Bonding together to fight HIV

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A collaborative team led by a Northeastern University professor may have altered the way we look at drug development for HIV by uncovering some unusual properties of a human protein called APOBEC3G (A3G).

In an article published in *Nature Chemistry*, Prof. Mark Williams and his graduate student Kathy Chaurasiya, along with several collaborators, show how these unusual properties help us to fight HIV infection.

APOBEC3G

It is well known that in response to virus infection, the body makes specific antibodies to counteract the infection. However, we are also born with another way to fight infection, namely through the action of defense proteins that are always present in our system. These proteins provide the first line of defense against invading pathogens. For example, we are all potentially protected against HIV because we have an antiviral protein called A3G. However, HIV has evolved a strategy to circumvent the activity of this protein by tricking our cells into destroying our own A3G proteins. This is where Prof. Williams's research comes into play.

A multi-functional protein

A3G moves along a DNA strand as part of its function as an enzyme, and when it reaches a particular one of the four bases in DNA, it chemically alters the DNA, causing HIV to mutate. This was originally

thought to be the only way A3G blocks HIV infection. However, some researchers found that even when A3G could not chemically alter the DNA, it still inhibited HIV. To explain this, Prof. Williams's collaborator Dr. Judith Levin from NIH, together with postdoctoral fellow Dr. Yasumasa Iwatani, proposed that A3G forms a roadblock that prevents the virus from making a DNA copy of its genome, thereby stopping HIV replication. This would require A3G to be more slow-acting, yet because the protein normally has to move fast to perform its chemical function, there seemed to be an apparent contradiction in the experimental results.

Professor Williams' research resolves this paradox and shows that the A3G protein does not always have the rapid movement needed for chemical function. Instead, its activity changes over time. "First, A3G is a really fast protein," said Williams. "Then, gradually over time, it becomes a slow protein and remains bound to the DNA, blocking replication."

Challenging popular opinion

Many researchers doubted that a protein could have both enzyme and roadblock functions. An enzyme is designed to act rapidly, so the idea of the A3G protein starting off fast, and then gradually slowing down seemed physically impossible. Professor Williams' collaborator Dr. Ioulia Rouzina from the University of Minnesota came up with the novel idea that when A3G proteins group together, they become slower over time. To test the idea, the Williams lab used an instrument called optical tweezers that allowed them to stretch single DNA molecules with A3G proteins bound. By measuring the change in DNA length over time as the proteins came on and off the DNA, they could show that the rates at which A3G bound to DNA became slower over time.

How does this happen? It was already known that A3G proteins bind to

each other and form a multi-protein complex. "Once the complex is formed, the A3G proteins are no longer able to move rapidly along the DNA strand as needed for chemical modification of the DNA," said Williams. "This suggests that slow binding can also block HIV replication."

Impact on HIV research

The A3G protein has at least two mechanisms by which it can block HIV replication. We have known for over 10 years that A3G can, in principle, provide protection from HIV. However, finding a drug that can counter the anti-A3G activity of the virus has been elusive. This new work has the potential to develop alternative approaches to HIV therapy and development of drugs that can enhance the roadblock activity of A3G. This provides an alternate pathway for drug development that has not previously been pursued.

More information: Oligomerization transforms human APOBEC3G from an efficient enzyme to a slowly dissociating nucleic acid-binding protein, DOI: 10.1038/nchem.1795

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