Parps: Rapidly Evolving Weapons in the War against Viral Infection

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Host-virus interactions are typified by evolutionary 'arms races,' wherein viral genes evolve to subvert host defenses and host defense genes in turn evolve to thwart infection. Genes involved in adding and removing post-translational modifications (PTMs) such as methylation, acetylation, and phosphorylation to proteins are common targets of conflict between host and virus (Adhya and Basu, 2010; Salomon and Orth, 2013). However, the involvement of other PTMs in this process, particularly ADP-ribosylation, is unclear. Proteins are ADP-ribosylated by poly-ADP-ribose polymerases (PARPs), which have been implicated in diverse cellular processes including the DNA damage response, chromosome segregation, and transcriptional regulation. Interestingly, several viruses require ADP-ribosylation for replication, and overexpression of PARP13 inhibits replication of a diverse group of viruses, highlighting the seemingly contradictory roles of PARPs in viral replication. The authors previously found evidence for positive selection (that is, a greater accumulation of mutations that alter protein sequence than those that do not) of primate PARP13, suggesting that it is involved in host-virus conflict. Despite this suggestive evidence, no clear model for how ADP-ribosylation might prevent viral replication has emerged. Reasoning that proteins involved in the regulation of ADP-ribosylation would show evidence of positive selection if they were the focus of a host-virus conflict, postdoctoral fellow Dr. Matthew Daugherty and colleagues in the laboratory of Dr. Harmit Malik (Basic Sciences Division) undertook an evolutionary analysis of human PARP genes and their primate orthologs, which revealed evidence for positive selection of these genes.

Using computational methods, the researchers confirmed positive selection of PARP13 and also found evidence for positive selection in PARP4, PARP9, PARP14, and PARP15. They then performed a detailed evolutionary analysis of PARP4, which encodes a component of the cytoplasmic ribonucleoprotein complex called the vault. While the functions of vaults are unclear, they are most highly expressed in immune cells, suggesting that they play a role in immunity. Alignment of seven PARP4 orthologs from multiple primate species revealed a ~360 amino acid stretch, encoded by the largest exon of PARP4, that displayed much greater diversity across species than the rest of the protein. Further analysis revealed that this exon was solely responsible for the signature of positive selection in PARP4.

The researchers next focused on PARP9, PARP14, and PARP15, which are unique in that they are the only human genes encoding proteins with both a PARP catalytic domain and a macrodomain, which is the only protein domain able to recognize mono-ADP-ribosylation. In contrast to the focused selection on exon 30 of PARP4, these macro-PARPs displayed positive selection throughout their coding regions. Strong signatures of positive selection were found within the macrodomain coding regions, but exclusion of these regions from the analysis did not result in a loss of positive selection signatures for the macro-PARP genes.

"We are really excited that these results implicate an important protein modification, ADP-ribosylation, in the antiviral response when it had previously been assumed to primarily play a 'housekeeping' role in cellular function," said Dr. Daugherty. "Moving forward, we are quite interested in understanding the molecular role that ADP-ribosylation serves in antiviral defense and how viruses might be fighting back against it. We are also interested in understanding how antiviral PARPs might affect other 'housekeeping' functions of ADP-ribosylation, such as the established functions for PARP proteins in DNA repair and as a target of potent anti-cancer therapies."

Daugherty MD, Young JM, Kerns JA, Malik HS. 2014. Rapid Evolution of PARP Genes Suggests a Broad Role for ADP-Ribosylation in Host-Virus Conflicts. *PLOS Genet* 10(5): e1004403.

See also: Adhya D, Basu A. 2010. Epigenetic modulation of host: new insights into immune evasion by viruses. *J Biosci* 35(4):647-663.

Salomon D, Orth K. 2013. What Pathogens Have Taught Us About Posttranslational Modifications. *Cell Host Microbe* 14(3):269-279.

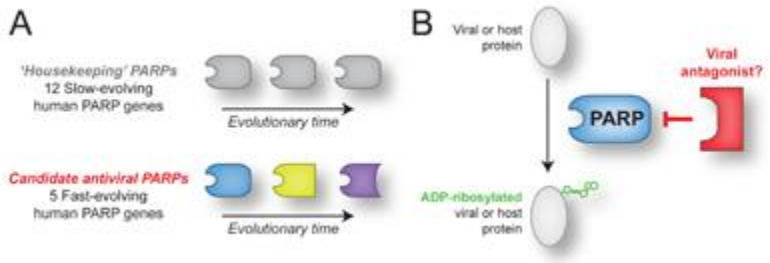

Image provided by Dr. Matthew Daugherty.

(A) Evolutionary trajectories of housekeeping and candidate antiviral PARPs. The sequences of housekeeping PARPs, not being under positive selection, remain relatively constant over evolutionary time. In contrast, candidate antiviral PARPs are under positive selection and so their sequences change over evolutionary time. (B) A model for a potential role of PARPs in antiviral defense. ADP-ribosylation of host and/or viral proteins may promote recruitment of antiviral effectors. Viral proteins may antagonize host ADP-ribosylation to inhibit this process.