

Observations over the last years demonstrated that extensive cell death with consecutive release of danger signals can cause immune-mediated tissue destruction.[25] Normal cell constituents, or their fragments, that can be released into the extracellular milieu during states of cellular stress or damage function as 'stress signals', 'alarmins' or 'damage-associated molecular patterns' (DAMPs). These DAMPs then interact with Toll-like receptors or other PRRs and consecutively activate multiple components of the human innate immune system (such as the recruitment of neutrophils and macrophages and the production of pro-inflammatory cytokines and chemokines).[24-27] The appearance in the extracellular space of molecules such as ATP or Adenosine, RNA or DNA, or of specific proteins, or fragments or proteins, such as histones, cyclophilins or fibrinogen, causes inflammatory and other immune-related processes (see **Table 1**). Extracellular matrix components become pro-inflammatory and chemoattractant to leucocytes when they are fragmented or released from the matrix,[25,28] a mechanism with astonishing similarity to the role played by fragments of the plant cell wall in resistance induction (see above).

Even mitochondria or their fragments locally activate the innate immunity when appearing in the extracellular space, likely because their history as independent microorganisms causes their recognition by Toll-like receptor 9,[29] a CpG-DNA signal transducer that usually recognizes bacterial DNA as a PAMP.[30]

Table 1. Selected DAMPs and corresponding molecules in plant damaged-self recognition

DAMP in human immune response	Reference	Damaged-self signal in plants	Reference
Extracellular* ATP	24,25	Extracellular ATP	2,37,38
Extracellular Adenosine	39,40	n.d.	
Extracellular RNA	24,25	n.d.	
Extracellular DNA	24,25	Extracellular DNA	41
HMGB1 (protein)	42,43	n.d.	
Histones	26	n.d.	
Components released from the extracellular matrix (soluble biglycan or fibrinogen)	25,28,44	Cell wall-derived pectines, oligogalacturonide fragments and oligosaccharides	10-12
Protein fragments (of, e.g., collagen or fibronectin)	45,46	Protein fragments (systemin, signaling peptides)	6-9,47

*In the context of this table, 'extracellular' refers explicitly to extracellular, but endogenous (that is, released from cells of the same individual) molecules; n.d., not determined

Why does our immune system respond to these molecules? Most authors argue that the appearance of endogenous molecules in the extracellular space represents a reliable signal of tissue disruption. Even the seemingly misapprehension of extracellular mitochondrial DNA by PAMP-sensitive Toll-like receptors can represent an adaptive benefit: extracellular mitochondria, or their fragments, reliably indicate cellular damage "since mitochondria or their components are not found in the extracellular space under normal conditions."[25] Thus, extracellular mitochondria indicate the need to increase innate immunity in order to prevent future infection in the same way as do pathogenic bacteria.

As discussed above for plant damaged-self recognition, the occurrence of GvHD and other sterile inflammatory processes lead us to ask why the human immune system uses DAMPs, instead of relying completely on PAMP perception or more sophisticated mechanisms to specifically recognize pathogens or their activity. In fact, the word "activity" might contain part of the answer. Epithelial cells of the intestine only respond to flagellin as a PAMP when also being exposed to increased extracellular concentrations of ATP.[31] Based on this observation, Ivison et al.[31] suggest that the integration of DAMP perception allows intestinal cells to distinguish damaging pathogens from commensals, which possess the same molecular signatures as pathogens but do not harm body cells.[31] As stated by Zeiser et al.,[25] the immune response needs active control to avoid collateral damage that might exceed the damaged caused by pathogens. Molecular indicators of the destruction of body cells by pathogenic microorganisms are thus used in addition to their biochemical identifiers to distinguish between friends and foes in the human intestinal microflora.

Evolutionary Explanations

Why do plants use damaged-self signals although they can perceive specific, herbivore-derived elicitors? It appears to be likely that the observations made by Zhang et al.[29] and by Ivison et al.[31] provide us with important parts of the answer. In the following paragraphs I discuss three potential benefits of damaged-self recognition: (1) providing the adequate biochemical background for an adaptive response to enemy-associated molecular patterns, (2) maintaining the evolutionary dominance over the response to damage and (3) allowing an adequate general response to tissue injury.

First, increasing resistance in response to the perception of elicitors from insect saliva provides an adaptive benefit only when these appear in the functional context of a wounded plant tissue. It is even tempting to speculate that most insect–derived elicitors have never come into contact with intact plant tissues over evolutionary times, so that no selection pressure existed upon their recognition in the absence of damaged-self signals. It is perhaps no coincidence that seemingly all published studies about the resistance-inducing activity of HAMPs from insect saliva had applied these compounds to slightly damaged tissues.

Second, elicitors that stem from the metabolism of the enemy can provide specific information on the identity of the attacking enemy, but they come with the disadvantage from the perspective of the plant that they are under the metabolic – and ultimately evolutionary – control of the enemy. To avoid this problem, plants and humans perceive invariable microbial molecules as PAMPs, because these have such central roles in the functioning of the microorganism that any major changes in their chemical nature appear to be unlikely. Still, successful pathogens might avoid the perception of PAMPs, as for example recently described for *Pseudomonas aeruginosa*, which secretes an alkaline protease that efficiently degrades the ligand of the Toll-like receptor, monomeric flagellin, without attacking the macromolecule that forms the vitally important flagella.[32] Many plants have also evolved the capacity to perceive such effectors (molecules secreted by plant enemies for host manipulation) and mount a more specific effector-triggered immunity.[22,33] It seems impossible, however, that plants evolve mechanisms for the perception of specific molecules that characterize all current and potential enemies. Furthermore, levels of specificity in these interactions are so high that single mutations can shift an incompatible toward a compatibale interaction, or vice versa. For example, in the interaction between the plant *Linum usitatissimum* and its fungal pathogen *Melampsora lini,* several interacting host resistance (R) and pathogen effector gene loci provide alternate resistance and infectivity.[34] Allelic variants at the *AvrP123* effector locus that confer recognition by one R gene (and thus cause resistance), almost always escape recognition by other R genes and then lead to successful infection.[34] To this end, the capacity to perceive damage by using endogenous danger signals appears a necessary prerequisite to be prepared for all types of current and potential future attack.

Finally, when considering the adaptive human response to the interaction of Toll-like receptor 9 with microbial molecules or fragments from human mitochondria,[29] we must also consider that highly specific responses are not necessarily required or adaptive under all circumstances. Injury breaches the outer protective layers of an organism, or organ, and the injured tissue is therefore prone to desiccation and infection. Thus, injury requires several countermeasures, and many of these are independent of the causal agent.[1] Counter-measures that are taken by plants upon tissue disruption include wound periderm formation, lignification of the cell walls and deposition of phenolic compounds. The impervious tissues that are formed in this context resist water loss as well as penetration by most pathogens[1] and are also less valuable food sources for herbivores. Thus, several resistance-related responses are required in all cases of injury and should therefore be activated upon the perception of danger signals. For example, reactive oxygen species (ROS) are produced in most organisms after multiple stresses including infection by pathogens, herbivore attack or physical damage.[18,35] ROS signaling induces multiple general resistance responses that involve DNA repair, programmed cell death, cell wall thickening and the accumulation of phenolic compounds.[35,36] Mittler et al.[35] have already suggested that the rather unspecific ROS signaling might serve to activate or prime the general cellular signaling network, whereas specificity is then achieved by interactions with other signals, such as small peptides or hormones. In summary, some responses will be invariably required in response to every type of injury and can be

triggered by endogenous danger signals upon their extracellular appearance, and specificity can be brought into the system by coupling certain responses to the coordinated action of more than one class of triggers (such as, e.g., the combination of damaged-self signals with specific PAMPs or HAMPs).

Perspectives

Information published over the last years indicates that plant damaged-self recognition and the role of DAMPs in triggering the immune response in humans show astonishing similarities. It remains to be investigated, however, whether these similarities represent homologies or phenotypically similar results of parallel developments. It also remains unanswered whether damaged-self recognition and plant responses to HAMPs interact during perception of damage by feeding insects. To that end, a first obvious experiment would be to apply HAMPs to undamaged plant tissue, in the absence of and in combination with damaged-self signals. Such experiments would help to understand whether damaged-self signals function as described above for extracellular ATP in the human intestine: as a necessary damage signal whose presence allows for the perception of other, more specific enemy-associated molecular patterns. Then, we need to search for the receptors of damaged-self signals in plants. Toll-like receptors emerge as the common theme in the perception of DAMPs in humans and thus represent good candidates for a search for similar sequences in plants. In summary, it appears that the similarities among the human immune system and plant damaged-self recognition require further studies. In any case, however, these similarities can help us to understand potential adaptive benefits of damaged-self recognition in plants.

Acknowledgments

I thank Anurag A. Agrawal, Jurriaan Ton and all participants of the 2010 Gordon Conference on Plant-Herbivore Interaction for many valuable comments on the concept of damaged-self recognition and CONACyT de Mexico (project 129678) for financial support.

References

1. Bostock RM, Stermer BA. Perspectives on wound-healing in resistance to pathogens. Annu Rev Phytopathol 1989; 27:343-71; http://dx.doi.org/10.1146/annurev.py.27.090189.002015
2. Heil M, Ibarra-Laclette E, Adame-Álvarez RM, Martínez O, Ramirez-Chávez E, Molina-Torres J, et al. How plants sense wounds: damaged-self recognition is based on plant-derived elicitors and induces octadecanoid signaling. PLoS One 2012; 7:e30537; PMID:22347382; http://dx.doi.org/10.1371/journal.pone.0030537
3. Mithöfer A, Wanner G, Boland W. Effects of feeding *Spodoptera littoralis* on lima bean leaves. II. Continuous mechanical wounding resembling insect feeding is sufficient to elicit herbivory-related volatile emission. Plant Physiol 2005; 137:1160-8; PMID:15728342; http://dx.doi.org/10.1104/pp.104.054460
4. Heil M. Damaged-self recognition in plant herbivore defence. Trends Plant Sci 2009; 14:356-63; PMID:19540148; http://dx.doi.org/10.1016/j.tplants.2009.04.002
5. Mattiacci L, Dicke M, Posthumus MA. beta-Glucosidase: an elicitor of herbivore-induced plant odor that attracts host-searching parasitic wasps. Proc Natl Acad Sci U S A 1995; 92:2036-40; PMID:11607516; http://dx.doi.org/10.1073/pnas.92.6.2036
6. Pearce G, Siems WF, Bhattacharya R, Chen YC, Ryan CA. Three hydroxyproline-rich glycopeptides derived from a single petunia polyprotein precursor activate defensin I, a pathogen defense response gene. J Biol Chem 2007; 282:17777-84; PMID:17449475; http://dx.doi.org/10.1074/jbc.M701543200
7. Pearce G, Yamaguchi Y, Barona G, Ryan CA. A subtilisin-like protein from soybean contains an embedded, cryptic signal that activates defense-related genes. Proc Natl Acad Sci U S A 2010; 107:14921-5; PMID:20679205; http://dx.doi.org/10.1073/pnas.1007568107
8. Ryan CA, Pearce G. Systemins: a functionally defined family of peptide signals that regulate defensive genes in Solanaceae species. Proc Natl Acad Sci U S A 2003; 100 (Suppl 2):14577-80; PMID:12949264; http://dx.doi.org/10.1073/pnas.1934788100
9. Yamaguchi Y, Barona G, Ryan CA, Pearce G. GmPep914, an 8 amino acid peptide isolated from soybean leaves, activates defense-related genes. Plant Physiol 2011; 156:132-42; http://dx.doi.org/10.1104/pp.111.173096
10. Doares SH, Narváez-Vasquez J, Conconi A, Ryan CA. Salicylic acid inhibits synthesis of proteinase-inhibitors in tomato leaves induced by systemin and jasmonic acid. Plant Physiol 1995; 108:1741-6; PMID:12228577
11. Bergey DR, Orozco-Cardenas M, de Moura DS, Ryan CA. A wound- and systemin-inducible polygalacturonase in tomato leaves. Proc Natl Acad Sci U S A 1999; 96:1756-60; PMID:9990097; http://dx.doi.org/10.1073/pnas.96.4.1756
12. Creelman RA, Mullet JE. Oligosaccharins, brassinolides, and jasmonates: nontraditional regulators of plant growth, development, and gene expression. Plant Cell 1997; 9:1211-23; PMID:9254935; http://dx.doi.org/10.1105/tpc.9.7.1211
13. Bonaventure G, Baldwin IT. New insights into the early biochemical activation of jasmonic acid biosynthesis in leaves. Plant Signal Behav 2010; 5:287-9; PMID:20037473; http://dx.doi.org/10.4161/psb.5.3.10713
14. Bonaventure G, VanDoorn A, Baldwin IT. Herbivore-associated elicitors: FAC signaling and metabolism. Trends Plant Sci 2011; 16:294-9; PMID:21354852; http://dx.doi.org/10.1016/j.tplants.2011.01.006
15. Doss RP, Oliver JE, Proebsting WM, Potter SW, Kuy S, Clement SL, et al. Bruchins: insect-derived plant regulators that stimulate neoplasm formation. Proc Natl Acad Sci U S A 2000; 97:6218-23; PMID:10811915; http://dx.doi.org/10.1073/pnas.110054697
16. Hilker M, Meiners T. Early herbivore alert: insect eggs induce plant defense. J Chem Ecol 2006; 32:1379-97; PMID:16718566; http://dx.doi.org/10.1007/s10886-006-9057-4
17. Meiners T, Hilker M. Induction of plant synomones by oviposition of a phytophagous insect. J Chem Ecol 2000; 26:221-32; http://dx.doi.org/10.1023/A:1005453830961
18. Wu JQ, Baldwin IT. New insights into plant responses to the attack from insect herbivores. Annu Rev Genet 2010; 44:1-24; PMID:20649414; http://dx.doi.org/10.1146/annurev-genet-102209-163500
19. Turlings TCJ, McCall PJ, Alborn HT, Tumlinson JH. An elicitor in caterpillar oral secretions that induces corn seedlings to emit chemical signals attractive to parasitic wasps. J Chem Ecol 1993; 19:411-25; http://dx.doi.org/10.1007/BF00994314
20. Torres J, Rivera A, Clark G, Roux SJ. Participation of extracellular nucleotides in the wound response of *Dasycladus vermicularis* and *Acetabularia acetabulum* (Dasycladales, Chlorophyta). J Phycol 2008; 44:1504-11; http://dx.doi.org/10.1111/j.1529-8817.2008.00602.x
21. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell 2010; 140:805-20; PMID:20303872; http://dx.doi.org/10.1016/j.cell.2010.01.022
22. Jones JDG, Dangl JL. The plant immune system. Nature 2006; 444:323-9; PMID:17108957; http://dx.doi.org/10.1038/nature05286
23. Jordan T, Schornack S, Lahaye T. Alternative splicing of transcripts encoding Toll-like plant resistance proteins—what's the functional relevance to innate immunity? Trends Plant Sci 2002; 7:392-8; PMID:12234730; http://dx.doi.org/10.1016/S1360-1385(02)02311-7
24. Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 2010; 10:826-37; PMID:21088683; http://dx.doi.org/10.1038/nri2873
25. Zeiser R, Penack O, Holler E, Idzko M. Danger signals activating innate immunity in graft-versus-host disease. J Mol Med (Berl) 2011; 89:833-45; PMID:21573893; http://dx.doi.org/10.1007/s00109-011-0767-x
26. Huang H, Evankovich J, Yan W, Nace G, Zhang L, Ross M, et al. Endogenous histones function as alarmins in sterile inflammatory liver injury through Toll-like receptor 9 in mice. Hepatology 2011; 54:999-1008; PMID:21721026; http://dx.doi.org/10.1002/hep.24501
27. Nace G, Evankovich J, Eid R, Tsung A. Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. J Innate Immun 2012; 4:6-15; PMID:22086146; http://dx.doi.org/10.1159/000334245
28. Schaefer L. Biglycan signaling: Toll-like receptors, the NLRP3-inflammasome and beyond. FEBS J 2010; 277:27-8.
29. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464:104-7; PMID:20203610; http://dx.doi.org/10.1038/nature08780
30. Kirschning CJ, Bauer S. Toll-like receptors: cellular signal transducers for exogenous molecular patterns causing immune responses. Int J Med Microbiol 2001; 291:251-60; PMID:11680785; http://dx.doi.org/10.1078/1438-4221-00128

31. Ivison SM, Himmel ME, Mayer M, Yao Y, Kifayet A, Levings MK, et al. The stress signal extracellular ATP modulates antiflagellin immune responses in intestinal epithelial cells. Inflamm Bowel Dis 2011; 17:319-33; PMID:20722064; http://dx.doi.org/10.1002/ibd.21428
32. Bardoel BW, van der Ent S, Pel MJC, Tommassen J, Pieterse CM, van Kessel KP, et al. Pseudomonas evades immune recognition of flagellin in both mammals and plants. PLoS Pathog 2011; 7:e1002206; PMID: 21901099; http://dx.doi.org/10.1371/journal.ppat.1002206
33. Schulze-Lefert P, Panstruga R. A molecular evolutionary concept connecting nonhost resistance, pathogen host range, and pathogen speciation. Trends Plant Sci 2011; 16:117-25; PMID:21317020; http://dx.doi.org/10.1016/j.tplants.2011.01.001
34. Dodds PN, Rathjen JP. Plant immunity: towards an integrated view of plant-pathogen interactions. Nat Rev Genet 2010; 11:539-48; PMID:20585331; http://dx.doi.org/10.1038/nrg2812
35. Mittler R, Vanderauwera S, Suzuki N, Miller G, Tognetti VB, Vandepoele K, et al. ROS signaling: the new wave? Trends Plant Sci 2011; 16:300-9; PMID: 21482172; http://dx.doi.org/10.1016/j.tplants.2011.03.007
36. Leitner M, Boland W, Mithöfer A. Direct and indirect defences induced by piercing-sucking and chewing herbivores in *Medicago truncatula*. New Phytol 2005; 167:597-606; PMID:15998409; http://dx.doi.org/10.1111/j.1469-8137.2005.01426.x
37. Chivasa S, Murphy AM, Hamilton JM, Lindsey K, Carr JP, Slabas AR. Extracellular ATP is a regulator of pathogen defence in plants. Plant J 2009; 60:436-48; PMID:19594709; http://dx.doi.org/10.1111/j.1365-313X.2009.03968.x
38. Roux SJ, Steinebrunner I. Extracellular ATP: an unexpected role as a signaler in plants. Trends Plant Sci 2007; 12:522-7; PMID:17928260; http://dx.doi.org/10.1016/j.tplants.2007.09.003
39. Haskó G, Cronstein BN. Adenosine: an endogenous regulator of innate immunity. Trends Immunol 2004; 25:33-9; PMID:14698282; http://dx.doi.org/10.1016/j.it.2003.11.003
40. Kumar V, Sharma A. Adenosine: an endogenous modulator of innate immune system with therapeutic potential. Eur J Pharmacol 2009; 616:7-15; PMID: 19464286; http://dx.doi.org/10.1016/j.ejphar.2009.05.005
41. Hawes MC, Curlango-Rivera G, Wen F, White GJ, Vanetten HD, Xiong Z. Extracellular DNA: the tip of root defenses? Plant Sci 2011; 180:741-5; PMID: 21497709; http://dx.doi.org/10.1016/j.plantsci.2011.02.007
42. Klune JR, Dhupar R, Cardinal J, Billiar TR, Tsung A. HMGB1: endogenous danger signaling. Mol Med 2008; 14:476-84; PMID:18431461; http://dx.doi.org/10.2119/2008-00034.Klune
43. Mathur S, Walley KR, Wang Y, Indrambarya T, Boyd JH. Extracellular heat shock protein 70 induces cardiomyocyte inflammation and contractile dysfunction via TLR2. Circ J 2011; 75:2445-52; PMID: 21817814; http://dx.doi.org/10.1253/circj.CJ-11-0194
44. Docherty NG, Godson C. Fibrinogen as a damage-associated mitogenic signal for the renal fibroblast. Kidney Int 2011; 80:1014-6; PMID:22042028; http://dx.doi.org/10.1038/ki.2011.266
45. Thomas AH, Edelman ER, Stultz CM. Collagen fragments modulate innate immunity. Exp Biol Med (Maywood) 2007; 232:406-11; PMID:17327474
46. Okamura Y, Watari M, Jerud ES, Young DW, Ishizaka ST, Rose J, et al. The extra domain A of fibronectin activates Toll-like receptor 4. J Biol Chem 2001; 276:10229-33; PMID:11150311; http://dx.doi.org/10.1074/jbc.M100099200
47. Chen YC, Siems WF, Pearce G, Ryan CA. Six peptide wound signals derived from a single precursor protein in *Ipomoea batatas* leaves activate the expression of the defense gene sporamin. J Biol Chem 2008; 283:11469-76; PMID:18299332; http://dx.doi.org/10.1074/jbc.M709002200