Activation of two different innate immune responses spotted in measles cases

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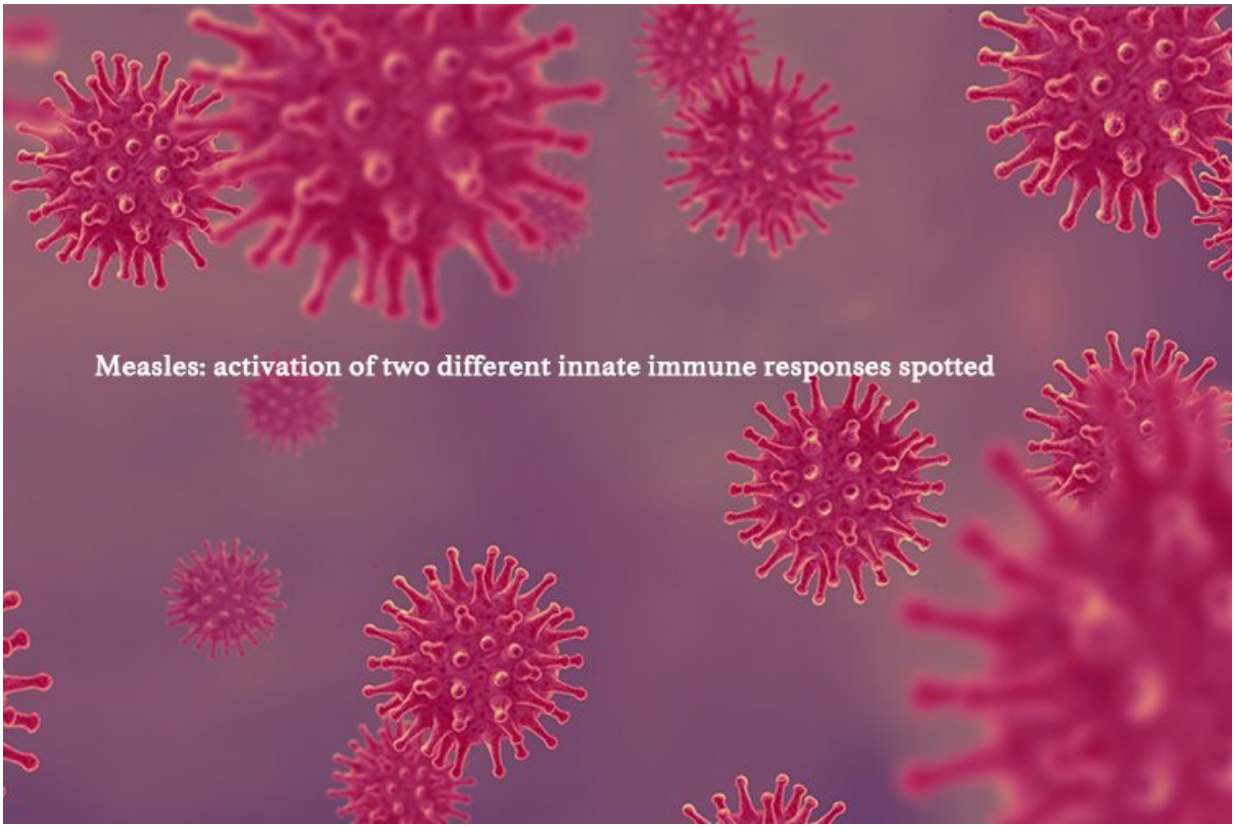

Researchers from The University of Tokyo Institute of Industrial Science describe a novel feature of the immune response to certain viruses such as measles. Credit: Institute of Industrial Science, the University of Tokyo

Researchers from The University of Tokyo Institute of Industrial

Science have found that infection with the measles virus activates not one but two branches of the innate immune system. This is because of the effect of the measles virus on mitochondria.

Measles is a significant disease worldwide, causing high levels of child mortality. Viral genomes can be made of either RNA or DNA, and the host immune response to each differs. RNA viruses such as the measles virus activate a molecule called RIG-I, whereas DNA viruses activate a different molecule called cGAS. These molecules then trigger a cascade of activation of other molecules such as interferon, leading to an immune response to the virus.

The team have now shown that infection with measles virus leads to the activation of both the RNA and DNA virus immune responses. Measles virus affects the mitochondria within the cell, interfering with their growth and division and causing them to fuse together. Mitochondria are essential for cellular energy production and contain a small circular DNA molecule, and the actions of the measles virus cause this mitochondrial DNA to be released into the cell. This release of DNA into the cytoplasm of the cell, where usually no DNA is found, triggers the cGAS immune response just as a DNA virus would. This response occurs after the immune response to RNA viruses caused by the measles virus itself.

"We first showed mitochondrial abnormalities in measles-infected cultured cells using imaging techniques," says lead author Hiroki Sato. "Then we confirmed the presence of mitochondrial DNA in the cytosol of infected cells through biochemical analysis, and then carried out experiments on mice lacking the cGAS protein to show that the immune response was also caused by the cGAS pathway."

This is the first time that single and negative strand RNA viruses have been shown to activate the cGAS pathway. "We suggest that there are

two steps to measles infection," says senior author Chieko Kai. "In the first, early phase, viral RNA replication is detected by the RNA-sensing immune response, and then in a second, later phase, mitochondrial downregulation and release of mitochondrial DNA cause prolonged interferon production."

The team then found evidence in previously published datasets to suggest that this response can also be triggered by other viruses that affect the growth and development of mitochondria. They therefore suggest that this is an important host mechanism for a full immune response to such viruses. Increased understanding of how the body works to combat an infection such as measles may help to eradicate this disease for good.

The article, "Downregulation of mitochondrial biogenesis by virus infection triggers antiviral responses by cyclic GMP-AMP synthase," was published in *PLOS Pathogens*.

More information: "Downregulation of mitochondrial biogenesis by virus infection triggers antiviral responses by cyclic GMP-AMP synthase", *PLOS Pathogens* (2021). DOI: 10.1371/journal.ppat.1009841

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