

T Cell 'Brakes' Lost During Human Evolution

A significant difference between human and chimpanzee immune cells may provide clues in the search to understand the diverse array of human immune-related diseases. Researchers at the University of California, San Diego (UCSD) School of Medicine have uncovered a specific type of molecule expressed on non-human primate T cells, but not human T cells. T cells are important orchestrators of the immune system.

In an NIH-funded study to be published on-line in advance of publication in Proceedings of the National Academy of Sciences the week of May 1-5, UCSD researchers report that – unlike T cells from chimpanzees, bonobos, and gorillas (the “great apes” which are human’s closest evolutionary relatives) – human T cells lack expression of certain “Siglec” molecules. Siglecs are immune-dampening proteins that bind to sialic acids, the complex sugars found on the outside of cells. Siglec molecules seem to regulate T cell activation in chimpanzees by restricting the degree of signaling from the T cell receptor, which normally triggers the response of T cells in the immune system.

“Siglecs are like ‘brakes’ that can slow down the activation of an immune cell upon stimulation,” said Ajit Varki, M.D., UCSD Professor of Medicine and Cellular and Molecular Medicine and co-director of UCSD Glycobiology Research and Training Center. “During human evolution, we seem to have shut off these brakes on our T cells, allowing them to become hyper-active.”

Human T cells respond much more robustly than chimpanzee cells do, a disparity that could be explained by the absence of human T cell Siglecs. The explanation for this human-specific evolutionary loss of Siglecs is currently unknown. The UCSD scientists speculate that this may have been due to a selective pressure by a microbe that once drove human ancestors to require a high level of T cell activation. Another possibility is that this phenotype was secondarily acquired, during the adjustment to the human-specific loss of the sialic acid Neu5Gc some three million years ago, and that the phenotype has been carried by all humans ever since.

The study raises warning flags about the stimulatory and potentially destructive potential of the absence of Siglec molecules in human T cells, compared to chimpanzees and other nonhuman primate counterparts.

This may explain some major differences in susceptibility to certain diseases between humans and great apes. One example is the lack of progression to AIDS in the great majority of chimpanzees infected with HIV virus. It could also account for the rarity of T-cell mediated liver damage, such as chronic active hepatitis, cirrhosis and cancer, following Hepatitis B or C infection in chimpanzees. In addition, several other common human T cell-mediated diseases, including bronchial asthma, rheumatoid arthritis and type 1 diabetes, have, so far, not been reported in chimpanzees or other great apes.

The study suggests that the expression of Siglecs on chimpanzee T cells in essence puts the brakes on the cells during chronic HIV infection, preventing progression to AIDS in chimpanzees. In contrast, the onset of human AIDS occurs more rapidly due to the loss of T cells, which are essentially “unprotected” by the regulatory Siglecs.

This study may also explain the severe human reactions observed in a recent clinical trial using a T cell activating anti-CD28 antibody produced by TeGenero, Inc. All six healthy volunteers who received doses at 500 times lower than what was tested in nonhuman primates became severely ill, requiring hospitalization.

“In retrospect, the absence of natural restrictions on activation, such as that provided by Siglecs, could have

predicted this striking disparity between humans and nonhuman primates,” said Varki. The human volunteers could have experienced rapid activation of T cells and a resulting “cytokine storm.” The research team asked for a sample of the anti-CD28 antibody from TeGenero in order to test it on chimpanzee blood, but the company declined their request.

While this family of molecules displays a striking difference between humans and nonhuman primates, the researchers point out that there may be other undiscovered factors that also contribute to the observed differences in immune function.

As our closest evolutionary cousins, chimpanzees share more than 99% identity in typical protein sequences with humans. For that reason, the common chimpanzee has long been assumed to be an effective animal model for human diseases.

“In fact, chimpanzee diseases may be much more disparate from human diseases than previously envisioned,” said Varki.

“The good news is that the loss of this brake system is not permanent, as we still have the Siglec genes in our genomes, and do continue to express them in other blood cell types,” said Varki. “It is reasonable to hope that drugs can be found to turn the Siglec brakes back on again in human T cells, to slow the T cells down when they become hyper-active and cause disease.”

Additional contributors to the paper include Dzung H. Nguyen, Nancy Hurtado-Ziola and Pascal Gagneux, also in the UCSD Glycobiology Research and Training Center and Departments of Medicine and Cellular and Molecular Medicine.

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