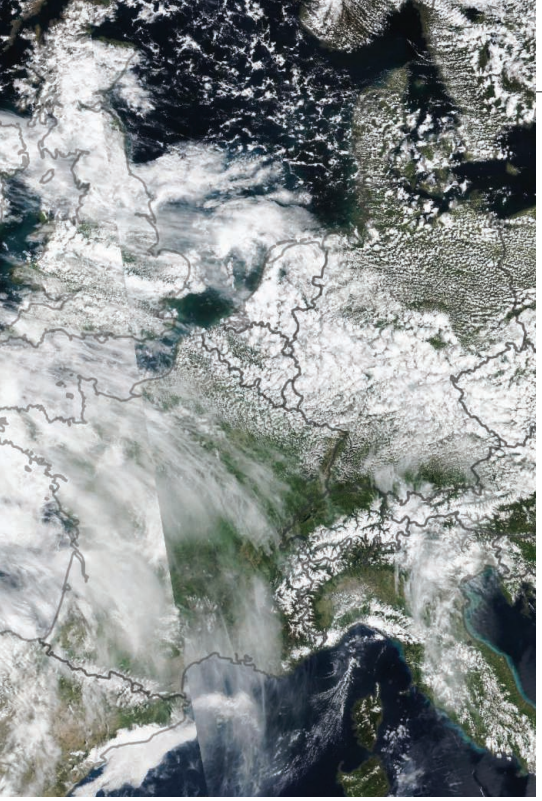
How an ancient microbial arms race remodeled human cells

Ann Gibbons

Science **369** (6503), 491-492.
DOI: 10.1126/science.369.6503.491



Researchers have discovered an untapped predictability in the North Atlantic Oscillation, a wind pattern that drives storms in Europe.

Oscillation (NAO), a large-scale wind pattern driven by the air pressure difference between Iceland and the Azores. The pressure difference reverses every few years, shunting the jet stream north or south; a more northerly jet stream drives warm, wet winters in northern Europe while drying out the continent's south, and vice versa. In previous attempts to project the pattern decades into the future, a single model might yield opposite forecasts in different runs. The uncertainty seemed "huge and irreducible," Smith says.

At first, the Met Office model did no better. But when the team ran the same model multiple times, with slightly different initial conditions, to forecast the NAO a season or a year into the future, a weak signal appeared in the ensemble average. Although it did not match the strength of the real NAO, it did match the overall pattern of its gyrations. But on individual model runs, the signal was drowning in noise.

The new work uses an ensemble of 169 model runs to find the same weak but predictable NAO pattern persisting for up to a decade. For each year since 1960, the team forecasted the NAO pattern 2 to 9 years in the future. When compared with weather records, the ensemble results showed the same pattern, ultimately explaining four-fifths of the NAO's behavior. The massive computational effort suggests changes in the NAO are more predictable than models capture by an order of magnitude, Smith says. It also suggests individual models aren't properly accounting for the ocean or atmospheric forces shaping the NAO.

The missed predictability appears to be universal. "This is being pursued everywhere," says Yochanan Kushnir, a climate scientist at Columbia University, whose team reported last week in *Scientific Reports* that rainfall in the Sahel zone is more predictable than models indicate. In forthcoming work, a group led by Benjamin Kirtman, an atmospheric scientist and model developer at the University of Miami, will flag similar missed predictability in wind patterns above many of the world's oceans.

Kirtman thinks something fundamental is wrong with the models' code. For the time being, he says, "You're probably making pretty profound mistakes in your climate change assessment" by relying on regional forecasts. For example, models predicted that the Horn of Africa, which is heavily influenced by Indian Ocean winds, would get wetter with climate change. But since the early 1990s, rains have plummeted and the region has dried.

The missing predictability also undermines so-called event attribution, which attempts to link extreme weather to climate change by using models to predict how sea surface warming is altering wind patterns. The changes in winds, in turn, affect the odds of extreme weather events, like hurricanes or floods. But the new work suggests "the probabilities they derive will probably not be correct," Smith says.

What's not clear yet is why climate models get circulation changes so wrong. One leading hypothesis is that the models fail to capture feedbacks into overall wind patterns from individual weather systems, called eddies. "Part of that eddy spectrum may simply be missing," Smith says. Models do try to approximate the effects of eddies, but at just kilometers across, they are too small to simulate directly. The problem could also reflect poor rendering of the stratosphere, or of interactions between the ocean and atmosphere. "It's fascinating," says Jennifer Kay, a climate scientist at the University of Colorado, Boulder. "But there's also a lot left unanswered."

While researchers around the globe hunt down the missing predictability, Smith and his colleagues will take advantage of the weak NAO signal they have in hand. The Met Office and its partners announced this month they will produce temperature and precipitation forecasts looking 5 years ahead, and will use the NAO signal to help calibrate regional climate forecasts for Europe and elsewhere.

But until modelers figure out how to confidently forecast changes in the winds, Smith says, "We can't take the models at face value." ■

HUMAN EVOLUTION

How an ancient microbial arms race remodeled human cells

Study traces genetic responses to pathogens back to ancestor of Neanderthals and modern humans

By **Ann Gibbons**

At a recent symposium on the evolution of infectious diseases, University of California, San Diego (UCSD), pathologist Nissi Varki noted that humans suffer from a long list of deadly diseases—including typhoid fever, cholera, mumps, whooping cough, and gonorrhea—that don't afflict apes and most other mammals. All of those pathogens follow the same well-trodden pathway to break into our cells: They manipulate sugar molecules called sialic acids. Hundreds of millions of these sugars stud the outer surface of every cell in the human body—and the sialic acids in humans are different from those in apes.

Varki and an international team of researchers have now traced how evolution may have scrambled to construct new defenses after that molecular vulnerability emerged in our distant ancestors. By analyzing modern human genomes and ancient DNA from our extinct cousins, the Neanderthals and Denisovans, the researchers detected a burst of evolution in our immune cells that occurred in an ancestor of all three types of human by at least 600,000 years ago.

As the researchers report in the current issue of *Genome Biology and Evolution*, these genetic changes may have sharpened the body's defenses against the pathogens that evolved to exploit sialic acids—but created new vulnerabilities. In an added irony, they note, humans' distinctive sialic acids were themselves once a defense against disease. The evolutionary saga is a vivid illustration of the competition between humans and microbes, says microbiologist Christine Szymanski of the University of Georgia, Athens, who is not a co-

author. "This gives us a human perspective on how we have to keep changing to keep pace."

The arena for this evolutionary arms race is the glycocalyx, a sugar coating that protects the outer membrane of all cells. It consists of a forest of molecules that sprout from the cell membrane. The sialic acids are at the tip of the tallest branches, sugar chains called glycans, which are rooted to fats and proteins deeper in the membrane.

Given their prominence and sheer number, sialic acids are usually the first molecules that invading pathogens encounter. Human cells are coated with one type of sialic acid, N-acetylneuraminic acid (Neu5Ac). But apes and most other mammals also carry a different one, N-glycolylneuraminic acid (Neu5Gc).

More than 2 million years ago, according to multiple molecular clock methods that estimate when mutations arose, a mutation in a gene on chromosome six made it impossible for human ancestors to make Neu5Gc anymore; instead, they made more of another sialic acid, Neu5Ac (*Science*, 4 September 1998, p. 1432). "We now know we had an ancient complete makeover of the surface of the human cells," says evolutionary biologist Pascal Gagneux of UCSD, a coauthor of the new paper. Birds, some bats, ferrets, and New World monkeys all separately made the same evolutionary change.

The change likely evolved as a defense against malaria, says UCSD physician-scientist Ajit Varki, senior author of the paper and Nissi Varki's spouse. Malarial parasites that infect chimpanzees were no longer able to bind with the altered sialic acids on our red blood cells (*Science*, 24 September 2010, p. 1586).

But in the next million years or so, that mutation became a liability, as Neu5Ac became a portal for a flurry of other pathogens. At the infectious disease symposium organized by UCSD's Center for Academic Research and Training in Anthropogeny, researchers described how multiple diseases evolved to use Neu5Ac to enter cells or to evade immune cells.

Coronaviruses appear to be no exception. "Most coronaviruses infect cells in two steps—first by recognizing abundant sialic acids as binding sites to gain a foothold, and then seeking out the higher affinity protein receptors like ACE2," Ajit Varki says. "Think of it like an initial handshake or introduction that is required before one can ask for a date." Two preprints suggest the novel coronavirus, SARS-CoV-2, also docks with sialic acids before binding with the ACE2 receptor to pierce human cells.

In past studies, Ajit Varki and Gagneux suggested the makeover of the cell and the loss of Neu5Gc may have even contributed to the origin of a new species in our genus *Homo*. If a woman with only Neu5Ac sialic acids mated with a man who still expressed Neu5Gc, her immune system may have rejected that man's sperm or the fetus that developed from it. This fertility barrier might have helped divide *Homo* populations into different species more than 2 million years ago, the researchers speculated.

But the sialic acid change also sparked a new arms race between pathogens and our ancestors. In the new study, the researchers scanned DNA for immune genes in six Neanderthals, two Denisovans, and 1000 humans, and looked at dozens of chimps, bonobos, gorillas, and orangutans as well. They found evolutionary changes that "markedly altered" one class of proteins—sialic acid-binding immunoglobulin-type lectins, or Siglecs—that usually sit on the surface of human immune cells and recognize sialic acids.

Siglecs are molecular sentries: They probe sialic acids to see whether they are familiar parts of our own bodies or foreign invaders. If Siglecs spot sialic acids that are damaged or missing, they signal immune cells to activate, rousing an inflammatory army to attack potential invaders or clean up damaged cells. If sialic acids instead appear to be normal parts of our own cells, other, inhibitory Siglecs throttle back immune defenses so as not to attack our own tissues (see graphic, below).

The researchers identified functional changes in the DNA of eight out of 13 Siglecs encoded by genes on chromosome 19 in humans, Neanderthals, and Denisovans. This hot spot of evolution appears only in Siglec gene variants, not in nearby genes on the chromosome, suggesting natural selection favored these changes, presumably because they helped fight pathogens that target Neu5Ac.

Apes did not show these changes, says first author Naazneen Khan, an evolutionary biologist now at the University of Kentucky. Given the mutations' presence in archaic hominins, this burst of evolution must have happened before our lineages diverged 600,000 years ago, but after the mutation in that altered sialic acid arose more than 2 million years ago, perhaps in *Homo erectus*, thought to be an ancestor of modern humans and Neanderthals.

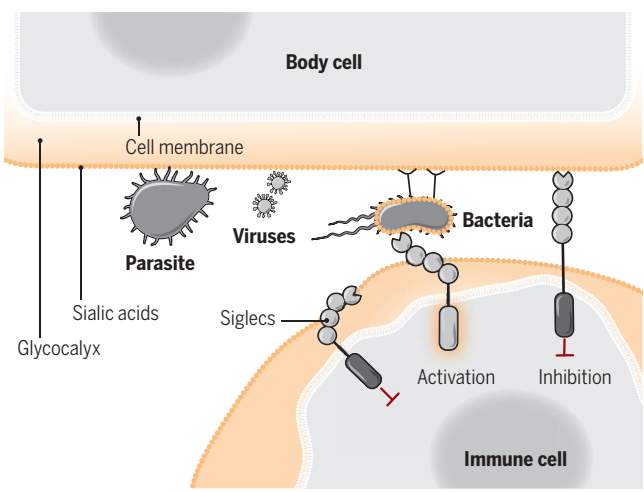
Most Siglecs are found on immune cells, but in the new paper, the team reports that several of the human Siglecs that underwent evolutionary changes are expressed in other types of human cells, including some in the placenta, cervix, pancreas, gut, and brain. Siglec changes may have been a side effect of intense battles with pathogens that infected these tissues, Nissi Varki suggests.

Although the recently mutated Siglecs protect us from pathogens, they may also contribute to other diseases. Some of the genetically changed Siglecs are associated with inflammation and autoimmune disorders such as asthma and with meningitis. The researchers suggest the altered Siglecs are constantly on high alert and do not dampen immune responses against our own tissues; they may even make some individuals more prone to the runaway inflammation seen in severe COVID-19.

Other researchers say the work underscores broad evolutionary principles. "This nicely shows that … natural selection is not always going for the optimal solution, because the optimal solution is changing all the time," says Rita Gerardy-Schahn, a glycobiologist at Hannover Medical School in Germany, who was not part of the new work. "What is best for natural selection in the short run may be the wrong selection tomorrow." ■

Battle at the cell surface

Some pathogens use sialic acids, which sit on the outer edge of the cell membrane, to invade a cell. Pathogens sometimes coat themselves in humanlike sialic acids to trick signaling molecules called sialic acid-binding immunoglobulin-type lectins (Siglecs) into inhibiting immune responses. But other Siglecs can instead turn on an immune response if they sense sialic acids on pathogens.



GRAPHIC: PASCAL GAGNEUX/UCSD, ADAPTED BY N. DESAI/*SCIENCE*