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"The coronavirus macrodomain counters antiviral PARP-mediated ADP-ribosylation"

Abstract

ADP-ribosylation is a ubiquitous post-translational modification present in all domains of life. ADP-ribose is added to target proteins by ADP-ribosyl transferases (ARTs) as either monomers or polymers. Most ADP-ribosylation is carried out by Diptheria-like ARTs, also known as PARPs. Several mono-ADP-ribosylating PARPs are known to be interferon induced, however there are relatively few reports of enzymatically active PARPs having anti-viral activities. Macrodomains are proteins that bind to and can remove ADP-ribose from a protein, and importantly, viruses from the Coronaviridae, Togaviridae, and Hepeviridae families all contain macrodomains that are critical for either replication or pathogenesis. Correlative evidence suggests that these proteins have evolved to counteract cellular ADP-ribosylation. However, this has yet to be conclusively demonstrated. Here, we established a primary macrophage cell culture system where the absence of the viral macrodomain led to poor replication and enhanced induction of interferon (IFN) following infection. Addition of PARP inhibitors 3-AB and XAV-939 led to enhanced replication of the mutant virus and dramatically reduced induction of IFN. We then treated these cells with siRNAs to the most abundantly expressed PARPs, and found that knockdown of either PARP12 or PARP14 led to enhanced replication of the mutant virus. PARP14 was also found to be both necessary and sufficient for induction of IFN following infection or poly I:C treatment in both mouse and human cells. In summary, these data demonstrate that the coronavirus macrodomain has evolved to counter PARP-mediated anti-viral ADP-ribosylation.

Bio Summary

Dr. Fehr is an Assistant Professor in Infectious Diseases in the Department of Molecular Biosciences. Dr. Fehr earned his Ph.D. from Washington University-St. Louis in the Molecular Microbiology Department where he studied the molecular virology of Human Cytomegalovirus. He recently completed a Postdoctoral Fellowship in the Laboratory of Stanley Perlman in the Department of Microbiology and Immunology at the University of Iowa where he studied how CoVs modulate the innate immune response. Dr. Fehr's current research will be based on viral factors that modulate the innate immune system, focusing on the interplay between viral macrodomains and mammalian PARP enzymes.