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# Scientists identify new and beneficial function of endogenous retroviruses in immune response

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Retroviruses are best known for causing contagious scourges such as AIDS, or more sporadically, cancer.

But researchers at UT Southwestern Medical Center and Karolinska Institutet in Stockholm, Sweden, found that endogenous retroviruses (ERV) also play a critical role in the body's immune defense against common bacterial and viral pathogens.

"Most scientists have become used to the view that retroviruses are generally harmful," said Nobel Laureate Dr. Bruce Beutler, Professor and Director of UT Southwestern's Center for the Genetics of Host Defense. "We have found that ERV fulfill at least one beneficial function critical to producing protective antibodies."

Retroviruses are able to insert into the genomic DNA of cells they infect, including germ cells. In this way, and by a process called retrotransposition, they have become a major part of the genome of each person. About 45 percent of a person's DNA is of retroviral origin, and some of the better preserved copies are termed "endogenous retroviruses" (ERV).

Writing in the journal *Science*, the researchers found that when B cells are activated by large polymeric antigens such as polysaccharides of bacteria, they rapidly produce protective antibodies in what is termed the

Type II T-independent antibody response. This response, central to the body's defense against common bacterial and viral pathogens, is dependent on ERV.

Within activated B cells, the ERV are driven to express RNA copies of themselves, which in turn are copied into DNA by an enzyme called reverse transcriptase. The RNA copies of ERV are detected by a protein called RIG-I, and the DNA copies are detected by another protein called cGAS. These two proteins send further signals that enable the B cells to sustain their activated state, proliferate, and produce antibodies.

Dr. Zhijian "James" Chen, Professor of Molecular Biology and the Center for Genetics of Host Defense and a Howard Hughes Medical Institute Investigator, discovered two of the key proteins examined in the study (MAVS and cGAS).

"These findings suggest that both the RNA and DNA sensing pathways play an important role in detecting ERV and activating adaptive immune responses," said Dr. Chen, who is also an investigator of Howard Hughes Medical Institute and holds the George L. MacGregor Distinguished Chair in Biomedical Science.

Mice lacking elements of the RIG-I or cGAS pathways show diminished responses to type II T-independent antigens, and mice lacking both pathways show almost no antibody response at all. Moreover, reverse transcriptase inhibiting drugs also partially inhibit the type II T-independent antibody response.

Dr. Ming Zeng, Post Doctoral Researcher in the Center for Genetics of Host Defense and lead author on the study, notes that mutations affecting an enzyme called TREX1, which normally degrades the DNA copies of retroviruses in the cytoplasm, are known to cause an autoimmune disease.

"But it seems that the ability of ERV DNA to activate B cells is physiological: it must happen for this type of T-independent antibody response to occur," he said.

What about the good vs. bad dichotomy that we have come to hold dear where host vs. retroviral DNA are concerned?

"Once retroviruses have become part of the host germline, they are subject to selection for beneficial effects just like any other part of the genome, and their ability to activate an innate immune response seems to have been utilized to the benefit of the host," said Dr. Gunilla Karlsson Hedestam, Professor at the Department of Microbiology, Tumor and Cell Biology at Karolinska Institutet.

Dr. Beutler questioned whether this will prove to be an isolated case of ERV being used for "good" purposes, and the possibility that not all may in fact be good.

"Perhaps the 'physiological' activation of ERV in B cells might represent a new link between inflammation and cancer," said Dr. Beutler, who shared the 2011 Nobel Prize in Physiology or Medicine for discovering an important family of receptors that allow mammals to sense infections when they occur, triggering a powerful inflammatory response.

Dr. Beutler is a UT Regental Professor, and holds the Raymond and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie, Sr. The goal of the Center for the Genetics of Host Defense is to advance the fundamental understanding of the genetics of immunity to aid in the treatment of infection, disorders of immunity, and autoimmunity.

**More information:** "MAVS, cGAS, and endogenous retroviruses in T-independent B cell responses," by M. Zeng et al. *Science*,