Malaria infections may be masking the extent of the emerging chikungunya epidemic

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Chikungunya virus is rapidly spreading around the world and encroaching into areas already plagued by malaria, which means that more people are falling ill with cases of both mosquito-borne infections. That might sound dire, but according to a new study by A*STAR scientists, prior exposure to malaria may help protect against complications of chikungunya.

That is the good news. The downside, according to Lisa Ng, a viral immunologist at the A*STAR Singapore Immunology Network (SIgN) who co-led the study, is that the protective benefit is probably masking the true scale of the global chikungunya epidemic—and as public health campaigns continue to aggressively target malaria without consideration of chikungunya, there could be unintended consequences.

"In co-endemic regions," Ng says, "a reduction in malaria cases could indirectly result in an increase in clinical cases of chikungunya fever."

To explore the health effects of co-contagion, Ng teamed up with SIgN executive director Laurent Rénia to infect mice with both the chikungunya virus, which causes fever and severe joint pain and two forms of rodent Plasmodium parasite responsible for malaria, one of the world's deadliest diseases. In a previous paper, the researchers had shown that co-infection with chikungunya protected the mice from the worst ravages of malaria. In this study, they considered the impact that malaria has on the extent of chikungunya-associated joint swelling.

Reporting in *Nature Communications*, the A*STAR team found that mice pre-infected with Plasmodium and then exposed to chikungunya virus four days later did not exhibit joint inflammation—and this was true whether the malaria parasite was an aggressive species that caused fatal brain swelling or a milder species that causes a non-lethal form of the disease. Furthermore, these mice also showed reduced levels of the chikungunya virus in the blood.

The protective effects were less pronounced among mice infected with both malaria and chikungunya at the same time. In that case, peak joint swelling declined, but the amount of chikungunya virus in the bloodstream was the same as in mice exposed to chikungunya virus alone. No beneficial effects were seen in mice that had completely recovered from a malarial infection, or when malaria was introduced four days after the chikungunya virus when the latter infection was already in full swing.

To explain their observations, the researchers looked closely at the immune mechanisms by which prior or concurrent exposure to malaria parasites safeguards against chikungunya virus-induced joint damage. They found that Plasmodium infection stimulated the production of a critical immune-modulating molecule called interferon-gamma that primed joint cells to be on the alert for viruses like chikungunya. The prior Plasmodium exposure also limited the number of pro-inflammatory T cells that normally infiltrate joint tissue and drive swelling in response to the virus.

Malaria's impact on the immune system was not all favourable for fighting chikungunya, though. Co-infection with Plasmodium also restricted the maturation of B-cells that are needed to make chikungunya-fighting antibodies. The team speculates that this could harm the immune system's ability to mount an adequate response should the body face a second infection with the virus.

To recreate only the immunological benefits of co-infection, without the negative consequences for B-cells (or having to expose people to dangerous viruses), Ng proposes a new drug strategy. Based on her team's finding that a cell signaling receptor protein called CXCR3 mediates the migration of pro-inflammatory T cells to the joints following chikungunya virus infection—and also to the brain following Plasmodium infection—she suggests targeting this receptor with drugs.

"Currently, there are several small molecules that could antagonize CXCR3 in patients," Ng says. "Perhaps the use of CXCR3-targeted therapies could be considered in regions where the diseases are co-endemic."

More information: Teck-Hui Teo et al. Plasmodium co-infection protects against chikungunya virus-induced pathologies, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06227-9

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