

Ajit Varki: On the origin of maladies

Some say language makes us human, others say it's art or free will. Ajit Varki points out how our diseases set us apart from the apes.

In India, Varki was a physician–scientist at the Christian Medical College in Vellore. After a few years he moved to the United States where he specialized in hematology, later became a leading glycobiologist, and most recently caught the evolution bug. He now codirects the Glycobiology Center at the University of California in San Diego and the Center for Academic Research and Training in Anthropogeny (the study of human origins).

Varki's interest in evolution began a decade ago while he was studying sialic acids—sugars that coat cell surfaces and modulate a variety of physiological and pathological process. He discovered that humans can't synthesize one kind of sialic acid (Neu5Gc) that other mammals can. However, in experiments conducted partly on himself, Varki found that humans incorporate Neu5Gc into their bodies when they eat red meat (1) and that this incorporation has implications for disease. For example, it may explain why diets rich in steaks and burgers might predispose some people to toxins (2) or lead to chronic inflammation (3). Meanwhile, sialic acid changes that are unique to humans help explain why we are susceptible to certain diseases, like *P. falciparum* malaria (4). With each new finding, Varki drills deeper into the question of what makes us human.

How did you transition from glycobiology into chimp biology?

After I found a sialic acid difference between chimps and humans, I wanted to know more about what makes humans different. I went to the Yerkes National Primate Research Center to educate myself about chimpanzees. I had assumed that because they're genetically so similar to us, their diseases were going to be similar to ours. But that wasn't the case! I learned that most of the common cancers of humans had never been reported in the great apes. Their heart attacks were completely different than ours. And things like

bronchial asthma and rheumatoid arthritis, which are common in humans, were uncommon in apes. Instead they tended to get strange types of renal failure, a different kind of cardiac disease, and so on. Then

I thought, well, if we're genetically so similar, but our diseases are so different, at least this should be a tractable problem.

And you approach this problem by comparing chimp and human genomes?

Yes, but not just the genomes. There's a complex interaction between our genomes, our phenomes [the set of possible phenotypes], and our environment. If you don't take a holistic view, you'll come up short. One of the things I've been involved in is trying to develop networks of people that range from linguists to philosophers to biochemists to neuroscientists to geneticists. They all talk different languages, but they have things to say to each other.

How might a philosopher or linguist influence a biologist's research?

Take the *FOXP2* story. A physician noticed that there was something unusual about a family who supposedly had dyslexia—but in fact it wasn't dyslexia because they had problems with articulation and grammar. Plus, it was a familial problem. The physician's finding was picked up by linguists and psychologists who showed that it was a global problem with aspects of articulation and the speech apparatus and not a problem of cognition. Eventually geneticists narrowed down the disorder to a point mutation in the gene *FOXP2*. Researchers later cloned *FOXP2* from human cDNA samples and revealed that this gene was uniquely changed in humans—two amino acids



Ajit and his wife and colleague, Nissi Varki, discuss their findings.

distinguished the human *FOXP2* protein from the one in chimpanzees. And recently there was a study in which researchers put the human *FOXP2* gene in a mouse and showed that there were slight changes in its vocalizations. None of this would have happened if people hadn't been talking across disciplines.

Understanding what makes us human is not a problem that will be solved by any one specialty. The worst thing you can do is to throw away clues that might seem irrelevant initially because they may turn out to be very important in the end.

TOXIC BURGERS

When did the nonhuman sialic acid Neu5Gc first cross your radar?

I started out as a physician–scientist, and one of my patients with a bone marrow disease, aplastic anemia, had an immune response to the horse serum that we were using to treat her. I read that this type of response was a reaction to sialic acid. At first I thought it didn't make sense because sialic acids are present throughout mammalian cells. A decade later, we discovered that humans were missing one kind of sialic acid that is present in other mammals due to a specific genetic event that occurred during human evolution.

Since then we've found more than 10 sialic acid–related differences between humans and chimpanzees. Sialic acids represent a “hotspot” [of mutation] in human evolution, and this seems to have implications for diseases.

“If you don't take a holistic view, you'll come up short.”

How so?

Certain pathogens recognize sialic acid on the surface of host cells and use it to invade. For example, human flu binds to one acid and the bird flu binds to another, so this may explain why the bird flu has a hard time jumping into humans. What is newer is the suggestion of molecular mimicry, in which the pathogen puts the sialic acid on itself. We think that by doing this, the pathogen gains protection from complement pathways and avoids antibody production.

Does having a unique sialic acid profile make humans more or less susceptible to infection?

It goes in both directions. Because humans are missing one kind of sialic acid, we are apparently resistant to some infections that animals get. One example is the malaria that afflicts the great apes in Africa. We found that this malaria parasite prefers to bind to a sialic acid that's missing in humans. And the human malaria parasite prefers to bind to the human sialic acid. So although we had a free ride from the original ape malaria because we lost one sialic acid, the parasites eventually won.

Neu5Gc is present in small amounts in some people. I've found that it originates from our diet—primarily from red meat. It turns out that it is present in mammalian foods, and as we eat them, the acid gets incorporated into our bodies even as we make an immune response against it. So this is the first example of what I call a “xeno-autoantigen.” It's a xenoantigen because it comes from an animal and not from humans, but it's also an autoantigen because it gets incorporated into us. Now we have a whole program focused on trying to understand the significance of anti-Neu5Gc antibodies, the presence of this nonhuman molecule in human tissues, and how that relates to the fact that there are various diseases associated with the consumption of red meat. So far we have evidence showing that it may increase inflammation in carcinomas, and we are looking into other diseases.

We also published a paper in 2008 showing that accumulating Neu5Gc from red meat can make you susceptible

to an *E. coli* toxin that prefers to bind to this nonhuman sialic acid (2).

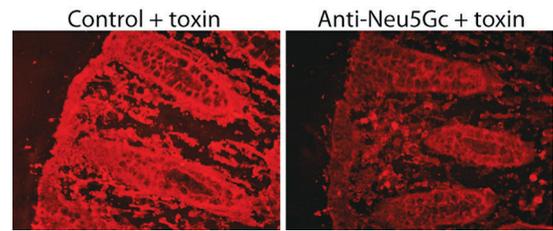
Do you still eat meat?

I haven't eaten red meat for five or six years since we first discovered this. I mean, I at least have to believe my own theory, right? Neu5Gc is not present in poultry, and there are very low amounts in fish, so I still eat these foods.

EARTHSHAKING SCIENCE**What else have you found by comparing humans with chimps?**

Humans have a lot of unusual changes in Siglecs [inhibitory receptors on white blood cells that dampen the immune response when they bind to sialic acid]. We've found that the level of expression of Siglecs in human leukocytes is significantly lower than that in chimpanzees, especially on T cells. We've published evidence that human T cells tend to be relatively overreactive, and we think that this may be because of loss of Siglec expression (5). When we first published this article, a science writer wrote an article about our work saying something about human T cells losing their brakes. I wouldn't say we've lost the brakes, but maybe we've lost the power of our brakes. In fact, humans have a relative preponderance of T cell-mediated disorders: rheumatoid arthritis, bronchial asthma, HIV with progression to AIDS, chronic hepatitis. It may be that our lymphocyte reactivity is set in a different state than that of our evolutionary ancestors.

Another thing about human Siglecs is that they turn up in unexpected places. Normally they're on circulating leukocytes. But we've found that in humans—but not in chimps—they show up on microglia in the brain. This is due to a gene conversion event that upregulates Siglec-11 and -16. We don't know exactly what this means, but microglia are not only involved in reacting to infectious agents but also in human inflammatory problems like Alzheimer's and HIV dementia.



MACMILLAN PUBLISHERS LTD: 2008. NATURE. 456: 651.

An *E. coli* toxin (red) preferentially binds Neu5Gc, a sialic acid that humans can't synthesize but can incorporate from red meat.

Do you encounter resistance when you jump from one scientific field into another?

We run into it a lot. Even though I'm a hematologist, I rarely publish in hematology journals. I'm into infectious diseases, immunology, neuroscience, reproductive biology, and so, yes, I encounter resistance to many of my findings. But the great thing about science is that it all comes out in the wash in the end. You just have to hope that it comes about in your lifetime. You don't want to be like Alfred Wegener, who died on an expedition trying to get more proof for plate tectonics because everybody was castigating him for how bad his theory was. Or Copernicus, who wrote his final treatise on the fact that the Earth went around the Sun on his deathbed.

I'm not saying that my work is nearly as important as theirs, but that all unexpected findings are met with skepticism. Of course, the nice thing about working on something totally different is that there isn't much competition, so you can take your time and do things right.

"It may be that our lymphocyte reactivity is set in a different state than that of our evolutionary ancestors."

1. Tangvoranuntakul, P., et al. 2003. *Proc. Natl. Acad. Sci. USA.* 100:12045–12050.
2. Byres, E., et al. 2008. *Nature.* 456:648–653.
3. Hedlund, M., et al. 2008. *Proc. Natl. Acad. Sci. USA.* 105:18936–18941.
4. Martin, M.J., et al. 2005. *Proc. Natl. Acad. Sci. USA.* 102:12819–12824.
5. Nguyen, D.H., et al. 2006. *Proc. Natl. Acad. Sci. USA.* 103:7765–7770.