IMMUNOLOGY

Danger, Microbes, and Homeostasis

Hosts may modulate their immune response by measuring a combination of signals from pathogens and damaged tissue.

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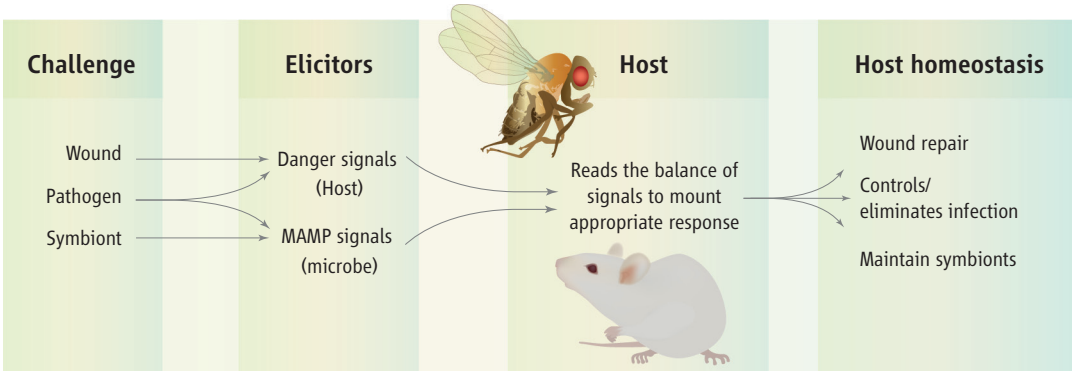
The immune system is conventionally viewed as a means to fight infection. It has become clear, however, that what is considered the "immune" system has also evolved to maintain homeostasis and regulate commensal microbes that normally inhabit the body. Such varied functions demand nuanced and context-appropriate control of immune responses. The thoughts on how immunity becomes activated include two views: by recognition of "nonself" molecules of infectious agents (*1*) or by recognition of "danger" signals—host molecules released by damaged host cells (*2*). Empirical evidence supports both models, but also reveals their limits. Insights from recent studies on insect immune systems, which are generalizable to vertebrates, suggest that the two models may be compatible. That is, a host determines the balance of nonself elicitors and danger signals to decide when to activate the immune system against pathogenic infection while also maintaining healthy relationships with commensals.

Bacterial associations with their hosts can be beneficial, damaging, or benign, depending on the context and the identity of players. It is generally believed that insects recognize bacteria through the presence of conserved molecules in the prokaryotic cell wall called "microbe-associated molecular patterns" (MAMPs). During infection, these molecules are recognized by pattern recognition receptors (PRRs) expressed by host cells, thereby triggering immune system activity and microbial elimination (*1*, *3*). The insect MAMP-PRR model is analogous to the distinction between self- and nonself molecules by the vertebrate immune system. But this concept of immunity poses a puzzle: If the immune system is hardwired to readily recognize and kill bacteria, how are symbiotic bacteria, which have enormous importance to the health and physiology of the host (*4*), maintained? Studies in insect model systems suggest that the joint presence of both MAMPs and danger signals may be required to launch a true defense response (*5*) and that insects have mechanisms for disregarding MAMPs presented in the absence of pathological damage to the host.

The animal gut is constantly exposed to potentially pathogenic bacteria that are ingested along with food. Yet, the gut is also the most important compartment of immune-modulated regulation of beneficial microbial communities that aid in digestion and nutritional assimilation (*4*). Beneficial microbes in both vertebrate and insect guts display MAMPs that are recognized by the immune system, yet immune activity is modulated such that the microbial community is actively regulated but not eliminated (*6*, *7*). Studies in the fruit fly *Drosophila melanogaster* have found that some MAMPs (peptidoglycan molecules) that are shed by bacteria in the gut induce expression of host proteins that degrade these MAMPs to a nonimmunostimulatory form (*6*, *8*). This negative-feedback loop dampens defense activity and allows the host to regulate commensal abundance without entirely eliminating the symbionts. Similar scenarios of the host inhibiting its defense response against mutualist symbionts have been described in bacteriomes, specialized organs where insects harbor mutualistic bacteria (*9*, *10*).

In addition to displaying MAMPs, true pathogens stimulate the release of danger signals by damaging host cells or secreting molecules that interfere with host biology. This combination of MAMPs and danger signals can override the homeostatic negative regulation of the insect immune system in tissues like the gut, resulting in a full-blown defense response that includes high expression of antibiotic proteins and biochemicals (*11*–*13*). Interestingly, the lower level of defense activity triggered even by commensals stimulates gut stem cell activity and epithelial renewal (*13*), providing an unexpected mechanism by which hosts and microbes interact to effect host homeostasis.



Elicitor ratio. Wounding, pathogen infection, and symbionts challenge the homeostasis of the host. A sterile wound generates exclusively danger signals, whereas symbionts display MAMPs without causing tissue damage that stimulates danger signals. Pathogens both display MAMPs and trigger danger signals, stimulating a robust immune response. The nature and strength of immune defense and homeostasis may be determined by the balance of danger and MAMP signals, combining the core tenets of the danger and infectious nonself models.

The reliance on the combination of danger signals and MAMPS to stimulate immune reactions is not restricted to gut tissues, but is a general property of defense activation. In the waxmoth *Galleria mellonella*, systemic bacterial and fungal infection results in damage to host cells and the release of collagen fragments and nucleic acids that synergize with MAMPs to stimulate an immune response (*14*). Extracellular collagen and nucleic acids are also danger signals in vertebrates (*15*, *16*). The expression of genes that encode antimicrobial peptides is induced by sterile wounding in insects, although this expression is transient in the absence of MAMPs (*17*).

The use of danger signals in combination with MAMPs may stem partly from an

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economical approach to defense. In infections, the damage caused by pathogenicity must be offset against the costs of deploying an immune response (*18*). Rather than striving to completely eliminate infections, the immune system might manage a persistent infection at a low and nondamaging level (*19*). This is analogous to the concept of "economic injury level" in agricultural pest control, whereby pests are not eradicated but are suppressed to a threshold where the cost of pest-driven damage is lower than the cost of further control. MAMPs indicate the presence of microbes, but if the microbes are doing little or no damage to the host, the cost of immune activity may exceed the benefit of clearing the infection. The presentation of damage-triggered danger signals in conjunction with MAMPs, however, indicates a severe infection that justifies the expense of a defense response.

The immune system cannot afford to be rampantly stimulated by benign foreign molecules, but needs to determine whether a signal indicates microbial nonself or danger. Insights from insect immunity point to the possibility that both types of elicitors may be important in combination. Perhaps neither MAMPs nor danger signals are by themselves a sufficient cue for optimal regulation of host immunity, but together they constitute a reliable indicator for modulating the immune response to yield both effective defense and homeostatic regulation of commensal microbial communities (see the figure). In this scenario, the two models of immune activation (*1*, *2*) as triggered by nonself versus by danger signals need not be considered mutually exclusive, but could be merged into a single model where the host reads the balance of signals to mount an appropriate immunological reaction.This measuring of signals may allow the host to effectively fight an infection, while maintaining healthy relationships with commensals.

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20. We thank O. Otti, A. Dobson, and S. Reynolds for comments on the manuscript.

10.1126/science.1200486

CELL BIOLOGY

Phosphatase Inhibition Delays Translational Recovery

A small molecule, guanabenz, increases survival of cells under stress.

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In cells, various signaling pathways help to maintain proteostasis—the proper concentrations, folding, and function of proteins. When a cell is under stress, upstream "stress sensors" within these pathways are activated, initiating a signaling cascade that minimizes the misfolding and aggregation of proteins, which can lead to disease (*1*–*3*). Stress sensors often respond to the accumulation of misfolded proteins within specific cell compartments by activating the transcription of proteostasis components, such as enzymes and "chaperone" proteins that assist with folding or by attenuating new protein synthesis. The propagation of stress-response signaling is often mediated by phosphorylation, or the addition of a phosphate group to the stress sensor and/or downstream signaling components. Because of the central importance of stress signaling pathways in maintaining the integrity of the cellular proteome, manipulating these pathways has become an attractive strategy for preventing the protein misfolding linked to numerous human diseases (*4*, *5*).

On page 91 of this issue, Tsaytler *et al*. take a step toward this goal. They demonstrate that the selective inhibition of a stress-induced phosphatase complex involved in a stress-signaling pathway that controls proteostasis in the endoplasmic reticulum (ER) increases cellular survival (*6*). This novel approach demonstrates the potential for manipulating stress-signaling cascades through direct targeting of a property that emerges from these complex signaling cascades (an emergent property), allowing for specific manipulation of stress signaling that is independent of pathways involved in general cellular homeostasis.

One of the best-characterized stress-responsive signaling pathways is called the unfolded protein response. It maintains proteostasis in the ER, where the secreted proteome is folded (*1*, *7*). The unfolded protein response comprises integrated signaling pathways that emanate from three transmembrane stress sensors localized in the ER: IRE1, ATF6, and PERK. These sensors are activated by the accumulation of misfolded proteins within the ER lumen. Activation of IRE1 and ATF6 enhances protein folding capacity within the ER lumen

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