

Crossing barriers: How the rabbit virus myxoma leapt into a new species

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A pair of European rabbits. Although the natural hosts of the MYXV virus are *Sylvilagus* rabbits (known in the Americas as cottontails), exposure of European rabbit populations to this virus proved 99% fatal, without any further adaptation of the virus to the European rabbit host. The highly contagious virus, spread through rabbit populations by fleas or mosquitos, produces a lethal rabbit disease known as myxomatosis. MYXV-Tol was found to cause a very similar lethal disease in hares. Credit: Public Domain

Viruses are among the most protean entities in nature, ceaselessly mutating and acquiring new characteristics. These tiny entities follow a simple and relentless imperative: infect as many host organisms as possible. Occasionally, a virus' genomic alterations enable it to leap from one species to another, in a process known as spillover.

In new research appearing in the journal *mBio*, Masmudur Rahman and his Arizona State University colleagues join international researchers to investigate one such spillover event, when the myxoma [virus](#) (MYXV) made a species leap from European rabbits to Iberian hares.

The study describes M159, a [virus protein](#) called a "host range factor" that arose very recently through a fortuitous gene pickup in the myxoma virus. The resultant hybrid strain, known as MYXV-Tol, has enabled the virus to expand its existing host range, traversing the species barrier and causing lethal disease in Iberian hares.

Researchers would like to better understand these genomic transitions, as spillover events have profound implications for both human and animal health. One such recent event, caused by mutations in a novel, SARS-like virus of unknown origin, is responsible for the global pandemic of COVID-19 disease, which has killed over five million people globally.

Understanding the subtle alterations enabling viruses to make species jumps may help better prepare for outbreaks of new diseases, limit their transmission, and perhaps allow researchers to outwit viral mechanisms that set the stage for spillover events. Human-engineered therapies against pathogens (including viruses) are part of a never-ending arms race between infectious agents and their host organisms.

In addition to its importance for the study of host- pathogen coevolution, myxoma virus has been investigated for its remarkable ability to target and kill human cancer cells, while leaving their normal healthy cell

counterparts unharmed. It is one of the most promising viruses available in the new field of virotherapy, which uses cancer fighting or oncolytic viruses, including myxoma.

The new study suggests that the M159 protein not only enables MYXV-Tol to leap over the species barrier and infect hares but also appears to help this strain replicate even better in human cancer cells, potentially improving MYXV as a cancer-fighting agent.

"M159 protein is a member of the poxvirus C7-like host range factors. In the future, identifying the protein(s) that interact with M159 in hares and human cancer cells will allow us to understand whether M159 targets similar or diverse signaling pathways," said Rahman.

Rahman is a researcher in the Biodesign Center for Immunotherapy, Vaccines and Virotherapy at ASU. He is joined by Grant McFadden, director of the center and by Arvind Varsani, a researcher in the Biodesign Center for Fundamental and Applied Microbiomics. McFadden, Varsani and Rahman are also researchers in ASU's School of Life Sciences. Additional ASU researchers include first author Ana Agueda-Pinto, Simona Kraberger, Anne Everts, Ami Gutierrez-Jensen and Honor L. Glenn.

Collaborators on the new study include researchers from Universidade do Porto, Vairão, Portugal; Universidad de Oviedo, Campus El Cristo, Oviedo, Spain; and (IRIAF), CIAG del Chaparrillo, Ciudad Real, Spain.

Specialized killer

In studying the mechanisms underlying the ability of viruses to cross species barriers, researchers rely on model organisms. The myxoma virus is a particularly attractive candidate for such investigations and is the most extensively researched field model for this type of study. This

fact is due to a historical event in which MYXV was used to control populations of European rabbits in Europe and Australia, beginning in 1950.

MYXV belongs to the poxvirus family of viruses, a very large assemblage of double-stranded DNA viruses which includes many benign members as well as the virus that once caused the notoriously lethal disease smallpox.

Many kinds of [viruses](#) have spillover potential. Annual outbreaks of influenza, for example, are the result of spillover events occurring when migratory birds, acting as reservoirs for the virus, spread the disease to other species, including ducks, chickens, pigs and humans. As the virus moves from species to species, mutating strains acquire new abilities to aid their transmission and ability to evade host immune defenses.

Although the natural hosts of the MYXV virus are *Sylvilagus* rabbits (known in the Americas as cottontails), exposure of European rabbit populations to this virus proved 99% fatal, without any further adaptation of the virus to the European rabbit host. The highly contagious virus, spread through rabbit populations by fleas or mosquitos, produces a lethal rabbit disease known as myxomatosis. MYXV-Tol was found to cause a very similar lethal disease in hares.

Over the long term, the rabbit control strategy with MYXV failed, as evolutionary selective pressures acting on both the virus and host resulted in MYXV-resistant rabbits and attenuated virus variants. Nevertheless, MYXV provides a valuable laboratory tool for the study of the poorly understood dance between [infectious agents](#) and the molecular transformations used by species to thwart them.

"Every time a virus leaps from one host species into another, we learn something new about Mother Nature," McFadden says. "In the case of

MYXV-Tol, we learned that the acquisition of a single new virus gene allowed this new virus strain access to a new host species that was previously resistant to the virus".

New virus on the block

Evidence suggests that Iberian hares had long been exposed to MYXV or a similar virus since at least the 1990's, with no resulting outbreak of myxomatosis occurring. Then, an altered virus strain known as MYXV-Tol appeared, seemingly out of nowhere. This new variant showed high similarity to the previously endemic form of the virus, known as MYXV-Lau, with one notable genomic exception. The new strain had acquired a small suite of new genes, which it acquired through recombination with an as-yet-unidentified poxvirus. The result was a supercharged variant that proved both infectious and highly lethal to hares living on the Iberian Peninsula, killing hundreds of them beginning in the Autumn of 2018.

Among the genes found in the MYXV-Tol variant was a gene coding for a protein known as M159. The new study explores this single protein as a possible culprit in MYXV-Tol's species-hopping capacity. The researchers examined laboratory cell lines of rabbit, hare and human cells exposed to MYXV variants with and without the M159 protein.

While strains containing the novel protein did not appear more infectious to cells of European rabbits, the M159-containing strains were now highly infectious to cells from European hares, whereas strains without the protein were not, establishing M159 as the key ingredient allowing MYXV to cross the species barrier.

The study also tested two human cancer cell lines that are normally resistant to MYXV, exposing them to the M159-enhanced version. The results were dramatic. Human pancreatic cancer and melanoma cells are

typically semipermissive or nonpermissive to MYXV, meaning that the virus usually replicates poorly in these cell types. However, when the M159 protein was inserted into the MYXV-Lau strain, viral replication in both cancer cell lines was significantly enhanced, suggesting the protein could be used to improve MYXV as a cancer-fighting agent against some classes of human tumors.

Further research promises to shed new light on the highly pathogenic MYXV-Tol variant as well as illuminate the mechanisms used by other poxviruses to spillover into new animal species, including humans.

More information: Ana Águeda-Pinto et al, Identification of a Novel Myxoma Virus C7-Like Host Range Factor That Enabled a Species Leap from Rabbits to Hares, *mBio* (2022). [DOI: 10.1128/mbio.03461-21](https://doi.org/10.1128/mbio.03461-21)

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