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RESEARCH HIGHLIGHT

The scent of a microbe: how host viral infection increases mosquito attraction

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Dengue and Zika are mosquito-borne viruses, requiring mosquito contact for infection. In a recent *Cell* article, Zhang et al. show that when mice and humans are infected with these viruses, skin production of the antimicrobial protein RELMα drops, allowing colonization with *Bacillus* spp. that generate a volatile small molecule called acetophenone, which increases mosquito seeking behavior to infected host skin.

Arboviruses have a complex life cycle. For these viruses to propagate, they must transit between arthropod vectors, such as mosquitos, and the vertebrate host. Thus, it is beneficial for mosquito-transmitted arboviruses to stimulate greater contact between mosquitos and virally infected hosts.[1] In the malaria life cycle, a parasite similarly infects humans through a mosquito vector. To increase the chances of transmission, the malaria parasite (*Plasmodium*) can change the odor of its infected host, leading to greater feeding behavior of mosquitos in the environment.[2,3] In a recent publication in *Cell*, Zhang and colleagues used mechanistic experimentation to determine whether a similar process occurs in arbovirus infections.[4]

Dengue and Zika are arboviruses that belong to the flavivirus genera. To determine whether viral infection impacted mosquito attraction, the authors used a three-cage olfactometer assay, where mosquitos were placed in a central chamber, with free access to two other flanking chambers. Mosquitos were able to select chambers with the odorants obtained from the air stream of mice infected with Dengue, Zika, or uninfected controls. For both laboratory strains of *Aedes aegypti* and strains obtained from the wild, the air stream from infected mice attracted more mosquitos. Next the authors deodorized the chamber with activated charcoal and a Super Q 80/100 mesh. In the absence of volatile small molecules, no difference was seen in the number of mosquitos that selected the air stream of the infected mice compared to the uninfected mice. These experiments show that flavivirus infection increases the attraction of mosquitos to infected mice through the production of a volatile odorant produced at the skin surface. (Fig. 1)

To probe this process further, the authors completed GC-MS/MS analysis of the odorants from Zika- or Dengue-infected mice, identifying 422 unique compounds. They honed in on the subset of small molecules that were significantly more or less abundant in infected mice compared to uninfected mice. To narrow down the list of candidate molecules further, they tested the ability of this set of molecules to cause electrical brain activity in the mosquito antenna, through electroantennography. Three odorants had the capacity to stimulate an electrophysical response in mosquitos and only one compound, acetophenone, had the ability to attract mosquitos when painted onto the skin of uninfected mice or the hand of human study subjects. Moreover, mice infected with Dengue or Zika, produced 10-fold greater amounts of acetophenone, compared to uninfected controls. Humans with dengue fever also had greater amounts of acetophenone in their armpits compared to control patients. Fever alone has been shown to change the production of volatile small molecules,[5] but using mouse models the authors were able to demonstrate that fever alone was not able to impact the differences seen between infected and uninfected mice.

As acetophenone has been characterized as a metabolic byproduct in bacteria,[6] the authors hypothesized that this odorant might originate from the skin microbiota. Indeed, when the skin microbiota was depleted by sonication brushing and spraying with 70% alcohol, mosquitos no longer displayed a preference for flavivirus-infected mice in the three chamber olfactometer experiment. Removal of the gut microbiota had no impact on mosquito attraction. Specific species of *Bacillus* have the capacity to generate acetophenone and were present at greater abundance in mice infected with flaviviruses. Thus, these experiments demonstrated that flavivirus infection drives changes in skin that allow for increased colonization with *Bacillus* spp. that generate the odorant acetophenone, which attracts mosquitos to the skin surface.

Using RNA-sequencing, the authors went on to determine how flavivirus infection alters the skin's transcriptional landscape. Dengue- and Zika-infected mouse skin showed large shifts in the expression of numerous metabolic genes, including *Fasn*, *Lpl*, and *Leptin*. Notably, mice infected with either Zika or Dengue virus also had lower expression of the antimicrobial protein, RELMα. RELMα is a member of the Resistin family of proteins expressed by epithelial cells, adipose tissue, and immune cells. Resistin was originally characterized for its role in metabolic phenotypes[7] and more recently has been shown to have bactericidal function in the gut and in the skin.[8,9] In this study, Zhang et al. confirm the bactericidal activity of RELMα, demonstrating that RELMα can kill the *Bacillus* species capable of generating acetophenone during flavivirus infections and suggesting that the decrease in RELMα during infection may drive the shift in the skin microbiota

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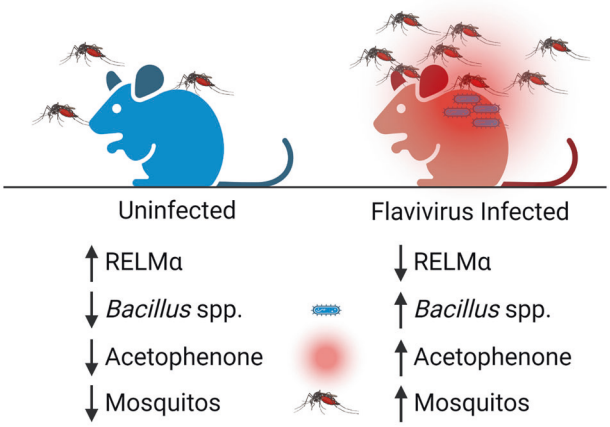

Fig. 1 Flavivirus infection impacts the microbiota through regulation of RELMα in the skin. During flavivirus infection, skin production of the antimicrobial protein RELMα decreases, allowing colonization with *Bacillus* spp. that generate the volatile molecule acetophenone. In turn, acetophenone attracts mosquitos to infected host skin.

observed in their experiments. RELMα expression requires vitamin A in the diet and treatment of mice with a synthetic vitamin A derivative isotretinoin boosts RELMα expression.[9] Thus, when flavivirus-infected mice were treated with isotretinoin, RELMα expression increased, *Bacillus* spp. were less abundant at the skin surface, and mosquitos were less attracted to infected skin. Retinoids do have broad impacts on the skin; thus future studies should test whether removal of RELMα in a knockout mouse model would be sufficient to drive expansion of *Bacillus* species and shift acetophenone production, or whether other changes at the skin surface during flavivirus infections are also required to allow for *Bacillus* colonization.

These series of experiments confirm the key function of vitamin A in regulating the expression of RELMα, as shown by Harris and colleagues in 2019.[9] However, neither study examined how retinoids, or vitamin A deprivation impacts the skin microbiota. In humans, it has been shown that an extended treatment with isotretinoin leads to skin dryness and shifts in the skin microbiome composition.[10] Additional studies should be completed to determine how short courses of isotretinoin treatment impact the microbiota and determine whether retinoids have therapeutic potential for infectious diseases.

Taken together, the experiments completed by Zhang and colleagues also reveal the centrality of the skin microbiota in the generation of small molecules that impact the interaction of the host with its environment. Though studies have been completed demonstrating an array of volatile small molecules present at the skin surface and their correlation with the microbiota,[11] fewer studies have resolved mechanistically how these metabolites impact the behavior of vertebrate-seeking organisms, or social interactions within species. This study shows that arboviruses stimulate production of a chemoattractant through immunological manipulation of the skin microbiome, thus attracting more mosquitoes and ensuring their own transmission.

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ADDITIONAL INFORMATION

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