Bench to Bedside

Newly Discovered Cellular Pathway Blocks Ebola, COVID-19 Viruses

Tracy Hampton, PhD

Faced with the urgent need for new antiviral strategies, investigators recently uncovered a surprising pathway that host cells use to protect against diverse viruses, including those that cause Ebola and coronavirus disease 2019 (COVID-19). The findings, published in *Science*, point to a potential novel treatment target.

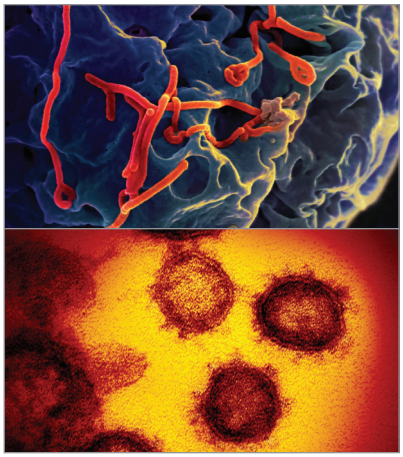
The work relied on an innovative screening approach—activating mobile genetic sequences within chromosomes called transposons—to look for genes that can prevent Ebola virus infection. DNA transposons' attractiveness for biomedical research lies in their adept ability to hop from place to place within the genome. These genetic segments are powerful forces of change, sometimes disrupting and other times augmenting gene expression.

"This platform is novel and different for several reasons: It both activates and inactivates genes in a truly genome-wide way, it is fast and inexpensive, and it can be easily applied to different cell types and organisms," the study's senior author, Adam Lacy-Hulbert, PhD, of the Benaroya Research Institute at Virginia Mason and the University of Washington in Seattle, said in an interview. Lacy-Hulbert noted that many conventional screens knock out host genes to identify those that a virus needs to replicate. "We were most interested in turning on genes and finding ones that protected the cell," he explained.

The strategy uncovered the major histocompatibility complex (MHC) class II transactivator (*CIITA*) gene as a promising candidate. In human cell lines, the gene induced Ebola virus resistance by activating a second gene's expression. Indeed, knockout experiments showed that *CIITA*-mediated resistance required the other gene, *CD74*.

Both genes play a role in the body's immune response, where they're associated with antigen presentation. The new study suggests that their antiviral activity may have preceded their known role in presenting antigens to the immune system.

"I think a major impact is the revelation that a gene (*CD74*) that was thought only to function in adaptive immunity (helping process MHCII) has a direct function in innate immunity (inhibiting viral entry by blocking fusion)," Duane Wesemann, MD, PhD, an associate professor and immunology faculty member at Harvard Medical School and a researcher at Brigham and Women's Hospital, noted by email. "This is a nice example of how genes were co-opted for other functions throughout evolution," added Wesemann, who was not involved with the study.



Human cells express 4 main types, or isoforms, of the CD74 protein, and only 1 of these isoforms, named p41, was critical for viral resistance in the scientists' experiments. Its expression fully restored Ebola virus resistance in *CIITA*-expressing *CD74*-knockout cells. Even in the absence of the *CIITA* gene, p41 expression induced antiviral activity.

The p41 isoform blocks cellular enzymes, or proteases, called *cathepsins* that Ebola viruses hijack for cell entry. Specifically, it inhibits cathepsin proteases from altering certain proteins on the Ebola virus coat. By doing so, it prevents the virus from fusing with and infecting the host cell. In fact, disrupting the isoform's cathepsin binding site completely inhibited its antiviral activity in the study.

"The pathway we found interferes with an early stage of viral entry that is common to many viruses: the processing of the viral coat protein by host cell proteases," Lacy-Hulbert said.

In recent months, he and his colleagues have been working to help understand, treat, and prevent COVID-19. Knowing that diverse viruses rely on cathepsins and other proteases, they next tested p41's potential against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Expressing p41 in cells blocked the virus's cathepsin-dependent entry pathway and completely abolished signs of cell destruction during viral exposure.

The strategy worked for inhibiting a range of *Ebolavirus* species, including Sudan, Zaire, and Reston, the distantly related Marburg virus, as well as a bat virus related to SARS-CoV-2 and viruses engineered to express SARS-CoV spike (S) proteins. Human coronaviruses have S proteins in common. They are indispensable for receptor recognition, viral attachment, and host cell entry and represent promising targets for COVID-19 vaccine and therapeutic research.

Anna Bruchez, PhD, the study's lead author and a pathology instructor at Case Western Reserve University, stressed the findings' broader implications against known and emerging pathogens. "Many viruses use cathepsin proteases to help them infect cells, and cells can upregulate *CIITA* and *CD74* during an immune response, so it will be interesting to see if expression levels of these genes are associated with differential clinical outcomes following infection," she said in an interview.

Moving forward, the findings may inspire new treatments that inhibit multiple virus types, including unknown future pathogens. "Ideally, we need to find a drug that can mimic the ability of CD74 to block viral processing," Lacy-Hulbert said. ■

Note: Source references are available through embedded hyperlinks in the article text online.

National Institute of Allergy and Infectious Diseases