Ticks Take Cues from Mammalian Interferon

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Interferons are considered a first line of immune defense restricted to vertebrates. In this issue of *Cell Host & Microbe*, Smith et al. (2016) demonstrate that mammalian interferon γ activates an antimicrobial response within ticks feeding on blood. The study suggests that arthropods have a parallel interferon-like defense system.

Blood-feeding arthropods such as ticks, mites, fleas, and mosquitoes transmit many different microbes to vertebrates, including humans. Unlike direct animal-to-animal transmission of pathogens, vector-borne transmission is complex and fascinating because three organisms (arthropod vector, vertebrate host, and microbial pathogen) interact in ways to promote or counter each other. In the case of Lyme disease, blacklegged ticks acquire the infection when larval or nymphal ticks feed on a mouse that is infected with *Borrelia burgdorferi*, the spirochete responsible for Lyme disease. Once infected, ticks can transmit the infection to another mouse or person during a subsequent blood meal.

Many groups have studied the complex interactions between vector, host, and the Lyme disease spirochete during transmission from an infected tick to a mouse (Caimano et al., 2016). Ticks require several days of continuous blood feeding to complete a blood meal. To promote successful blood feeding, tick salivary glands contain a veritable pharmacy of different molecules that modulate vertebrate blood physiology and immunity (Francischetti et al., 2009). Microbes transmitted by ticks are bystander beneficiaries of these activities, and many studies have demonstrated how pathogens directly and indirectly benefit from the salivary proteins of their arthropod vectors (de Silva et al., 2009). Lyme disease spirochetes also directly coat their surfaces with vector salivary molecules to evade host immunity and establish infection in the mammalian host (Narasimhan et al., 2007; Ramamoorthi et al., 2005). While we know quite a bit about spirochete transmission from tick to host, the process by which uninfected ticks acquire the infection from infected mice has been less well-studied.

In this issue of *Cell Host and Microbe*, Smith and colleagues describe an antimicrobial defense pathway in ticks that is activated by mouse interferon γ acquired in a blood meal. When blacklegged ticks fed on mice infected with the Lyme disease spirochete, interferon γ in the blood meal activated an "interferon-like" defense mechanism in the tick and controlled the spirochete infection within the tick. The broad implications of the study are that (1) arthropods have a parallel "interferon" system and (2) antimicrobial effects of vertebrate interferon can extend to arthropods during blood feeding.

To examine how ticks acquire Lyme disease spirochetes when feeding on infected mice, Smith and colleagues allowed ticks to feed on mice that were naive or infected with *B. burgdorferi* and compared the expression 270 tick genes with potential roles in immune pathways. They identified a Rho GTPase (IGTPase) that was selectively induced in ticks that fed on infected mice compared to uninfected mice. Knockdown studies established that the IGTPase controlled the burden of spirochetes within the feeding tick. The investigators also made the unexpected and intriguing observation that the tick IGTPase was induced by mouse interferon γ in the blood meal and not the actual bacteria entering the tick gut. In other words, ticks appear to be testing the "purity" of their blood meal by sensing vertebrate cytokines present in the blood.

The fundamental components of the vertebrate interferon system are a family transcription factors designated as interferon regulatory factors (IRFs), which induce the expression of interferons. Secreted interferons bind to cell-surface interferon receptors, which are linked via Janus kinase (JAK)-signaling transducer activator of transcription (STAT) signaling pathways to downstream transcription factors to increase the expression of many interferon-stimulated genes (ISGs) with specific antiviral and other effector functions. While the interferon system has long been considered a vertebrate-specific immune pathway, recent studies suggest a parallel system exists in some invertebrates as well. Li and colleagues recently described an antiviral system in shrimps with remarkable similarities to the vertebrate interferon system. This antiviral pathway in shrimps has an IRF-like transcription factor, a secreted interferon-like cytokine that activates a JAK/STAT signaling pathway, which induced the expression of proteins and an antiviral state in shrimps (Li et al., 2015). Moreover, the shrimp IRF was capable of recognizing mammalian ISG elements and inducing the expressing of mammalian ISGs.

In this most recent work, Smith and colleagues go on to demonstrate that mouse interferon γ activated the tick IGTPase in a STAT-dependent manner, providing further evidence for an interferon-like system in ticks. Activation of the pathway in ticks led to the secretion of an antimicrobial protein designated Dae2 (Domesticated amidase effector2) that suppressed the replication of Lyme disease spirochetes within the tick. It is worth noting that shrimps, ticks, and insects are all arthropods, and these studies may be the beginning of the uncovering of a parallel interferon system in this class of organisms that include blood-feeding arthropods.

Another interesting twist to this study is the fact that Dae2 is an antimicrobial peptide that ticks have acquired from prokaryotes (Dunning Hotopp and Estes, 2014). Chou et al. recently described many examples of horizontal gene transfer of antimicrobial peptides between

bacteria and eukaryotes (Chou et al., 2015). The emerging theme from these studies is that eukaryotes, including ticks, have been able to augment their innate immune defenses by acquiring prokaryotic antimicrobial genes and incorporating them into existing defense pathways. Thus, arthropods appear to have interferon-like systems that have been augmented by horizontal gene transfer from prokaryotes and that can cross-communicate with vertebrate interferons.

The next step is to determine if these examples from ticks and shrimps are interesting outliers or representative of a widespread parallel interferon system in arthropods. It is conceivable that the system may be nonfunctional in some species and well-developed in others, especially arthropods that rely on vertebrate blood as their main food source. In vertebrates, the primary role of the interferon response is to defend against viruses, and similarly the system may also have evolved in arthropods primarily as an antiviral defense mechanism. We need to explore if arboviruses such as dengue, Zika, tick-borne encephalitis, and chikungunya are also regulated by cross-talk between interferon systems in their arthropod vectors and vertebrate hosts.

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