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GE PRIZE-WINNING ESSAY

Why Old World Monkeys Are Resistant to HIV-1

Matthew Stremlau

Humans have been exposed to retroviruses for millions of years. Indeed, a significant portion of our genome consists of endogenous retroviruses—reminders of our vulnerability to past infections. The HIV/AIDS epidemic, which began nearly a century ago when simian immunodeficiency virus (SIV) passed from chimpanzees into a human host, is the latest episode in the long-standing coevolutionary struggle between retroviruses and their hosts.

Human immunodeficiency virus type 1 (HIV-1) causes AIDS in humans, and to a lesser extent, in chimpanzees (1, 2). However, not long after the discovery of HIV-1, scientists realized that certain primate species were resistant to HIV-1 infection. In particular, monkeys from Africa and Asia, referred to as Old World monkeys, could not be infected with HIV-1 and did not develop AIDS (3). This discovery brought both excitement and frustration. The block to HIV-1 replication in Old World monkey cells hindered efforts to develop an animal model for testing drugs and vaccines. On the other hand, Old World monkeys had evolved for millions of years in Africa—the epicenter of the current HIV-1 epidemic. Perhaps exposure to past HIV-1-like epidemics led to the emergence of an antiviral defense that protected them against HIV-1.

Determining the cause of HIV-1 resistance in Old World monkey cells stymied HIV researchers for nearly two decades. An early view was that the block resulted from expression of an incompatible receptor on the surface of Old World monkey cells. However, identification of the HIV-1 co-receptor in the mid-1990s disproved this hypothesis. Subsequent studies demonstrated that HIV-1 could enter Old World monkey cells, but a block that targeted the viral capsid prevented the establishment of a permanent infection (4).

Using a genetic screen, we identified

GE Healthcare and *Science* are pleased to present the prize-winning essay by Matt Stremlau, a regional winner for North America who is the Grand Prize winner of the GE & *Science* Prize for Young Life Scientists.



TRIM5 α as the primary block to HIV-1 replication in Old World monkey cells (5). The expression of rhesus monkey TRIM5 α in human cells potently inhibited HIV-1 infection and prevented the accumulation of reverse transcripts. Importantly, reducing the expression of TRIM5 α in rhesus monkey cells with small interfering RNA relieved the block to HIV-1. We initially hypothesized that TRIM5 α functioned as a cofactor necessary for capsid uncoating. However, subsequent findings argued against this hypothesis. First, knocking down human TRIM5 α showed no effects on HIV-1 replication in human cells. Second, rodent cells, which do not express TRIM5 α , supported HIV-1 infection if engineered to express an appropriate receptor. Finally, human TRIM5 α does not associate with the HIV-1 capsid in biochemical assays. Thus, TRIM5 α appeared to have evolved primarily as an inhibitory factor aimed at thwarting viral replication, rather than a host factor co-opted by HIV-1 to promote infection.

Further evidence that TRIM5 α functions primarily as a modulator of innate immunity against retroviruses emerged from comparing the sequences of TRIM5 α orthologs from different primate species. We found dramatic length variation, and an unusually high ratio of nonsynonymous to synonymous changes in the C-terminal domain of TRIM5 α orthologs (6) suggesting that TRIM5 α has been subjected to strong positive selective pressure during primate evolution. Furthermore, episodic changes in the TRIM5 α C-terminal domain coincide with periods of retroviral epidemics (6). Indeed, a recent report suggests that selective changes occurred in the TRIM5 α lineage during acquisition of resistance to an ancient retrovirus. These changes may have had the unfortunate conse-

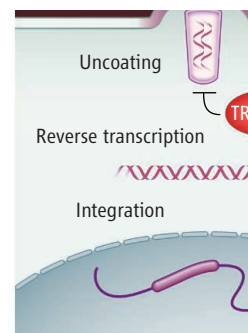
Premature disassembly of the HIV-1 capsid is caused by the rhesus monkey protein, TRIM5 α , and a single amino acid change in human TRIM5 α confers similar anti-HIV-1 activity.

quence of attenuating TRIM5 α potency against HIV-1 (7).

Does TRIM5 α have the ability to block infection by other retroviruses? We found that TRIM5 α from various Old World monkey species conferred potent resistance to HIV-1, but not SIV (5). New World monkey TRIM5 α proteins, in contrast, blocked SIV but not HIV-1 infection. Human TRIM5 α inhibited N-MLV and EIAV replication (8, 9). Thus, the variation among TRIM5 orthologs accounts for the observed patterns of post-entry blocks to retroviral replication among primate species.

To determine why Old World monkey TRIM5 α , but not human TRIM5 α , potently blocks HIV-1, we systematically altered the human sequence to more closely resemble the monkey sequence. Remarkably, we found that a single amino acid determines the antiviral potency of human TRIM5 α (10). If a positively charged arginine residue in the C-terminal domain of human TRIM5 α is either deleted or replaced with an uncharged amino acid, human cells gain the ability to inhibit HIV-1 infection (11). Perhaps some humans have already acquired this change and are naturally resistant to HIV-1 infection.

How does TRIM5 α inhibit infection? Following viral entry into the host cell, the capsid core, which encases the viral RNA, must disassemble to allow reverse transcription



Blocking HIV: Rhesus Monkey TRIM5 α targets the viral capsid to block HIV-1 replication.

of the viral RNA into DNA (see the figure). Host factors that mediate capsid uncoating are presumed to exist, but have not been identified.

Because early studies demonstrated that sequences within the capsid determined susceptibility to the block, we asked if TRIM5 α associated with the capsid. The association of TRIM5 α with the capsid was dependent on the C-terminal domain and the association was necessary for restriction (12). TRIM5 α proteins from various Old World monkey species bound

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the HIV-1 capsid; however, TRIM5 α variants that did not restrict HIV, such as New World monkey TRIM5 α , did not associate with the capsid cores. Human TRIM5 α exhibited a very weak association with the HIV-1 capsid cores, explaining the lower potency of human TRIM5 α in blocking HIV-1 infection (12).

Why does association of TRIM5 α with the viral capsid inhibit infection? Previous studies of HIV-1 capsid mutants suggest that capsid disassembly may be a temporally regulated process with either too rapid or too slow disassembly compromising viral infectivity (13). By following the fate of viral cores in the cytosol just after viral entry, we found that TRIM5 α caused capsid cores to undergo rapid, and premature, disassembly (12, 14). Accelerated uncoating of the capsid correlated with the ability of TRIM5 α variants from different species to restrict HIV-1, SIV, and N-MLV infections. Future studies are needed to determine how TRIM5 α promotes rapid disassembly of capsid and why accelerated disassembly is detrimental to infection. Perhaps accelerated

disassembly of the retroviral capsid prematurely exposes the viral RNA or viral enzymes to degradation.

The discovery of TRIM5 α not only answered a long-standing question in the HIV field, it also revealed a new pathway that protects cells from retroviral infection. The human genome encodes more than 50 members of the TRIM family. Recently, TRIM25 was shown to be essential for RIG-I-mediated antiviral activity (15) and TRIM family members such as TRIM1, TRIM19 (PML), and TRIM22, may block other viruses (16).

At a time when policy-makers and the public express frustration over our inability to produce an HIV vaccine, it is hoped that the discovery of TRIM5 α will precipitate new ideas for how to protect human hosts from retroviral infection. Perhaps in the case of retroviruses, innate intracellular immunity mediated by factors like TRIM5 α and APOBEC play a particularly crucial role. Efforts aimed at enhancing these innate immune defenses may ultimately prove

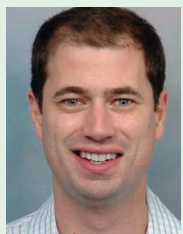
to be more effective at protecting humans from HIV than vaccine strategies aimed primarily at stimulating humoral or cellular immune responses.

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2007 Grand Prize Winner



Matt Stremlau, the author of the prize-winning essay and a North American regional winner, received his B.S. in chemistry from Haverford College. After graduation, he spent 1 year as a Henry Luce Fellow at the National Laboratory for Agrobiotechnology in Beijing, China, before beginning graduate studies at Harvard University. Here Dr. Stremlau investigated retroviral restriction in nonhuman primates in

Dr. Joe Sodroski's laboratory. He currently works in the U.S. Global AIDS Coordinator's Office at the State Department as an American Association for the Advancement of Science Fellow. Dr. Stremlau plans to start a postdoctoral fellowship in 2008 and is interested in emerging biotechnologies relevant to the developing world.

Regional Winners

North America: Bo Huang for his essay "Molecular Accounting of a Cell." Dr. Huang was born in Chongqing, China. He graduated with honors in 2001 with a B.S. degree in chemistry from Peking University. As a graduate fellow at Stanford University, under the direction of Dr. Richard N. Zare, he worked on the development of microfluidic devices for the analysis of individual cells using single-molecule detection. Now, as a postdoctoral fellow at Harvard University, he is working with Dr. Xiaowei Zhuang on a fluorescence microscopy technique that can achieve molecular-scale resolution in biological samples.



Europe: Mikaela Rapp, for her essay "The Ins and Outs of Membrane Proteins." Dr. Rapp grew up in Stockholm, Sweden. As a Ph.D. student in the group of Dr. Gunnar von Heijne at Stockholm University, she performed a global topology analysis of the



E. coli inner membrane proteome. Dr. Rapp defended her thesis in December 2006 and is currently learning membrane protein crystallography in the laboratory of Dr. Mika Jormakka at the Centenary Institute in Sydney, Australia. She plans to continue her scientific career as a postdoctoral fellow in the laboratory of Dr. Pär Nordlund at Karolinska Institute, Stockholm, Sweden.

Japan: Takeshi Imai for his essay "Axonal Wiring Specificity by Differential cAMP Levels of the Mouse Olfactory System." Dr. Imai was born in Tokyo in 1978 and grew up in Ina, a small southern city in Nagano, Japan. In 2001, he received a B.S. degree in biophysics and biochemistry from the University of Tokyo and remained there to pursue graduate studies in Dr. Hitoshi Sakano's laboratory, where he investigated the molecular mechanisms of the odorant receptor. He completed his Ph.D. in September 2006 but stayed on in Dr. Sakano's lab as a postdoctoral fellow.



All other countries: Manuel de la Mata for his essay "The Transcriptional Control of Alternative Splicing." Dr. de la Mata was born in Santa Rosa, Argentina. He majored in chemistry at the University of Córdoba, Argentina, and then entered a Ph.D. program at the University of Buenos Aires, where he studied the coupling of transcription with alternative splicing in the group of Dr. Alberto Kornblihtt. He defended his thesis in December 2006 and is currently a postdoctoral fellow in the Facultad de Ciencias Exactas y Naturales at the University of Buenos Aires.



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ERRATUM

Post date 21 December 2007

Essays: "GE & *Science* Prize for Young Life Scientists: regional winners" (7 December 2007, p. 1566). The photograph of Bo Huang was placed next to the biography of Takeshi Imai, and the photograph of Takeshi Imai was placed next to the biography of Bo Huang. The photographs were correct in the online version.