www.ThePharmaJournal.com

The Pharma Innovation

Rishi Raj
JRF Student MBAC, Agwanpur,
Saharsa, Bihar, India

Kumari Shyam Lata
PG Student, MLT Collage,
Saharsa, Bihar, India

Vishakha Raj
Bsc. Nursing Student, IGIMS,
Patna, Bihar, India

Dr. Mukul Kumar
Assistant Professor-Cum-JR.
Scientist, Department of
Biochemistry and Crop
Physiology. MBAC, Agwanpur,
BAU, Sabour, Bihar, India

The defense mechanism of plant

Rishi Raj, Kumari Shyam Lata, Vishakha Raj and Dr. Mukul Kumar

DOI: https://doi.org/10.22271/tpi.2020.v9.i10e.5258

Abstract
According to the state of food security and nutrition, Hunger has increased in many countries in which the economy has slowed down, mostly in middle-income countries. If nothing changes, the immense challenge of achieving the Zero Hunger Target by 2030. The causes of food scarcity might include factors such as unavailability of food due to less production of particular crops/vegetables (due to attack of pests/microbes), it becomes harder to fulfill the basic needs of life especially for poor. Therefore, we need to primarily focus on understanding the interaction between plants and microbes at the molecular level and underlying mechanisms of plant disease and which will help out to solve the global needs of food and resources. Plants have a natural defense mechanism/immune system to react to infections which subdivides into two parts. The first part identifies and reacts to molecules common to different classes of microbes, including non-pathogen. The function of the second part is to react to pathogens virulence factors, either directly or by affecting the host targets. We can also see the intricacies or reciprocation between plants and pathogen attackers. A vast and deep comprehension of plant defense mechanisms will defiantly solve the issue, like food scarcity.

Keywords: Microbial-or pathogen-associated molecular patterns (MAMPS or PAMPs), pattern recognition receptors (PRRs), PAMP-triggered immunity (PTI), hypersensitive response (HR), effector-triggered immunity (ETI)

Introduction
The defense mechanism plant, a system that allows plants to resist attack from a large variety of its enemy. Here, we provide a strategic plan that plants adapt during its immunity. Plant diseases caused by pathogens and microbes are a continuous threat to crop losses and global food security which have devastating effects on both smallholder and factory farming [1-3], the subsequent impact can also be seen in the food supply. The estimated impact of pre-harvest yield loss in crops caused by disease vary, but at least 30% of global agricultural production is affected annually [5]. If we do not take proper action it can badly impact on agriculture, economy, and society of any nation. Perhaps the best-known example would be the Irish potato famine in the mid-1800s, where potato late blight disease (caused by the filamentous plant pathogen Phytophthora infestans) contributed to mass emigration from Ireland [4]. In current agriculture practice, plant diseases are largely controlled by chemicals, but this is unsustainable in the long-term due to environmental concerns and also for future needs of resources. Our focus will be on the cell surface and intracellular immune receptors. We also try to explain how these receptors recognize the signatures of pathogens and pests then activate immune pathways. The interaction between a pathogen and its host is like an evolutionary process, which has been taking place from a long history of warfare with its enemy and they are being constantly changing themselves to fight against natural selection and win over on one another. Though Plants suffer from a disease, their ability to react to infection is crucial for survival. The disease develops only when the pathogen is successful in escaping the multiple layers of host defenses [6-8]. The immune system of plants has similarities with the innate immune system of animals [9-11]. But as plants lack an adaptive immune system, they depend completely and only on innate immunity to perceive microbial pathogens and pests. This review will provide that conceptually, plant immunity can be bifurcated into the cell-surface receptor immunity and intracellular immunity [12].

We also focus on current knowledge of intracellular perception of cell surface receptor and intracellular pathogens, activation of NLRs, and the downstream signaling components.

Corresponding Author:
Dr. Mukul Kumar
Assistant Professor-Cum-JR.
Scientist, Department of
Biochemistry and Crop
Physiology. MBAC, Agwanpur,
BAU, Sabour, Bihar, India

Cell-surface receptor immunity

It is provided by pattern recognition receptors/ receptor-like kinases/ Cell surface receptor/ receptor-like proteins (PRRs)/ (RLKs) / CRT)/ RLPs) which recognize microbe/pathogen/ damage-associated molecular patterns (MAMPs /PAMPs / DAMPs respectively) such as bacterial flagellin or fungal chitin and trigger to [13-16]. Highly adapted pathogens sometime breach pattern- triggered immunity (PTI) by injecting pathogen- encoded proteins called effectors into plant cells [17].
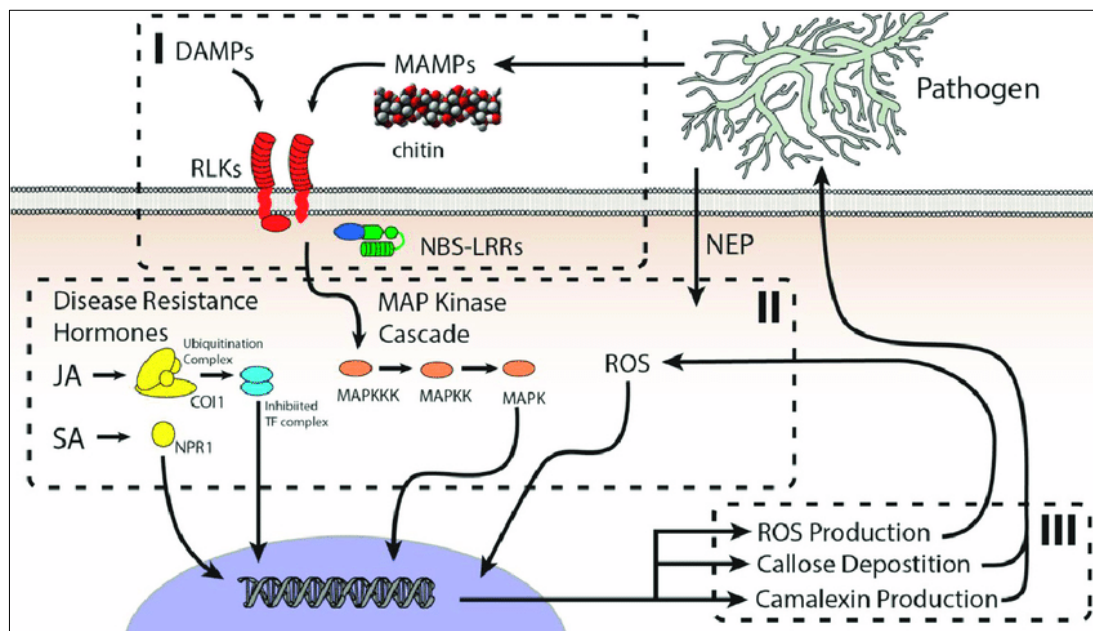

Fig 1: The above model can be predicted in the three ways: FIRST recognition, SECOND signal transduction, and THIRD defense response.

Firstly, damage-associated molecular patterns DAMPs) and MAMPs/PAMPs recognized by plant either by symplastically detected via cytoplasmic NBS-LRRs or by apoplastically detected via RLKs. Secondly, the MAP Kinase pathway which allows the signal transduction of DAMPs/ MAMPs/PAMPs and activates a series of transcription factors like the WRKY gene. Thirdly, this signal causes the production of specific defense responses which include callose deposition, reactive oxygen species (ROS) production, and various specialized metabolism (here camalexin) [18].

Types of cell-surface receptors

These are transmembrane receptors and the best-studied class of plant PRRs is receptor-like kinases (RLKs), which feature an ectodomain of leucine-rich repeats (LRRs) involved in MAMP perception, and an intracellular kinase domain, involved in signal transduction relay via MAPK cascades, resulting in MAMP-triggered immunity (MTI) [19].

RLKs contain a variable extracellular domain that mediates ligand recognition. Plant RLKs that have been identified mostly belong to the family of non-RD kinases in which conserved arginine in the catalytic loop is absent and they often associate in dynamic complexes with membrane-bound RLKs that are functional RD kinases (such as BAK1 and SERKs), which operate as coreceptors for perception to initiate immune signaling [20-23]. In reference to RLPs, they exhibit a similar overall structure to RLKs, and only contain a lacking kinase domain, a short intracellular tail, and require a partner co-receptor to signal [24-25].

The LysM-type RLKs LYK5 (Lysin motif receptor kinase 5) and CERK1 (Chitin elicitor receptor kinase 1) [26-27] bind fungal chitin oligomers and, Arabidopsis LRR-type RLKs, FLS2 (Flagellin-sensitive 2), and EFR (elongation factor Tu (EF-Tu) receptor) [28-29], are amongst the best characterized cell-surface immune receptors.

EFR recognize peptide epitopes from the N-termini of bacterial flagellin (flg22) and bacterial EF-Tu (elf18) respectively [30].

Recognition of peptide

Many subfamilies of cell-surface receptors is protein ligands LRR-RLKs which preferentially bind peptides or proteins as ligands [31-33]. LRR-RLKs from rice and solanaceous plants have also been characterized in Arabidopsis FLS2 and EFR. The rice cell-surface receptor Xa21 binds RaxX21-sY and a tyrosine-sulfated protein from bacteria [34]. The conserved epitopes derived from bacterial cold shock protein bind to the cell-surface receptors from tomato (CORE) and tobacco (NbCSPR) [35-37]. Likewise, Arabidopsis RLP23 binds the epitope nlp-20, a conserved peptide derived from ethylene-inducing peptide1- like proteins of bacterial and filamentous pathogens [38].

Recognition of carbohydrate

Several different classes of receptors capable of sensing different carbohydrate ligands also have been found. Carbohydrate MAMPs such as bacterial peptidoglycan (PGN), lipopolysaccharide (LPS), and fungal chitin are perceived by LysM-RLKs/LysM-RLPs and LectinRK LORE [39-40].

Regulation of cell-surface receptor

For maintaining cell-surface receptors in an inactive state in the absence of ligand binding, plants employ various strategies that include ubiquitination by E3 ligases and the regulation of phosphorylation state [40-44]. Therefore, the plant cell-surface immune receptors activity is tightly controlled mainly Phosphorylation to prevent any inappropriate signaling [40].

To prevent the potentially harmful effects of autoinduction

plants use phosphatases to negatively regulate cell-surface receptors. For example, dephosphorylates BAK1/EFR to control defense signaling, Arabidopsis PP2A (Protein Phosphatase 2A), a serine/threonine phosphatase [4-47]. Similarly, PP2C38 regulates ligand-induced phosphorylation of BIK1, moderating signaling by this key transducer of cell-surface immunity [40]. The use of pseudo kinases, such as BIR1 and BIR2 to negatively regulate cell surface immunity could also be a Second strategy. They are catalytically inactive but interact with BAK1 in its resting state, preventing the association of LRR-RLKs [48-50]. This inhibitory interaction is relieved by ligand binding and thus leading to the formation of activated immune complexes.

Immunity can also be regulated by controlled degradation through ubiquitination. Two closely related E3-ubiquitin ligases, PUB25 and PUB26, together with both a calcium-dependent protein kinase CPK28 and a heterotrimeric G protein, form a regulatory module and maintain BIK1 homeostasis [49]. Similarly, PUB12 and PUB13 polyubiquitinate and mediate degradation of ligand-bound FLS2 [51-53].

Intracellular immunity
Effectors: Master manipulators of plant cells
Master manipulators of plant cells that promote infection are the effectors. For the best understanding of the interplay between the pathogens/pests and the plant immune system, let's first discuss the effectors and their role in promoting host infection. The term 'effectors' is used to define protein molecules secreted by microbial pathogens and microbes to promote signal transduction from extracellular to intracellular of the host [53]. These effectors can be delivered to the extracellular space or deployed to the inside of host cells. Therefore, in the broadest definition, the molecules including microbes, plants, and animals to modulate the activity of another organism (plant) are effectors.

Interaction between the extracellular and intracellular immune response to deal with pathogens.
These interactions can be understood by four phases proposed by Jones and Dangl known as the 'Zigzag model' [54]. It mainly explains that two branches PTI (Pattern-Triggered Immunity) and ETI (Effector-Triggered Immunity) [54].

PTI is mainly dependent on the upon conserved plasma membrane-associated extracellular Pattern-Recognition Receptors (PRRs) [55-56], such as Receptor-Like Kinases (RLKs) and Receptor-Like Proteins. RLPs and RLKs are similar but the only difference is that RLPs lack a cytoplasmic kinase domain. PTI is mostly achieved without the death of the host plant cells. RLPs detecting highly conserved microbial features (a.k.a. Pathogen-Associated Molecular Patterns, PAMPs) such as bacterial cell wall-derived peptidoglycans or flagella fragments in the host apoplast. When secreted proteins, knowns as effectors, move inside the host, some of the effectors act on PTI to neutralize it and other effectors tries to manipulate the host cell metabolism and use the nutrients host [57-58]. same host plant might have highly variable intracellular receptors known as disease resistance (R) proteins that can recognize effectors and try to encounter or neutralize the effector, after the successful encounter of effectors activation of ETI. ETI is often led to programmed cell death of the affected cell, which also called as a hypersensitive response (HR) [59-60].
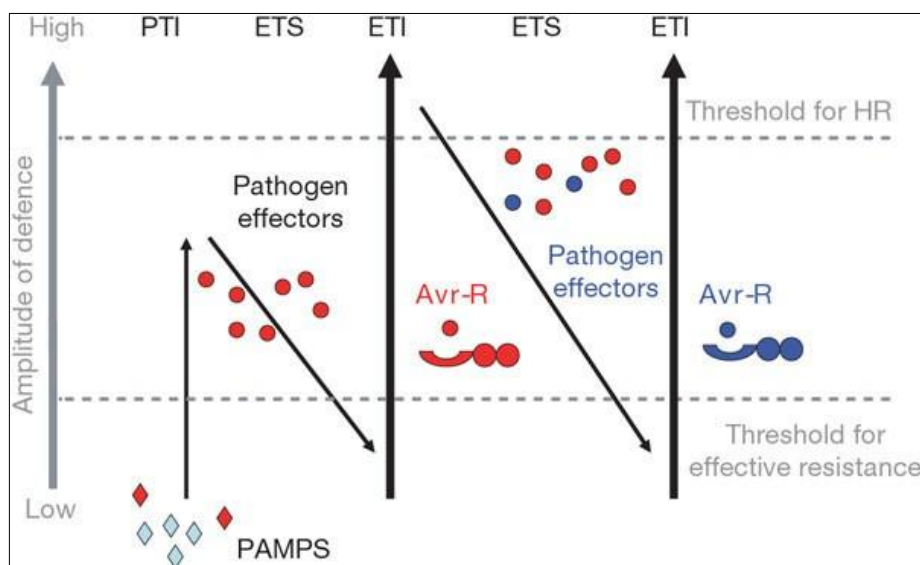

Fig 2: The above 'Zigzag model' can be explain in Four phase.

Phase 1: - PAMPs DAMPs/ MAMPs) are recognized by PRRs, thus contributing in activating PAMP-triggered immunity (PTI) and then this PAMP-triggered immunity (PTI) will try to block or retarded further colonization of pathogen. A tag of war occurs between host immune system and pathogens, and in some instances, pathogen might win the first phase. Then,

In phase 2, Effectors are spread out by successful pathogens which lead to pathogen virulence and these effectors can interfere with PTI and therefore, resulting in effector-triggered susceptibility (ETS).

In phase 3, One of the NB-LRR proteins specifically recognizes the effector, resulting in effector-triggered immunity (ETI) and this ETI is an accelerated and amplified PTI response which results in disease resistance and, usually, at the infection site a hypersensitive cell death response (HR) occurs. Also, this recognition of effector is either indirect, or directly through NB-LRR.

In phase 4, through the gain of new effectors through horizontal gene flow, pathogens will be driven to avoid ETI

by one of the two ways either by acquiring additional effectors that suppress ETI or by shedding or diversifying the recognized effector gene. Natural selection might result in favor of new plant NB-LRR alleles that result in new *R* specificities so that ETI can be triggered again.

So this tug of war between pathogen and plant immune system can be summarized as follows, Both PTI and ETI join together for a rapid explosion/burst of extracellular reactive oxygen species (ROS), which cascade the activation of mitogen- activated protein kinases (MAPKs) and calcium-dependent protein kinases (CPKs), which increase in cytosolic calcium, change in ion fluxes, increase of phytohormones, thus overall reprogramming of the host plant for death signal [61-62]. During ETI, the amplitude of these responses is much higher than in PTI and this often leads to induction of a type of programmed cell death (also called as the hypersensitive response (HR)) at the site of infection that results in the overall restriction of the pathogen by localized cell death. On the other hand, pathogens are likely to contribute to the suppression of one or more components of PTI or ETI. These vice versa process mainly depend upon, in which way natural selection favor the process [63].

HR (hypersensitive response)
A form of programmed cell death- the hypersensitive

response (HR), is often lead to the inhibition of pathogen growth due to NB-LRRs in plants. HR is a specific and unique type of cell death. The chloroplast has an important role in HR firstly, many effectors have chloroplast localization signals [65], sometime these effectors, have shown to suppress immunity [66-67]. Secondly, HR make up a very important source of security signaling molecules for example as reactive nitrogen oxide intermediates (NOI), reactive oxygen species (ROS), defense hormones jasmonic acid (JA) and salicylic acid (SA).Thirdly, light is also required for HR development in many cases. During the final stages some of its typical hallmarks are vacuolization and chloroplast disruption [64]. Thus, ROS produced by plant organelles such as chloroplast, mitochondria and peroxisomes contribute to the HR response. Thus, in plants the molecular events that lead to HR are given below. ETI are partly overlapping with those associated with MTI, including accumulation of SA, ROS and NOI, activation of MAPK cascades, changes in intracellular calcium levels, transcriptional reprogramming and synthesis of antimicrobial compounds [64].

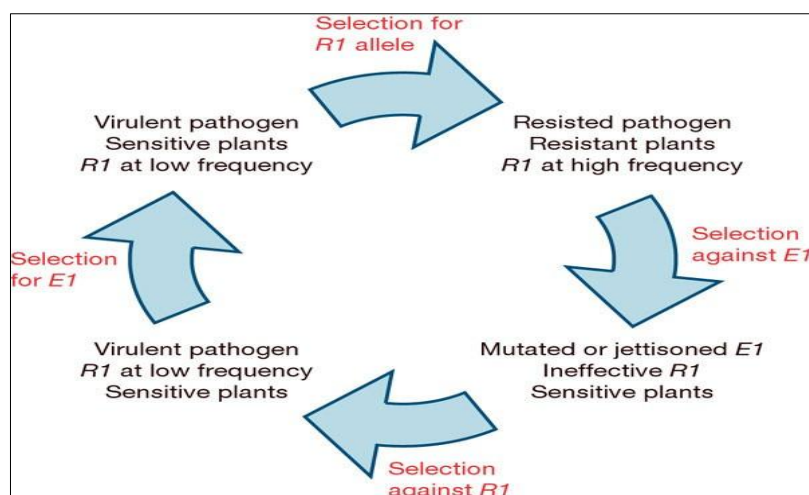### Co-evolution of *R* genes (plant) and the effector (pathogen)

Fig 3: Co-evolution of *R* genes (plant) and the effector (pathogen)

A pathogen has an effector gene (*E1*) that is sensed by a rare *R1* allele (top). This led to selection of an elevated frequency of *R1* in the population. Pathogens in which the effector is mutated are then selected, because they can grow on *R1*-containing plants (right). *R1* effectiveness erodes, and, because at least some *R* genes have associated fitness costs [68], plants carrying *R1* can have reduced fitness (bottom), resulting in reduced *R1* frequencies. The pathogen population will still contain individuals with *E1*. In the absence of *R1*, *E1* will confer increased fitness, and its frequency in the population will increase (left). This will lead to resumption of selection for *R1* (top). In populations of plants and pathogens, this cycle is continuously turning, with scores of effectors and many alleles at various *R* loci in play [69].

References
1. Savary S, Willocquet L, Pethybridge SJ, Esker P, McRoberts N, Nelson A. The global burden of pathogens and pests on major food crops. Nature Ecology & Evolution 2019;3:430-439.
2. Bebber DP, Gurr SJ. Crop-destroying fungal and oomycete pathogens challenge food security. Fungal Genetics and Biology 2015;74:62-64.
3. Fisher MC, Henk DA, Briggs CJ, Brownstein JS, Madoff LC, McCraw SL, *et al*. Emerging fungal threats to animal, plant and ecosystem health. Nature 2012;484:186-194.
4. TURNER RS. After the famine: Plant pathology, Phytophthora infestans, and the late blight of potatoes, 1845—1960. Historical Studies in the Physical and Biological Sciences 2005;35:341-370.
5. Savary S, Willocquet L, Pethybridge SJ, Esker P, McRoberts N, Nelson A. The global burden of pathogens and pests on major food crops. Nat Ecol Evol 2019;3:430-439.
6. Dangl JL, Jones JDG. Plant pathogens and integrated defence responses to infection. *Nature* 2001;411:826-

833.

7. Ausubel FM. Are innate immune signaling pathways in plants and animals conserved? *Nature Immunol* 2005;6:973-979.

8. Chisholm ST, Coaker G, Day B, Staskawicz BJ. Host–microbe interactions: shaping the evolution of the plant immune response. *Cell* 2006;124:803-814.

9. Bentham A, Burdett H, Anderson PA, Williams SJ, Kobe B. Animal NLRs provide structural insights into plant NLR function. Annals of Botany 2016;119:698-702.

10. Jones JDG, Vance RE, Dangl JL. Intracellular innate immune surveillance devices in plants and animals. Science 2016, 354, aaf6395.

11. Meunier E, Broz P. Evolutionary Convergence and Divergence in NLR Function and Structure. Trends Immunol 2017;38:744-757.

12. Wang W, Feng B, Zhou J.-M, Tang D. Plant immune signaling: Advancing on two frontiers. Journal of Integrative Plant Biology 2020;62:2-24.

13. Macho Alberto P, Cyril Zipfel. Plant PRRs and the activation of innate immune signaling. *Molecular cell* 2014;54(2):263-272.

14. Meier N, Hatch C, Nagalakshmi U, Dinesh- Kumar SP. Perspectives on intracellular perception of plant viruses. Molecular plant pathology 2019;20(9):1185-1190.

15. Jones JD, Dangl JL. The plant immune system. Nature 2006;444:323-329. [PubMed] [Google Scholar]

16. Eckardt NA. The plant cell reviews plant immunity: receptor-like kinases, ROS-RLK crosstalk, quantitative resistance, and the growth/defense trade-off, 2017.

17. Corwin JA, Kliebenstein DJ. Quantitative resistance: more than just perception of a pathogen. Plant Cell 2017;29:655-665.

18. Corwin JA, Kliebenstein DJ. Quantitative resistance: more than just perception of a pathogen. The Plant Cell 2017;29(4):655-665

19. Turner RS. After the famine: Plant pathology, Phytophthora infestans, and the late blight of potatoes, 1845-1960. Historical Studies in the Physical and Biological Sciences 2005;35:341-370.

20. Böhm H, Albert I, Fan L, Reinhard A, Nürnberger T. Immune receptor complexes at the plant cell surface. Current Opinion in Plant Biology 2014;20:47-54.

21. Macho Alberto P, Zipfel C. Plant PRRs and the Activation of Innate Immune Signaling. Molecular Cell 2014;54:263-272.

22. Dardick C, Schwessinger B, Ronald P. Non-arginine-aspartate (nonRD) kinases are associated with innate immune receptors that recognize conserved microbial signatures. Current Opinion in Plant Biology 2012;15:358-366.

23. Ma X, Xu G, He P, Shan L. SERKing Coreceptors for Receptors. Trends in Plant Science 2016;21:1017-1033.

24. Jamieson PA, Shan L, He P. Plant cell surface molecular cypher: Receptor-like proteins and their roles in immunity and development. Plant Sci 2018;274:242-251.

25. Burkart RC, Stahl Y. Dynamic complexity: plant receptor complexes at the plasma membrane. Current Opinion in Plant Biology 2017;40:15-21.

26. Miya A, Albert P, Shinya T, Desaki Y, Ichimura K, Shirasu K, *et al*. CERK1, a LysM receptor kinase, is essential for chitin elicitor signaling in Arabidopsis. Proceedings of the National Academy of Sciences 2007;104:1961.

27. Cao Y, Liang Y, Tanaka K, Nguyen CT, Jedrzejczak RP, Joachimiak A, *et al*. The kinase LYK5 is a major chitin receptor in Arabidopsis and forms a chitin-induced complex with related kinase CERK1. Elife 2014;3:e03766.

28. Kunze G, Zipfel C, Robatzek S, Niehaus K, Boller T, Felix G. The N Terminus of Bacterial Elongation Factor Tu Elicits Innate Immunity in Arabidopsis Plants. The Plant Cell 2004;16:3496.

29. Chinchilla D, Zipfel C, Robatzek S, Kemmerling B, Nürnberger T, Jones JDG, *et al*. A flagellin-induced complex of the receptor FLS2 and BAK1 initiates plant defence. Nature 2007;448:497-500.

30. Zipfel C, Kunze G, Chinchilla D, Caniard A, Jones JDG, Boller T, *et al*. Perception of the Bacterial PAMP EF-Tu by the Receptor EFR Restricts *Agrobacterium*-Mediated Transformation. Cell 2006;125:749-760.

31. Albert M. Peptides as triggers of plant defence. Journal of Experimental Botany 2013;64:5269-5279.

32. Mott GA, Middleton MA, Desveaux D, Guttman DS. Peptides and small molecules of the plant-pathogen apoplastic arena. Frontiers in plant science 2014;5:677-677.

33. Smakowska-Luzan E, Mott GA, Parys K, Stegmann M, Howton TC, Layeghifard M, *et al*. An extracellular network of Arabidopsis leucine-rich repeat receptor kinases. Nature. 2018; 553:342-346.

34. Pruitt RN, Schwessinger B, Joe A, Thomas N, Liu F, Albert M, *et al*. The rice immune receptor XA21 recognizes a tyrosine-sulfated protein from a Gram-negative bacterium. Sci Adv 2015;1:e1500245-e1500245.

35. Felix G, Boller T. Molecular Sensing of Bacteria in Plants: The Highly Conserved Rna-Binding Motif Rnp-1 Of Bacterial Cold Shock Proteins Is Recognized As An Elicitor Signal In Tobacco. Journal of Biological Chemistry 2003;278:6201-6208.

36. Wang L, Albert M, Einig E, Fürst U, Krust D, Felix G. The patternrecognition receptor CORE of Solanaceae detects bacterial cold-shock protein. Nature Plants 2016;2:16185.

37. Wei Y, Caceres-Moreno C, Jimenez-Gongora T, Wang K, Sang Y, LozanoDuran R, *et al*. The Ralstonia solanacearum csp22 peptide, but not flagellin-derived peptides, is perceived by plants from the Solanaceae family. Plant Biotechnology Journal 2018;16:1349-1362.

38. Albert I, Böhm H, Albert M, Feiler CE, Imkampe J, Wallmeroth N, *et al*. An RLP23–SOBIR1–BAK1 complex mediates NLP-triggered immunity. Nature Plants 2015;1:15140.

39. Wan J, Zhang X.-C, Neece D, Ramonell KM, Clough S, Kim S.-Y, *et al*. A LysM receptor-like kinase plays a critical role in chitin signaling and fungal resistance in Arabidopsis. The Plant cell 2008;20:471-481.

40. Ranf S, Gisch N, Schäffer M, Illig T, Westphal L, Knirel YA, *et al*. A lectin S-domain receptor kinase mediates lipopolysaccharide sensing in Arabidopsis thaliana. Nature Immunology 2015;16:426-433.

41. Couto D, Zipfel C. Regulation of pattern recognition receptor signalling in plants. Nature Reviews Immunology 2016;16:537-552.

42. Gómez-Gómez L, Bauer Z, Boller T. Both the Extracellular LeucineRich Repeat Domain and the Kinase Activity of FLS2 Are Required for Flagellin Binding and

Signaling in Arabidopsis. The Plant Cell 2001;13:1155.

43. Ding Z, Wang H, Liang X, Morris ER, Gallazzi F, Pandit S, *et al*. Phosphoprotein and Phosphopeptide Interactions with the FHA Domain from Arabidopsis Kinase-Associated Protein Phosphatase. Biochemistry 2007;46:2684-2696.

44. Park C.-J, Caddell DF, Ronald PC. Protein phosphorylation in plant immunity: insights into the regulation of pattern recognition receptor-mediated signaling. Frontiers in plant science 2012;3:177-177.

45. Segonzac C, Macho AP, Sanmartín M, Ntoukakis V, Sánchez-Serrano JJ, Zipfel C. Negative control of BAK1 by protein phosphatase 2A during plant innate immunity. EMBO J 2014;33:2069-2079.

46. Durian G, Rahikainen M, Alegre S, Brosché M, Kangasjärvi S. Protein Phosphatase 2A in the Regulatory Network Underlying Biotic Stress Resistance in Plants. Frontiers in Plant Science 2016;7:812.

47. 47. Halter, T., Imkampe, J., Blaum, B. S., Stehle, T., and Kemmerling, B. (2014) BIR2 affects complex formation of BAK1 with ligand binding receptors in plant defense. Plant Signaling & Behavior 9, e28944

48. Halter T, Imkampe J, Blaum BS, Stehle T, Kemmerling B. BIR2 affects complex formation of BAK1 with ligand binding receptors in plant defense. Plant Signaling & Behavior 2014;9:e28944.

49. Halter T, Imkampe J, Mazzotta S, Wierzba M, Postel S, Bücherl C, *et al*. The Leucine-Rich Repeat Receptor Kinase BIR2 Is a Negative Regulator of BAK1 in Plant Immunity. Current Biology 2014;24:134-143.

50. Liu Y, Huang X, Li M, He P, Zhang Y. Loss-of-function of Arabidopsis receptor-like kinase BIR1 activates cell death and defense responses mediated by BAK1 and SOBIR1. New Phytologist 2016;212:637-645.

51. Robatzek S, Chinchilla D, Boller T. Ligand-induced endocytosis of the pattern recognition receptor FLS2 in Arabidopsis. Genes Dev 2006;20:537-542.

52. Lu D, Lin W, Gao X, Wu S, Cheng C, Avila J, *et al*. Direct Ubiquitination of Pattern Recognition Receptor FLS2 Attenuates Plant Innate Immunity. Science 2011;332:1439.

53. Smith JM, Salamango DJ, Leslie ME, Collins CA, Heese A. Sensitivity to Flg22 Is Modulated by Ligand-Induced Degradation and de Novo Synthesis of the Endogenous Flagellin-Receptor Flagellin-Sensing 2. Plant Physiology 2014;164:440.

54. Hogenhout SA, Van der Hoorn RAL, Terauchi R, Kamoun S. Emerging concepts in effector biology of plant-associated organisms. Molecular Plant-Microbe Interactions 2009;22:115-122.

55. Kanyuka K, Rudd JJ. Cell surface immune receptors: the guardians of the plant's extracellular spaces. Current opinion in plant biology 2019;50:1-8.

56. Zipfel C. Plant pattern-recognition receptors. Trends in immunology 2014;35(7):345-351.

57. Boutrot F, Zipfel C. Function, discovery, and exploitation of plant pattern recognition receptors for broad-spectrum disease resistance. Annual review of phytopathology 2017;55:257-286.

58. Khan M, Seto D, Subramaniam R, Desveaux D. Oh, the places they'll go! A survey of phytopathogen effectors and their host targets. The Plant Journal 2018;93(4):651-663.

59. Toruño TY, Stergiopoulos I, Coaker G. Plant-pathogen effectors: cellular probes interfering with plant defenses in spatial and temporal manners. Annual review of phytopathology 2016;54:419-441.

60. Katagiri F, Tsuda K. Understanding the plant immune system. Molecular plant-microbe interactions 2010;23(12):1531-1536.

61. Dickman MB, Fluhr R. Centrality of host cell death in plant-microbe interactions. Annual review of phytopathology 2013;51:543-570.

62. Tang D, Wang G, Zhou JM. Receptor kinases in plant-pathogen interactions: more than pattern recognition. The Plant Cell 2017;29(4):618-637.

63. Yu X, Feng B, He P, Shan L. From chaos to harmony: responses and signaling upon microbial pattern recognition. Annual review of phytopathology 2017;55:109-137.

64. Meier N, Hatch C, Nagalakshmi U, Dinesh- Kumar SP. Perspectives on intracellular perception of plant viruses. Molecular plant pathology 2019;20(9):1185-1190.

65. Mur LA, Kenton P, Lloyd AJ, Ougham H, Prats E. The hypersensitive response; the centenary is upon us but how much do we know? J Exp Bot 2008;59:501-520.

66. Guttman DS, Vinatzer BA, Sarkar SF, Ranall MV, Kettler G, Greenberg JT. A functional screen for the type III (Hrp) secretome of the plant pathogen Pseudomonas syringae. Science 2002;295:1722-1726.

67. Fu ZQ, Guo M, Jeong BR, Tian F, Elthon TE, Cerny RL *et al*. A type III effector ADP-ribosylates RNA-binding proteins and quells plant immunity. Nature 2007; 447:284-288.

68. Jelenska J, Yao N, Vinatzer BA, Wright CM, Brodsky JL, Greenberg JT. AJ domain virulence effector of pseudomonas syringae remodels host chloroplasts and suppresses defenses. Curr Biol 2007;17:499-508.

69. Van der Hoorn RA, De Wit PJ, Joosten MH. Balancing selection favors guarding resistance proteins. Trends Plant Sci 2002;7:67-71.

70. Jones JD, Dangl JL. The plant immune system. Nature 2006;444(7117):323-329.