

## HIV uses autophagy for its own means

Virus avoids degradation and turns pathway into a helping hand for virion production.

**N**ot satisfied with simply thwarting its host's defensive maneuvers, HIV actually twists one to its advantage, based on new findings from Kyei et al. (1). The research suggests that autophagy—often used to capture and destroy invaders—aids in protein processing steps essential to HIV proliferation.

Autophagy is probably better known for its role in stress response pathways, particularly during bouts of nutritional deprivation. But in 2004, independent publications from the laboratories of Vojo Deretic and Tamotsu Yoshimori implicated autophagy in mammalian cell-autonomous defense mechanisms against pathogens (2, 3). Many publications have since revealed that a range of intracellular pathogens from bacteria to viruses to protozoa are targets for autophagosomes, which eventually acidify and become lytic bags of bug destruction (4).

Deretic figured the pathogenic targets didn't necessarily stop there. "We thought that autophagy would be a cool device to capture and digest incoming HIV virions," he says. "So, we thought if we induced autophagy, maybe it would digest HIV." In the new work, his group shows that the opposite occurred—virus levels were increased when the researchers chemically induced autophagocytosis in macrophages.

Conversely, blocking autophagocytosis lessened virus production. Reduced viral levels were accompanied by a blockade in the processing of Gag—a key precursor protein for virus assembly. The group found that Gag localized to complexes containing an autophagy protein, LC3. "It looked paradoxical," says Deretic. "But only if you didn't know something else. And that is a finding in yeast that autophagy is not only degradative, but can also serve in some biosynthetic pathways," including the trafficking of the Cvt protein to the vacuole (5). Together, the results suggest that Gag may piggyback on autophagosomes



(L-R) George Kyei, Christina Dinkins, Vojo Deretic, and colleagues found that the HIV Gag protein (green) localized to autophagosomes (red). Another HIV protein, Nef, blocks the later stages of autophagosome maturation to allow full Gag processing and increase viral yield.

or their components, perhaps for locomotive services, to complete its maturation.

The findings help explain a 2008 functional genomics screen that linked autophagy proteins with increased HIV replication (6). During normal HIV invasion in macrophages, Deretic's group found, immature autophagosomes accumulated. But late stages of maturation—those that create degradative organelles—did not occur.

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The group then sought the viral agitator that blocks autophagosome maturation and allows Gag processing. Their primary candidate was an HIV protein called Nef, which interacts with the vacuolar proton ATPase and, they thought, might thereby block acidification steps necessary to make a degradative organelle. Using a mutant virus, the group showed that HIV lacking Nef no longer profited from increased autophagy and was instead degraded.

It is not yet clear exactly how Nef blocks autophagosome maturation. The authors found the viral protein in complexes with autophagy regulatory proteins, including a central regulator of the autophagosomal pathway called Beclin 1. A Nef mutation that interfered with its Beclin 1 interaction no longer led to increases in early autophagosomal markers. Beclin 1 is also hijacked by another viral protein—herpesvirus vBcl-2—but the

herpesvirus blockade of autophagocytosis appears to happen at a much earlier stage (7).

Clinical applications, although tempting, may be far down the road. If the idea is to kill the virus using drugs such as rapamycin, which induces autophagy, it will first be necessary to block Nef, notes Deretic. The idea is not without natural support. "There were cases in Australia involving HIV strains that lacked Nef," he says. "And these people would not progress to AIDS, meaning the virus is disabled."

Deretic has other exciting ideas. Highly active anti-retroviral therapy often does a smashing job clearing viral loads from the blood. But the pathogen can persist in particular locales such as gut lymphoid tissue (8). "My hope," says Deretic, "is to go after these reservoirs and chew up the virus that for some reason is not readily accessible or susceptible to the anti-retroviral therapy. I have great hope that autophagy will help us with that. This is something we didn't have on our radar screens just five years ago."

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