New defense mechanism against viruses discovered

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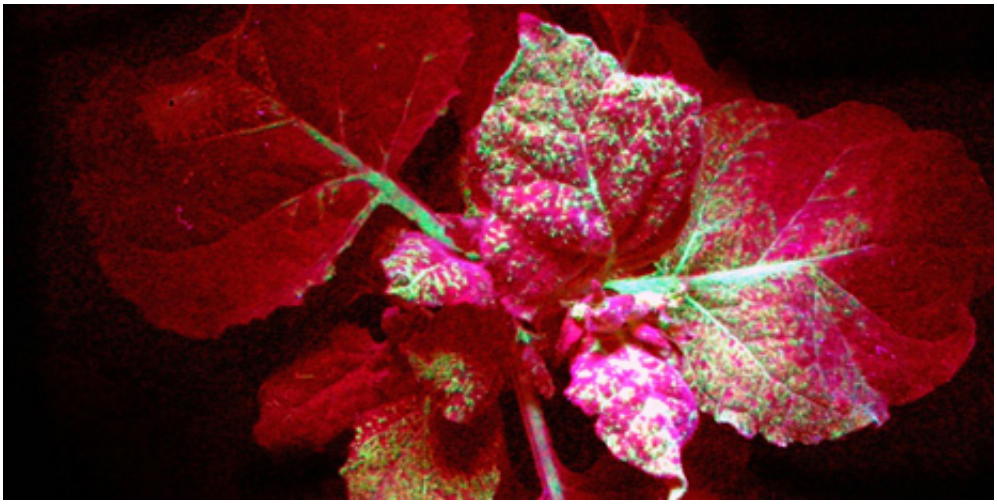

Tabaco plant infected by potato virus X. Photograph from an experiment in which virus infected areas are fluorescing green under UV light. Credit: Garcia et al. Cell Host & Microbe 2014

Researchers have discovered that a known quality control mechanism in human, animal and plant cells is active against viruses. They think it might represent one of the oldest defense mechanisms against viruses in evolutionary history.

When it comes to defence against viruses, the immune system has an arsenal of weapons at its disposal including killer cells, antibodies and messenger molecules, to name just a few. When a pathogen attacks the body, the immune system usually activates the appropriate mechanisms.

However, some of the mechanisms do not have to be triggered; they are continuously active as a standing army. Researchers from ETH Zurich, in collaboration with scientists from the University of Bern, have now discovered a new form of this so-called innate immune defence. They have shown that it acts against particular viruses with a genome in the form of single-stranded, positive-sense RNA. Many known pathogens, such as hepatitis C, tick-borne encephalitis, polio, SARS, yellow fever and dengue fever viruses belong to this group, as well as potyviruses, a group of plant viruses that can cause severe damage to economically important crops.

Researchers led by Ari Helenius, Professor of Biochemistry at ETH Zurich, discovered the mechanism during their research with human cells in cell culture and a model virus that is frequently used in basic research, the Semliki Forest virus. In an extensive screening process, the scientists turned off individual genes inside host cells; they discovered that the cells were more susceptible to infection by the virus if the genes of a cellular quality control and regulatory system for RNA, known as NMD (nonsense-mediated mRNA decay), were turned off.

Viruses identified as incorrect cellular RNA

In a parallel large-scale screening effort, Olivier Voinnet, Professor of RNA Biology at ETH Zurich, and his colleagues realised that this mechanism is also acting against viruses in plants. They used the model plant Arabidopsis thaliana and potato virus X for their investigation. Helenius and Voinnet's groups have published their two research papers on human cells and plants in the latest edition of the journal *Cell Host & Microbe* – the former in collaboration with the group of Oliver Mühlemann, a professor at the University of Bern, who has dealt intensively with the NMD system in recent years.

The NMD system has been known for some time in biology as a quality

control and regulatory mechanism that eliminates incorrectly fabricated and non-functional messenger RNA molecules in cells. However, the new studies show that this system also serves a second function: It ensures that the genome of certain RNA viruses is broken down, thereby preventing them from replicating in host cells. "The RNA genome of these viruses bears certain similarities to incorrect messenger RNA molecules in human, animal and plant cells and is identified as such by the NMD system," explains Giuseppe Balistreri, post-doctoral fellow and lead author of one of the two studies.

Oldest defence mechanism

The researchers believe that the NMD system provides a first line of defence against infection by this class of viruses. "The mechanism attacks the viral genome directly before it can multiply in the host cell," say both Helenius and Voinnet. The ETH scientists also believe that this is one of the oldest defence mechanisms against viruses in evolutionary history, as the NMD system is so fundamental that it is found in all higher organisms; i.e. people, animals, plants and fungi.

However, the mechanism is not 100 per cent efficient. "If it were, then RNA viruses wouldn't exist at all," says Helenius. Instead, the viruses have evolved ways to avoid or actively suppress the NMD system, as both ETH research groups suggest in their respective studies. "Viruses and their hosts are engaged in an endless battle, of which the NMD system is a previously unsuspected yet significant component," says Voinnet. "In this battle, the NMD mechanism likely contributed to shape the genomes of RNA viruses as we see them today."

NCCR RNA & Disease

The two research projects were carried out within the National Centre

for Competence in Research (NCCR) RNA & Disease. Sixteen research groups from five Swiss universities are working together in this focus area of the Swiss National Science Foundation. They are studying the role of RNA biology in diseases. The University of Bern is the NCCR's leading house and ETH Zurich is the co-leading house.

More information: Balistreri G, Horvath P, Schweingruber C, Zünd D, McInerney G, Merits A, Mühlemann O, Azzalin C, Helenius A: The Host Nonsense-Mediated mRNA Decay Pathway Restrics Mammalian RNA Virus Replication. *Cell Host & Microbe* 2014, 16: 403-411, DOI: 10.1016/j.chom.2014.08.007

Garcia D, Garcia S, Voinnet O: Nonsense-Mediated Decay Serves as a General Virus Restriction Mechanism in Plants. *Cell Host & Microbe*, Online publication 21 August 2014, DOI: 10.1016/j.chom.2014.08.001

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