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# New view of HIV entry may lead to next generation of inhibitors

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Scientists may need to rethink the design of drugs meant to block HIV from infecting human cells, according to a study that appears in the May 1st issue of the journal *Cell*, a Cell Press publication. That's because the new report shows that HIV doesn't enter cells in the way that experts had generally assumed it did.

Rather than fusing directly with the plasma membrane at cells' outer surfaces to release its contents, HIV fusion primarily occurs via smaller, membrane-bound compartments inside of cells known as endosomes, the new research shows. The discovery implies that anti-HIV drugs known as fusion inhibitors might be more effective in blocking HIV if they too can do their work inside of cells, where fusion takes place.

"We show that HIV fusion occurs virtually exclusively from endosomes," said Gregory Melikian of the University of Maryland School of Medicine. "It appears that it is this path to entry that leads to infection."

"In order to efficiently block intracellular fusion events, the next generation of HIV entry inhibitors must be able to permeate the cell membrane," he continued. Drugs that act on the endocytic machinery itself might also prove useful in limiting HIV infection.

Endosomes form in a process known as endocytosis by which cells take in material by engulfing and pinching off a portion of the cell membrane to form a smaller vesicle. Enveloped viruses that depend on low pH for

entry are known to initiate infection by fusion with acidic endosomes. However, entry sites for pH-independent viruses, including HIV, had not yet been clearly defined.

In the new study, Melikian and his colleagues relied on a series of imaging studies to literally watch as HIV-1, the virus that normally infects humans, enters cells. Those experiments showed that complete viral fusion occurs not on the cell surface, but in endosomes. While HIV's envelope sometimes did mix with the cell's plasma membrane, in those cases delivery of the viral contents did not occur.

"Time-resolved imaging of single viruses and differential blocking of fusion by site-specific and universal inhibitors revealed that HIV-1 co-opts the endocytic machinery to enter into and fuse with target cells," the researchers wrote. "By contrast, fusion with the plasma membrane did not progress beyond the lipid mixing step, suggesting that endosomal entry is the pathway that leads to productive infection."

HIV-1 interacted with receptors on the cell surface leading to its internalization long before endosomal fusion, they show. That process minimized the surface exposure of conserved viral epitopes - portions of macromolecules that are recognized by the immune system -- during fusion and reducing the efficacy of inhibitors targeting these epitopes.

The researchers also found that HIV-1's release from endosomes depend on dynamins, enzymes that are important to the formation of new endosomes and their fusion with other membranes. Melikian said that dynamins may provide an additional driving force to expand pores and permit the release of the HIV-1 core out into the cell.

While Melikian said he hopes the findings will have practical implications, it does deliver some bad news for those on a mission to fight HIV. That's because the endosomal path to entry would offer the

virus several advantages, including sheltering HIV from antibodies and inhibitors that target key portions of the virus during the unusually slow fusion reaction.

The new result may also have relevance for other so-called pH-independent viruses, all of which were assumed to enter via fusion with the plasma membrane, Melikian said. After all, he noted, HIV has been a "poster child" for that group. "This may be a universal trend. Endosomes may be universally more conducive to viral entry."

Source: Cell Press (news : web)