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How one virus uses mimicry to replicate successfully

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Both viruses and cancers subvert the growth-control machinery in a cell to serve their own needs. According to a new study, at least one virus uses mimicry to gain access to that machinery.

A common target for both is a cell protein called the retinoblastoma protein, or pRb, which serves to block cell division when potentially cancer-causing gene mutations are present. First identified in pediatric tumors of the retina, this tumor suppressor protein has since been found to play a role in many other forms of cancer when disrupted.

A number of viruses produce proteins that specifically target pRb, and scientists have studied these viruses and their proteins closely to better understand how normal cells can turn cancerous. Among such viruses are the adenoviruses, which produce a protein called E1A that interferes with pRb and its ability to control unwanted cell division. Adenoviruses are not themselves cancer causing, but a better understanding of how they interact with pRb might well shed light on related mechanisms used by other viruses to trigger cancers. For example, a protein that is functionally equivalent to E1A from human papillomavirus, called E7, causes cervical cancer in the cells it infects.

Until now, investigators had been unable to obtain detailed information about how E1A disrupts the normal function of pRb. In a new study, however, featured on the cover of the November 1 issue of the journal *Genes & Development*, researchers at The Wistar Institute have solved the three-dimensional structure of a molecular complex of pRb and

E1A, providing the first atomic view of the viral E1A protein in action.

The findings show that that E1A operates in a novel way, mimicking a normal cellular protein called E2F that ordinarily binds to pRb in a controlled and regulated fashion.

“The structural similarities between E1A and E2F are surprising and striking,” says Ronen Marmorstein, Ph.D., a professor in the Gene Expression and Regulation Program at Wistar and senior author on the study. “Looking at the structure it became obvious how this viral protein disrupts the activity of pRb.”

pRb is a member of the “pocket-protein family,” because it has a pocket within which proteins can bind. For pRb to function normally, it needs to bind a molecular complex incorporating the E2F protein. When pRb is bound to this complex, it acts as a growth suppressor, inhibiting cell division.

In their study, Marmorstein and a colleague showed that E1A disables pRb and its ability to control cell division by mimicking E2F and occupying the same pocket where E2F would normally bind.

“Looking at the structure, we see that the E1A protein displaces E2F by binding to a specific location on pRb,” Marmorstein says. “By knocking out pRb in this manner, E1A forces cells to start dividing uncontrollably, a hallmark of cancer.”

This approach to targeting pRb is quite different from methods used by other viral proteins, he adds.

The study provides the first structural information on the E1A protein. In developing the required crystals for the structure determination, Xin Liu, the lead author on the study, first had to identify suitable binding

partners for the protein.

“Because E1A is so flexible, it needs binding partners to crystallize,” Liu says.

By forming a complex with pRb and these binding partners, the researchers were able to crystallize the protein and then analyze its structure using a technique called X-ray crystallography. Their studies revealed how each component of the complex worked in three-dimensional detail.

The scientists are now working to analyze the structure of larger regions of the E1A protein bound to pRb and other cellular E1A targets to more fully characterize how this viral mechanism might cause cancer.

Source: The Wistar Institute

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