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Gene neighbors may have taken turns battling retroviruses

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A cluster of antiviral genes in humans has likely battled retroviral invasions for millions of years. New research by Sara Sawyer, Ph.D., a postdoctoral research fellow in the Basic Sciences Division at Fred Hutchinson Cancer Center, now finds that in addition to the previously identified TRIM5 gene that can defend against retroviruses like HIV, a related gene right next door, called TRIM22, may have participated in antiviral defense.

These findings, published Dec. 21 in the open-access journal *PLoS Pathogens*, show that both TRIM5 and TRIM22 exhibit the hallmarks of rapid evolutionary adaptation (positive selection) required to defeat new retroviral invasions. However, their genetic proximity has resulted in positive selection in either TRIM5 or TRIM22, but not both. This suggests that at various times over the past millions of years, both genes alternately have defended against retroviruses.

“The identification of novel antiviral genes is important to understanding the genetic basis of differential human susceptibility to viral diseases,” said Sawyer, the paper’s lead author. She conducted the research in collaboration with senior author Harmit Singh Malik, Ph.D., of the Center’s Basic Sciences Division and co-author Michael Emerman, Ph.D., of the Center’s Human Biology Division.

The recent identification of TRIM5 as one of the genetic means that protect rhesus monkeys against HIV infection has opened up a new area of research in HIV biology. Previous work had shown that TRIM5 has

been locked in genetic conflict with retroviruses throughout most of primate evolution, characterized by a higher than expected rate of amino acid change, referred to as positive selection.

The new Hutchinson Center study now suggests that one of the closest genes in evolutionary age and genetic proximity, TRIM22, also has the same hallmarks. However, unlike TRIM5, TRIM22 did not have antiviral activity against any modern viruses tested. “We are at an interesting point in this kind of research,” Emerman said. “Instead of looking at which unknown antiviral gene protected against a given virus, we now need to ask which unknown virus may have been defeated by a given candidate antiviral gene. It is possible that this virus no longer exists today, but may have only existed in our evolutionary past.”

TRIM5 and TRIM22 also appear to have discordant evolution in other mammals. Whereas the cow genome contains an expansion of TRIM5 genes and no TRIM22 gene, the dog genome encodes TRIM22 but has lost TRIM5. In spite of this evolutionary discordance, amino acid residues in TRIM22 found to be under positive selection are in remarkable proximity to those found previously to be critically important for TRIM5’s antiviral activity. Thus, despite an ancient separation of the TRIM5 and TRIM22 genes, the “rules” by which they might combat viruses appear to be constant.

“This research was conducted via computer analysis and in tissue-culture cells and has not yet been tested in model organisms. Nonetheless, the evolutionary means to identify other potential antiviral TRIM genes in the human genome may identify novel candidates for therapeutic intervention,” Malik said.

Source: Fred Hutchinson Cancer Research Center