Evolutionary battle scars' identify enhanced antiviral activity

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Rapid evolution of a protein produced by an immunity gene is associated with increased antiviral activity in humans, a finding that suggests evolutionary biology and virology together can accelerate the discovery of viral-defense mechanisms, according to researchers at Fred Hutchinson Cancer Research Center in Seattle, Washington.

These findings, published January 25 in the open-access journal *PLoS Genetics*, present a striking example by which evolutionary studies can directly lead to biomedically important discoveries in the field of infectious diseases.

The immunity gene, called ZAP, is a key player in a newly discovered branch of antiviral defenses in mammals referred to as “intrinsic immunity.” Host proteins like ZAP can target intracellular stages of the viral life cycle to inhibit viral activity. The ZAP gene, first discovered in rats, thwarts a variety of divergent viruses, from retroviruses (like HIV) to alphaviruses (like Sindbis) to filoviruses (like Ebola).

Researchers believe ZAP functions by virtue of its RNA-binding abilities, which recognize specific sequences of the virus and target their viral RNA for destruction. Host-virus interactions are a classic example of genetic conflict in which both entities try to gain an evolutionary advantage over the other. This “back-and-forth” evolution is predicted to result in rapid changes of both host and viral proteins, which results in an evolutionary signature of positive selection, especially at the direct interaction interface.

“This suggests that we might be able to deduce host-virus conflicts purely by looking at rapidly evolving protein segments,” said Dr. Julie Kerns, postdoctoral researcher and the lead author of the study, which was conducted in collaboration with Drs. Harmit Singh Malik and Michael Emerman, respectively from the Basic Sciences and Human Biology Divisions of the Center.

The researchers found that there has been very little sequence evolution in the RNA-binding domain, which suggests that human ZAP may be similar to the rat gene in its viral RNA-binding specificity. However, surprisingly, the rapid evolution characteristic of “intrinsic immunity” genes was concentrated in a protein domain that was not even present in the originally discovered rat gene.

The authors found that humans encode two protein versions, or isoforms, from a single ZAP gene: a shorter version similar to the original rat gene and a longer version that possesses a rapidly evolving poly (ADP-ribose) polymerase (PARP)-like domain. In virological assays, the longer human ZAP protein isoform has higher antiviral activity. Thus, positive selection correctly predicted the more potent antiviral isoform of this protein.

The authors further suggest that ZAP is locked in a conflict with alphaviruses. The discovery of a potential human gene that can restrict alphaviral infection is particularly timely as the mosquito-borne alphavirus, Chikungunya, was responsible for a large epidemic in parts of Southeast Asia in 2006 and is now threatening to invade parts of Europe. The researchers believe this finding has important implications for the understanding of intrinsic immunity against viruses, and could potentially serve as a guide in the development of antiviral therapeutics.

“We think that a particular alphaviral protein may be playing an evolutionary ‘cat-and-mouse’ game with the ZAP gene,” Malik said.

“Identifying this protein could lead to novel ways to tackle diseases caused by alphaviruses.”

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