Toothed whales have survived millions of years without key antiviral proteins

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Researchers at the Stanford University School of Medicine have determined that toothed whales lack functional Mx genes—a surprising discovery, since all 56 other sequenced mammals in the study possess these genes to fight off viruses like HIV, measles and flu.

Modern toothed whales, including dolphins, orcas and sperm whales,

have inherited defunct copies of the Mx1 and Mx2 genes, profoundly altering their immune systems. The basic role of these Mx genes is to make proteins that fight viral infections. The researchers hope that understanding this newly discovered mysterious genetic anomaly will help preserve these cetaceans as they face extensive die-offs.

"Given how important the Mx genes seem to be in fighting off disease in humans and other mammals, it's striking to see a species lose them both and go about its business for millions of years," said Gill Bejerano, Ph.D., associate professor of developmental biology, of computer science and of pediatrics. "It's hard to determine if this is related to the die-offs. We hope that our observations will provide particular targets to go after when carcasses wash ashore, so we can better understand what is happening."

Bejerano is the senior author of a paper, to be published online June 15 in the *Proceedings of the National Academy of Sciences*, that describes the work. The lead author is graduate student Benjamin Braun.

Double-pronged strategy

Bejerano said his lab team began investigating Mx genes because, in primates, they are engaged in an arms race against rapidly evolving viral proteins. In order to determine the state of the Mx genes in mammals, he and his colleagues compared the genomes of 60 mammals.

"We compared the whole-genome sequence of four toothed whales, a baleen whale and dozens of related mammals like cows and humans," said Bejerano. "When we looked carefully at the genome sequences, it was very clear that the Mx genes are completely messed up only in the toothed whales."

The scientists identified a variety of Mx1 and Mx2 mutations, including

deleted sections of genes and DNA sequences that prematurely truncate protein synthesis, in the toothed whales' genomes that would prevent the genes from making functional proteins. Strikingly, all other mammals screened had healthy-looking Mx genes.

In addition to using comparative genomic analyses, the researchers performed transcriptomic analysis to validate that these mutations prevent Mx1 and Mx2 genes from producing functional proteins.

"Genes are used to make RNA and, from them, to make proteins," Bejerano said. "So we obtained RNA samples from two toothed whales, a baleen whale and two closely related species. When we looked at the output—the RNA that the genes were trying to make—there was nothing like a functional Mx RNA coming out of these messed up gene loci in the toothed whales."

He added, "Our double-pronged approach allows us to say with confidence that Mx proteins simply do not exist in toothed whales anymore."

Intriguing hypothesis

The investigators were particularly intrigued by the genomic difference observed between the toothed and baleen whales, because they share a common ancestor. Instead of teeth, baleen whales have baleen plates, which they use to filter food from water.

"The simplest, most likely scenario is that the common ancestor of the toothed whales lost both Mx genes shortly after the baleens and toothed whales split about 33-37 million years ago," Bejerano said. "It's tempting to think that this common ancestor was subjected to a very nasty virus that was exploiting the Mx1 and Mx2 genes. Their option was to lose both genes or die. We can't know for sure, but it's a tempting hypothesis

based on how some viruses seem to exploit Mx genes today."

Bejerano hopes these observations will inspire other researchers to collect samples and do in vitro experiments to determine whether toothed whales' immune systems are compromised or whether they've instead developed intriguing compensatory mutations. Ultimately, this understanding may help scientists fight human diseases, such as autoimmune disorders.

"It's likely that the toothed whales' immune system is very different from ours," Bejerano said. "I think this will open up very exciting research avenues, either to better protect the compromised whales, or to study their different viral defenses, and someday add them to our own arsenal. We're putting the genomic discovery out there, and we hope immunologists will follow up on it.

"Every single genome sequenced is a treasure trove of secrets," Bejerano said. "This is an amazing time to be a thoughtful genomicist. And hopefully, we've helped make it a slightly better time to be a toothed whale."

More information: Mx1 and Mx2 key antiviral proteins are surprisingly lost in toothed whales, www.pnas.org/cgi/doi/10.1073/pnas.1501844112

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