Scientists find measles' natural nemesis

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Scientists at The Scripps Research Institute have found that a known enzyme in cells protects against measles virus, likely by altering the virus's genetic material, RNA. Cells lacking the enzyme become highly vulnerable to the virus's destructive effects. The enzyme also protects against several other respiratory viruses, including influenza A.

"We believe that host cells use this RNA-editing enzyme to slow these viruses' ability to replicate," said Michael B. A. Oldstone, the study's senior author and a professor at Scripps Research's La Jolla, California campus. The study's first authors are Simone V. Ward, a senior research associate in the Scripps Research Oldstone laboratory, and Cyril X. George of the University of California, Santa Barbara.

The finding represents a significant improvement in the understanding of measles infections, which still kill about 150,000 children and adults around the world every year. The paper, which was published recently in Proceedings of the National Academy of Sciences, has prompted commentaries in the journals *Nature Reviews Microbiology* and *Viruses*.

The focus of the study was the enzyme ADAR1 ("adenosine deaminase acting on RNA, 1"), which is known to be produced in high amounts in measles-infected cells. ADAR1 has been suspected as a "restriction factor" that inhibits viral replication.

ADAR1's role against measles has been difficult to nail down, however. In mice genetically engineered to be infectable by measles – a virus that normally infects only humans – ADAR1 is required for embryonic

development, as in all mice. Thus the standard "gene knockout" technique, which would enable scientists to see how measles infections proceed without ADAR1, hasn't been feasible.

In this study, Ward, George, and Oldstone, and their colleagues knocked out only one of the two forms of ADAR1 produced in cells. This form, p150, is the one produced in response to infections. For reasons that still aren't clear, mouse embryos cannot grow for long without p150, so the researchers used a standard technique to "immortalize" these p150-knockout embryonic cells—ensuring their continuous supply—and in this way created a useful cell model.

When infected by measles virus, the p150-knockout cells succumbed quickly compared to immortalized control cells that produced p150 normally. "When I looked at the cells only 21 hours after infection, the p150-knockout cells already showed the signs of cell damage typical of measles infection," said Ward. "But the control cells looked exactly like uninfected cells."

In further tests, Ward found p150 also provided significant protection for cells against Newcastle disease virus, Sendai virus, canine distemper virus, and influenza A virus – which are all respiratory viruses like measles, and all members of the paramyxovirus or orthomyxovirus families.

Nine years ago, it was reported that a cellular enzyme known as APOBEC3G protects cells from DNA-based viruses such as HIV, by mutating viral genes. "We're now showing that an analogous gene-editing enzyme also seems to exist for RNA viruses," said Oldstone.

With the new cell model, and advanced "conditional knockout" techniques that allow genes to be disrupted in specific organs in adult mice, Ward, Oldstone, and their colleagues now hope to study

ADAR1-p150's role in more detail.

One key issue to be resolved is the enzyme's role during brain infections. Measles virus usually results in a relatively mild illness lasting only a week or two, but in rare cases it spreads to the brain and becomes a persistent, always fatal infection known as subacute sclerosing panencephalitis (SSPE). In such cases, the virus doesn't have to spread via cell-to-cell contact, thus exposing itself to the immune system; it can spread more stealthily along the axons and dendrites that connect neurons.

"What we hope to show with our ongoing work is that host neurons are using ADAR1 to slow down this process, turning it into a gradual neurological disease," said Oldstone. ADAR1 might also be exacerbating the neurological symptoms of SSPE, he adds, because its enzymatic activity is known to affect the production of the important neurotransmitter receptors for serotonin and glutamate: "It's an enzyme that has multiple roles," Oldstone concluded.

More information: In addition to Ward and Oldstone, authors of the paper, "RNA editing enzyme adenosine deaminase is a restriction factor for controlling measles virus replication that also is required for embryogenesis," are, Megan J. Welch, Li-Ying Liou, Juan C. de la Torre, and Hanna Lewicki of Scripps Research; Bumsuk Hahm of Scripps Research and the University of Missouri; and Cyril X. George and Charles E. Samuel of the University of California, Santa Barbara. For more information, see www.pnas.org/content/108/1/331.abstract

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