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Wistar Scientists Uncover New Viral Mechanism for Evading Immunity, Identifying a New Drug Target

PHILADELPHIA — (THURSDAY, MAY 22) — Researchers at The Wistar Institute have identified a previously unknown mechanism by which viruses can reprogram mitochondrial structure to silence immune responses and ensure successful viral reproduction. The findings, published in *Nature Microbiology*, reveal how the virus-encoded protein vBcl-2 can hijack a host enzyme called NM23-H2 to dismantle mitochondrial immune signaling, highlighting a new potential point of viral vulnerability that could be exploited through drug discovery.

"This is a foundational insight into how viruses can reengineer the architecture of the mitochondrion, an organelle that is key to immune function, to their advantage," said **Chengyu Liang, M.D., Ph.D.,** professor and co-leader of the Molecular & Cellular Oncogenesis Program at The Wistar Institute Ellen and Ronald Caplan Cancer Center and senior author of the study. "It adds a new dimension to our knowledge of the Bcl-2 family in a way that broadens our understanding of virus-host interactions and opens a new window into potential therapeutic targeting."

At the center of the discovery is a small viral protein known as vBcl-2 from Kaposi's sarcoma-associated herpesvirus (KSHV), a herpesvirus that can cause cancer in people with HIV and other forms of immune suppression. Long thought to function mainly by blocking cell death-related pathways, Liang and the research team found that vBcl-2 plays a much more sophisticated role: remodeling mitochondrial shape at a specific moment in the viral lifecycle to prevent activation of antiviral immune defenses.

The researchers discovered that vBcl-2 binds to and activates the host enzyme NM23-H2, recruiting it to mitochondria where it provides GTP to power the mitochondrial fission machinery. This triggers mitochondrial fragmentation at a time when these organelles should remain connected, preventing the assembly of a critical immune signaling platform called MAVS that normally triggers Type I interferon responses—the cell's front-line antiviral defense.

"Rather than blocking a single immune protein, the virus destabilizes the entire immune signaling hub," said Liang. "It's like if there was a disaster and FEMA couldn't function—in this scenario, MAVS is FEMA. The cell can't coordinate its immune signaling to respond to the viral infection because the platform that would do the coordinating isn't working."

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Importantly, other herpesviruses such as Epstein-Barr virus encode similar Bcl-2 proteins, suggesting that mitochondrial reshaping may be a strategy used by many persistent viruses across this family. The manipulation of mitochondrial structure appears to be a novel viral immune evasion strategy that allows the virus to complete its late-stage assembly and exit from the cell nucleus.

In the absence of vBcl-2-induced mitochondrial fragmentation, the researchers found that interferon signaling activates two key antiviral proteins—TRIM22 and MxB—which trap virus particles in the nucleus and prevent their release. By disrupting MAVS assembly through mitochondrial fission, the virus stops these genes from ever being activated, thereby evading this cellular defense mechanism. Future research to fully characterize these interferon target genes is another area of interest for Liang's lab.

The research team also identified a small-molecule compound, VBNI-1, that disrupts the interaction between the viral protein vBcl-2 and the host enzyme NM23-H2. In lab models, VBNI-1 blocked mitochondrial fission, restored immune signaling, and halted viral escape, all without showing toxicity to uninfected cells.

"We now have a candidate drug that targets the virus-mitochondria interface," said Liang. "Our findings offer hope for KSHV treatment, as there is currently no vaccine or cure, and potentially for treatment for other herpesviruses in the future."

The work represents a major cross-disciplinary collaboration between virologists, cell biologists, structural biologists, immunologists, and drug development experts. Wistar's own infrastructure—including imaging core, Proteomics and Metabolomics Facility, Bioinformatics Facility, Molecular Screening and Protein Expression Facility—played a central role in advancing the study.

"This discovery is a perfect example of what happens when we collaborate to follow basic science questions through to their deeper biological logic," said Liang. "We started by asking why a small viral protein is essential for replication and ended up uncovering an entirely new principle of immune regulation via mitochondria that could lead to novel therapies for KSHV-associated diseases."

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