The evolution of mucus: How did we get all this slime?

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Petar Pajic, UB PhD student in biological sciences, prepares a saliva sample for separation and analysis. In the new study, the team used a gel electrophoresis technique to separate mucins from other proteins in the saliva of various mammals. Credit: Douglas Levere / University at Buffalo

From the slime coating slugs to the saliva in our mouths, many slippery

bodily fluids contain mucus. So how did this marvel of biology evolve?

In mammals, the answer is many times, and often in a surprising way, according to a new study on proteins called mucins. These molecules have a variety of functions, but as a family, they are known as components of mucus, where they contribute to the substance's gooey consistency.

Through a comparison of mucin genes in 49 mammal species, scientists identified 15 instances in which new mucins appear to have evolved through an additive process that transformed a non-mucin protein into a mucin.

The scientists propose that each of these "mucinization" events began with a protein that wasn't a mucin. At some point, evolution tacked a new section onto this non-mucin base: one consisting of a short chain of building blocks called amino acids that are decorated with sugar molecules. Over time, this new region got duplicated, with multiple copies added on to elongate the protein even further, making it a mucin.

The doubled regions, called "repeats," are key to a mucin's function, say University at Buffalo researchers Omer Gokcumen and Stefan Ruhl, the senior authors of the study, and Petar Pajic, the first author.

The sugars coating these sections protrude outward like the bristles of a bottle brush, and they bestow mucins with the slimy property that's vital to many important tasks that these proteins carry out.

The research will be published on Aug. 26 in *Science Advances.*

Vials of saliva collected from various mammals, including a pig. Credit: Douglas Levere / University at Buffalo

"I don't think it was previously known that protein function can evolve this way, from a protein gaining repeated sequences. A protein that isn't a mucin becomes a mucin just by gaining repeats. This is an important way that evolution makes slime. It's an evolutionary trick, and we now document this happening over and over again," says Gokcumen, Ph.D., associate professor of biological sciences in the UB College of Arts and Sciences.

"The repeats we see in mucins are called 'PTS repeats' for their high content of the amino acids proline, threonine and serine, and they aid mucins in their important biological functions that range from

lubricating and protecting tissue surfaces to helping make our food slippery so that we can swallow it," says Stefan Ruhl, DDS, Ph.D., interim dean of the UB School of Dental Medicine and professor of oral biology. "Beneficial microbes have evolved to live on mucus-coated surfaces, while mucus can at the same time also act as a protective barrier and defend against disease by shielding us from unwanted pathogenic intruders."

"Not many people know that the first mucin which had been purified and biochemically characterized came from a salivary gland," Ruhl adds. "My lab has been studying mucins in saliva for the last 30 years, mostly because they protect teeth from decay and because they help balance the microbiota in the oral cavity."

The intriguing evolution of an 'amazing life trait'

"I think this paper is really interesting," Gokcumen says. "It's one of those times where we got lucky. We were studying saliva, and then we found something that's interesting and cool and decided to look into it."

While studying saliva, the team noticed that a small salivary mucin in humans called MUC7 was not present in mice. The rodents did, however, have a similarly sized salivary mucin called MUC10. The scientists wanted to know: Were these two proteins related from an evolutionary perspective?

The answer was no. But what the research uncovered next was a surprise. While MUC10 did not appear to be related to MUC7, a protein found in human tears called PROL1 did share a portion of MUC10's structure. PROL1 looked a lot like MUC10, minus the sugar-coated bottlebrush repeats that make MUC10 a mucin.

Petar Pajic, UB PhD student in biological sciences, uses a gel electrophoresis technique to separate mucins from other proteins in a saliva sample. Credit: Douglas Levere / University at Buffalo

"We think that somehow that tear gene ends up repurposed," Gokcumen says. "It gains the repeats that give it the mucin function, and it's now abundantly expressed in mouse and rat saliva."

The scientists wondered whether other mucins might have formed the same way. They began to investigate and discovered multiple examples of the same phenomena. Though many mucins share common ancestry among various groups of mammals, the team documented 15 instances in which evolution appeared to have converted non-mucin proteins into mucins via the addition of PTS repeats.

And this was "with a pretty conservative look," Gokcumen says, noting that the study focused on one region of the genome in a few dozen mammal species. He calls slime an "amazing life trait," and he's curious whether the same evolutionary mechanism might have driven the formation of some mucins in slugs, slime eels and other critters. More research is needed to find an answer.

"How new gene functions evolve is still a question we are asking today," says Pajic, a UB Ph.D. student in biological sciences. "Thus, we are adding to this discourse by providing evidence of a new mechanism, where gaining repeated sequences within a gene births a novel function."

"I think this could have even broader implications, both in understanding adaptive evolution and in possibly explaining certain disease-causing variants," Pajic adds. "If these mucins keep evolving from non-mucins over and over again in different species at different times, it suggests that there is some sort of adaptive pressure that makes it beneficial. And then, at the other end of the spectrum, maybe if this mechanism goes 'off the rails'—happening too much, or in the wrong tissue—then maybe it can lead to disease like certain cancers or mucosal illnesses."

The study on mucins demonstrates how a long-time partnership between evolutionary biologists and dental researchers at UB is yielding new insights into genes and proteins that are also important to human health.

"My team has been studying mucins for many decades, and my collaboration with Dr. Gokcumen has brought this research to a new level by revealing all these exciting novel insights into their evolutionary genetics," Ruhl says. "At this advanced stage of my career, it is also immensely gratifying to see that the flame of scientific curiosity is being carried on by a new generation of young investigators like Petar Pajic."

More information: Petar Pajic et al, A mechanism of gene evolution

generating mucin function, *Science Advances* (2022). DOI: 10.1126/sciadv.abm8757.
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