Trial and error in viral evolution: The difference between fading out, pandemic

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Viruses evolve quickly. A small tweak to the genetic makeup of a mostly mild strain of influenza can give rise to the next pandemic. An equally small change to the same strain in a different setting can fade it into obscurity. The right trait at the right time is everything.

A group of scientists from the Virginia Tech Carilion Research Institute, the Virginia-Maryland College of Veterinary Medicine, the National Institutes of Health, and Yale University are studying exactly how viral evolution occurs, and how that knowledge might help prevent disease.

They published their conclusions today in *Nature Reviews Microbiology*.

The researchers analyzed multiple studies on three well-known and varied viral families, all of which have genomes that consist of segments of genetic material called RNA. RNA viruses are ubiquitous in nature, infecting most animals, including humans, plants, and bacteria.

Viruses have large populations and fast replication cycles, so they make ideal models to study evolution. Changes appear quickly. In a matter of weeks, researchers can test whether a mutation or particular genetic combination becomes desirable for the offspring virus under controlled laboratory conditions.

"Genetic diversity is the clay that selection pressure molds in the process of evolution," said Sarah McDonald, an assistant professor at the Virginia Tech Carilion Research Institute and an author on the paper.

"We're learning how viruses molecularly regulate their genetic diversity, and how various selection pressures allow for the emergence of some strains over others."

Segmented RNA viruses can replicate with a single parental line, but they can also reshuffle their segments with another virus to create a hybrid virus in a process called reassortment.

"Conceptually, reassortment shares some features with sexual reproduction in more complex organisms," said McDonald, who is also an assistant professor at the Virginia-Maryland College of Veterinary Medicine. "Two parent viruses infect one host cell and swap genetic material, resulting in a genetically different offspring virus."

Whether for humans or viruses, there's an obvious evolutionary advantage of having two separate gene pools convene: increased genetic diversity. The offspring have the potential to contain the right mix of their parents' traits to better adapt to their current environment. However, there's also the possibility that the offspring will fare worse than their parents.

"The progeny virus needs to be at least as fit, if not fitter, than its parents," McDonald said. The intrinsic capacity to replicate, as well as how well the virus can resist a host's immune system are only two of the pressures that can decide whether the new virus will become a pandemic or just die out.

In their review, the researchers noted that RNA viruses from different genetic families have not been observed reassorting, even when they infect the same host cell. It'd be like a houseplant crossbreeding with a fish. There are the physical limitations, but more importantly the genes are incompatible.

Yet, even in genetically similar viruses, restrictions limit the rise of new strains. In influenza A, for example, the reassorted segments of RNA coded to a specific function are packaged together.

Three different segments all have a role to play in how the virus packages its replicated genetic material, so if one of the segments is included in the new virus, so are the other two segments. That limits the possible genetic options since it's impossible for one segment to join two new segments to make a completely original combination.

"It's likely that molecular failures at the level of segment assortment and packaging are one major reason for the lower-than-expected frequency of reassortments in the laboratory setting," McDonald said. "Subtle differences in how the RNA interacts may result in the successful reassortments that result in hybrid progeny."

The researchers linked trends across the three viral families, and they're working to understand how the viruses increase their genetic diversity and how selection pressures act on that diversity to promote or temper the emergence of newer, possibly more deadly viral variants in nature.

"Some key outstanding questions remain unanswered, but we may discover the answers within the scope of current research studies," McDonald said. "With those answers, we'll not only inform disease prevention and control strategies, but we'll also be able to shed light on our basic understanding of organismal evolution."

More information: Reassortment in segmented RNA viruses: mechanisms and outcomes, *Nature Reviews Microbiology* (2016) DOI: 10.1038/nrmicro.2016.46 , www.nature.com/nrmicro/journal … nrmicro.2016.46.html

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