Blocking 'gateway mutations' could prevent polio vaccine from re-evolving virulence

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Credit: National Cancer Institute

A relentless vaccination campaign has succeeded in eradicating the polio virus from most of the world, reducing the burden of the disease by 99 percent since the year 2000 and preventing more than 13 million children from contracting the disease, according to World Health Organization estimates. However, in regions where vaccination has remained incomplete, on rare occasions the weakened virus used in the vaccine has evolved the ability to escape the vaccinated person and spread to other, unprotected individuals.

Now a new study led by researchers at UC San Francisco and Tel-Aviv University in Israel has revealed that in every vaccine-derived polio outbreak, the polio virus used the same three evolutionary steps to evolve from harmless vaccine into a regional menace. In the new study – published online March 23, 2017, in *Cell* – the researchers mapped out these key steps, identifying so-called "gatekeeper mutations" that must occur before the vaccine can evolve and regain full virulence. They have used this knowledge to develop a new polio vaccine that should be unable to escape and cause outbreaks, which they hope to put into clinical trials soon.

"If one could get everyone fully vaccinated, this would prevent the virus from being able to spread and evolve, but particularly in areas of the world that are riddled with conflict and poverty, it is very hard to get full coverage," said Raul Andino, PhD, a professor of microbiology and immunology at UCSF and senior author of the new study. "Thus, it has been critical to understand how the virus manages to evolve virulence, and come up with strategies to stop it."

Live Vaccine Advantages

Polio eradication efforts in many parts of the world have relied on an oral vaccine consisting of an "attenuated" virus whose ability to reproduce and spread in humans has been significantly weakened. In contrast to other vaccines that consist of "killed" viruses or virus particles, the live polio vaccine has several advantages: in addition to being cheap and easy to produce in developing nations, the live vaccine confers immunity in the gut, where the polio virus reproduces. As a result, the live vaccine confers lifelong immunity after a single treatment, which is key in parts of the world where doctors may only have one opportunity to administer the vaccine.

However, on two dozen or more occasions since the year 2000, the live vaccine has re-evolved the ability to infect unvaccinated people and, in communities where vaccination is still inconsistent or incomplete, it can circulate widely, allowing the virus to fully readapt to human hosts and leading to hundreds of cases of childhood paralysis.

In their new study, Andino and colleagues took advantage of a unique natural evolutionary experiment: Each of the dozens of well-documented vaccine-derived polio epidemics derived, by definition, from a genetically identical parent virus: the vaccine. And in each case, natural selection drove the same evolutionary transformation: from safe vaccine to dangerous epidemic virus. As a result, the researchers were able to use newly developed genetic tools to study the commonalities between these events to discover the key evolutionary steps that are required to enable a breakout.

Following the Same Evolutionary Trajectory

To the researchers' surprise, they found that nearly all epidemic strains had followed the same evolutionary trajectory: First, three gatekeeper mutations dramatically increase the ability of the virus to make copies of itself, allowing it to quickly out-compete non-mutant virus strains. Second, two genetic swaps with common (and harmless) human viruses living in the human gut allow the polio virus to circulate more efficiently in human hosts. Finally, after just a few additional mutations, the virus becomes almost indistinguishable from wild polio virus.

Laboratory experiments in which the researchers forced viruses derived from the polio vaccine to compete for resources in cell culture not only produced the same three evolutionary steps, but revealed that the specific genetic changes had to be acquired in the same order: if the initial gateway mutations did not occur, none of the rest could either.

This discovery led the researchers to develop a new vaccine strain in which the initial gateway mutations that give mutant viruses the reproductive edge are much less likely to occur, essentially blocking the evolutionary pathway that has produced all vaccine-derived polio outbreaks. Andino and his team are now moving this improved vaccine toward phase 1 clinical trials to assess whether it can provide immunity against polio without the risk of re-evolving virulence.

"We started out just trying to understand the nature of viral evolution using the natural experiment of virus-derived polio outbreaks," Andino said. "It's tremendously exciting that from this very basic research, we have ended up with something that could contribute to preventing thousands of children from becoming paralyzed and eventually eradicating this terrible disease completely."

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