Virulence 5:7, 695–696; October 1, 2014; © 2014 Landes Bioscience

Pathogens

J Amaranath Govindan[1,2,*] and Gary Ruvkun[1,2]

[1]Department of Molecular Biology; Massachusetts General Hospital; Boston, MA USA; [2]Department of Genetics; Harvard Medical School; Boston, MA USA

A long-standing question in immunity is how the host detects pathogens. Since many microbes are also beneficial for the host, accurate discrimination between non-pathogens and pathogens is important. Traditionally, the microbe-associated molecular patterns (MAMPs) are thought to induce the innate immune response via the Toll-like receptor signaling.[1,2] Since many pathogenic as well as nonpathogenic microbes share the same MAMPs, this model is insufficient to explain why immunity is initiated only against pathogenic bacteria and not against the others. An alternative model is the so-called damage-associated molecular pattern (DAMP) hypothesis.[3,4] In this model, the host immune cells detects the DAMP signals such as the uric acid or high-mobility group box 1 (HMGB1) released by infected cells and triggers innate immune response via the Toll-like receptor signaling.[5-8] However, whether this is a bonafide response to the pathogen or the pathological response of the host is not yet clear.[5,7] Another celebrated theory on how host detects pathogens is effector triggered immunity (ETI).[9-11] First described in plants, the ETI theory suggests that the host detects virulence effector proteins from the pathogens directly or via effects on the host cellular homeostasis and responds to it by inducing beneficial innate immune responses.[9,10,12] While host "resistance" proteins that directly detect microbial effectors are found in plants, there is no evidence for such proteins in animals in the literature. In animals, recent studies provide evidence that the bacterial effectors are recognized indirectly because of their effects on cellular homeostasis.[13] Studies from worms,[14-16] flies,[10,17] and mammalian cell culture[18-20] have found that the host cells detects and responds to deficits in key cellular processes induced by the microbial effectors rather than detecting the microbes themselves. According to these studies, the pathogen-derived virulence factors or effectors or toxins induce decrement in the essential cellular processes such as protein translation or mitochondrial respiration or actomyosin cytoskeleton.[15] The host surveillance pathways detects these changes in essential cellular processes and responds to it by mounting an innate immune response as well as xenobiotic detoxification responses.[15] Since changes in these essential cellular processes are most likely to be caused by microbial virulence factors or toxins in the host's evolutionary history, an innate immune response to such an insult is a well-calculated response. In this special focus, the authors review recent developments in the effector triggered immunity field. Rajamuthiah and Mylonakis[21] review the recent studies, which provide evidence that the bacterial effectors are recognized indirectly because of the effects on cellular homeostasis. The host employs different strategies to detect pathogens including discuss on how effectors not only trigger immune response but also evade immune response or suppress immunity. Pathogenic bacteria frequently employ type secretory systems to deliver effector proteins to the host. Bacterial toxins are secreted into the immediate environment by pathogenic bacteria using either the type I, type II and type V secretory system while the type III secretion system injects the effector proteins into the host cell cytoplasm. Jayamani and Mylonakis[22] review the various effectors employed by *E.coli* and their effects on the host cellular processes. In addition, they provide detailed account on how these effectors trigger host immune response. Historically, the ETI was first described in plants. In this special focus, Wu et al.[23] comment on recent developments in how plants deploy the ETI to combat pathogens. Hurley et al.[24] review recent efforts to identify plant proteins involved in ETI using a proteomics approach. Although, initially the ETI was described as a response of plants against pathogenic bacterial effectors, recent studies have shown that plant combat fungal effectors using the same strategy. In this special focus, Chaudhari et al.[25] review how pathogenic fungal effectors and how the plants detect and initiate immune response against them. Pathogenic fungal effectors trigger immune response via modulation of cellular process; also they reprogram the host cells to induce structural changes that aid in the infection. Wang et al.[26] also discusses on how necrotrophic fungal effectors trigger innate ETI. In addition, Wang et al.[26] also provides an account on necrotrophic fungi trigger innate immune response via the classical MAMP as well as DAMP response. Wang et pathways thereby making the host hypersusceptible to the fungal infection. They discuss on how a fungal small RNA that acts as virulence effector to suppress host immune response. The relative contribution of these different pathways as well as the outcomes of the response is described in detail. Many pathogenic bacteria employ type III secretion system (T3SS) to inject effector proteins into the host cells. One of the best-known pathogen that employs T3SS to deliver virulence factors is *Yersinia*. YopM is one of the virulence factors that are delivered via the T3SS into host cells. Also, there is evidence that YopM could penetrate host cells independent of T3SS. YopM was previously thought to induce cytokine secretion by its interaction with host cell kinases RSK1 and PRK2. Hofling et al.,[27] provide evidence that the *Yersinia* effector protein YopM induce cytokine production independent of its interaction with host cell kinases RSK1 and PRK2. They propose that YopM might induce cytokine production via other unknown cellular components. Human respiratory syncytial virus (hRSV) has developed several

*Correspondence to: J Amaranath Govindan; Email: govindan@molbio.mgh.harvard.edu
Submitted: 09/23/2014; Accepted: 09/23/2014; Published Online: 10/07/2014
http://dx.doi.org/10.4161/viru.36667

strategies to interfere with critical functions of the immune system. Several hRSV proteins can modulate directly the function of either innate or adaptive immune cells. Espinoza et al.[28] review how the hRSV viral effectors dampen the immune system.

References

1. Medzhitov R. Approaching the asymptote: 20 years later. Immunity 2009; 30:766-75; PMID:19538928; http://dx.doi.org/10.1016/j.immuni.2009.06.004
2. Janeway CA Jr. Approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb Symp Quant Biol 1989; 54:1-13; PMID:2700931; http://dx.doi.org/10.1101/SQB.1989.054.01.003
3. Matzinger P. The danger model: a renewed sense of self. Science 2002; 296:301-5; PMID:11951032; http://dx.doi.org/10.1126/science.1071059
4. Vance RER, Isberg RRR, Portnoy DAD. Patterns of pathogenesis: discrimination of pathogenic and nonpathogenic microbes by the innate immune system. Cell Host Microbe 2009; 6:10-21; PMID:19616762; http://dx.doi.org/10.1016/j.chom.2009.06.007
5. Kono H, Rock KL. How dying cells alert the immune system to danger. Nat Rev Immunol 2008; 8:279-89; PMID:18340345; http://dx.doi.org/10.1038/nri2215
6. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002; 418:191-5; PMID:12110890; http://dx.doi.org/10.1038/nature00858
7. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007; 81:1-5; PMID:17032697; http://dx.doi.org/10.1189/jlb.0306164
8. Rosin DL, Okusa MD. Dangers within: DAMP responses to damage and cell death in kidney disease. J Am Soc Nephrol 2011; 22:416-25; PMID:21335516; http://dx.doi.org/10.1681/ASN.2010040430
9. Jones JDG, Dangl JL. The plant immune system. Nature 2006; 444:323-9; PMID:17108957; http://dx.doi.org/10.1038/nature05286
10. Stuart LM, Paquette N, Boyer L. Effector-triggered versus pattern-triggered immunity: how animals sense pathogens. Nat Rev Immunol 2013; 13:199-206; PMID:23411798; http://dx.doi.org/10.1038/nri3398
11. Chisholm ST, Coaker G, Day B, Staskawicz BJ. Host-microbe interactions: shaping the evolution of the plant immune response. Cell 2006; 124:803-14; PMID:16497589; http://dx.doi.org/10.1016/j.cell.2006.02.008
12. Göhre V, Robatzek S. Breaking the barriers: microbial effector molecules subvert plant immunity. Annu Rev Phytopathol 2008; 46:189-215; PMID:18422429; http://dx.doi.org/10.1146/annurev.phyto.46.120407.110050
13. Kleino A, Silverman N. UnZIPping mechanisms of effector-triggered immunity in animals. Cell Host Microbe 2012; 11:320-2; PMID:22520459; http://dx.doi.org/10.1016/j.chom.2012.04.002
14. Dunbar TLT, Yan ZZ, Balla KMK, Smelkinson MGM, Troemel ERE. C. elegans detects pathogen-induced translational inhibition to activate immune signaling. Cell Host Microbe 2012; 11:375-86; PMID:22520465; http://dx.doi.org/10.1016/j.chom.2012.02.008
15. Melo JA, Ruvkun G. Inactivation of conserved C. elegans genes engages.
16. McEwan DLD, Kirienko NVN, Ausubel FMF. Host translational inhibition by Pseudomonas aeruginosa Exotoxin A Triggers an immune response in Caenorhabditis elegans. Cell Host Microbe 2012; 11:364-74; PMID:22520464; http://dx.doi.org/10.1016/j.chom.2012.02.007
17. Boyer L, Magoc L, Dejardin S, Cappillino M, Paquette N, Hinault C, Charriere GM, Ip WKE, Fracchia S, Hennessy E, et al. Pathogen-derived effectors trigger protective immunity via activation of the Rac2 enzyme and the IMD or Rip kinase signaling pathway. Immunity 2011; 35:536-49; PMID:22018470; http://dx.doi.org/10.1016/j.immuni.2011.08.015
18. Fontana MF, Banga S, Barry KC, Shen X, Tan Y, Luo Z-Q, Vance RE. Secreted bacterial effectors that inhibit host protein synthesis are critical for induction of the innate immune response to virulent Legionella pneumophila. PLoS Pathog 2011; 7:e1001289; PMID:21390206; http://dx.doi.org/10.1371/journal.ppat.1001289
19. Fontana MF, Shin S, Vance RE. Activation of host mitogen-activated protein kinases by secreted Legionella pneumophila effectors that inhibit host protein translation. Infect Immun 2012; 80:3570-5; PMID:22851749; http://dx.doi.org/10.1128/IAI.00557-12
20. Asrat S, Dugan AS, Isberg RR. The frustrated host response to Legionella pneumophila is bypassed by MyD88-dependent translation of pro-inflammatory cytokines. PLoS Pathog 2014; 10:e1004229; PMID:25058342; http://dx.doi.org/10.1371/journal.ppat.1004229
21. Rajamuthiah R, Mylonakis E. Effector triggered immunity: Activation of innate immunity in metazoans by bacterial effectors. Virulence 2014; 5:697-702; PMID: 24802615; http://dx.doi.org/10.4161/viru.29091
22. Jayamani E, Mylonakis E. Effector triggered manipulation of host immune response elicited by different pathotypes of Escherichia coli. Virulence 2014; 5:733-739; PMID: 25090027; http://dx.doi.org/10.4161/viru.29948
23. Wu L, Chen H, Curtis C, Fu ZQ. Go in for the kill: How plants deploy effector-triggered immunity to combat pathogens. Virulence 2014; 5:710-721; PMID: 25101626; http://dx.doi.org/10.4161/viru.29755
24. Hurley B, Subramaniam R, Guttman DS, Desveaux D. Proteomics of effector-triggered immunity (ETI) in plants. Virulence 2014; 5:752-760; http://dx.doi.org/10.4161/viru.36329
25. Chaudhari P, Ahmed B, Joly DL, Germain H. Effector biology during biotrophic invasion of plant cells. Virulence 2014; 5:703-709; PMID: 24972269; http://dx.doi.org/10.4161/viru.29652
26. Wang X, Jiang N, Liu J, Liu W, Wang GL. The role of effectors and host immunity in plant–necrotrophic fungal interactions. Virulence 2014; 5:722-732; http://dx.doi.org/10.4161/viru.29798
27. Höfling S, Scharnert J, Cromme C, Bertrand J, Pap T, Schmidt MA, Rüter C. Manipulation of pro-inflammatory cytokine production by the bacterial cell-penetrating effector protein YopM is independent of its interaction with host cell kinases RSK1 and PRK2. Virulence 2014; 5:761-771; PMID: 24799669; http://dx.doi.org/10.4161/viru.29062
28. Espinoza JA, Bohmwald K, Céspedes PF, Riedel CA, Bueno SM, Kalergis AM. Modulation of host adaptive immunity by hRSV proteins. Virulence 2014; 5:740-751; http://dx.doi.org/10.4161/viru.32225