

# How Cells Clean House

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Section: BIOLOGY

Worn-out proteins, malfunctioning organelles, invading microorganisms: all are swept up by tiny internal "Vacuum cleaners" that keep a living cell healthy. If the process, called autophagy, can be kept in good working order, aging itself might be delayed.

### [KEY CONCEPTS](#)

- Inside the cytoplasm of a living cell, organelles called autophagosomes continually engulf bits of cytoplasm, along with damaged cell parts and invading bacteria and viruses. The "sweepings" are carried to digestive organelles for breakup and recycling. The process is called autophagy.
- Cell biologists are learning about autophagy in great detail by tracing the protein signals that drive and control the process.
- A fuller understanding of autophagy is opening up new options for treating cancer, infectious disease, immune disorders and dementia, and it may one day even help to slow down aging.

--The Editors

Every once in a while biologists come to realize that what was at one time regarded as a minor and relatively obscure cellular process is, in fact, of central importance. Not only is the process ubiquitous, but by virtue of that ubiquity it also plays a role in a broad range of normal and disease states. So it was with the discovery of the role of nitric oxide in the circulatory system, a discovery that led to a Nobel Prize, as well as to many beneficial drugs. Now another formerly obscure process known as autophagy is suddenly claiming extraordinary scientific attention.

In basic outline, autophagy (from the Greek, meaning "self-eating") is simple enough. Within every cell but outside the nucleus lies the cytoplasm, a kind of formless jelly supported by a skeletal matrix, in which a vast and intricate population of large molecules, or macromolecules, and specialized functional subunits called organelles is suspended. The workings of the cytoplasm are so complex--rather like some of today's computer systems--that it is constantly

becoming gummed up with the detritus of its ongoing operations. Autophagy is, in part, a cleanup process: the trash hauling that enables a cell whose cytoplasm is clotted with old bits of protein and other unwanted sludge to be cleaned out.

Refurbishing the cytoplasm can give new life to any cell, but it is particularly important to cells such as neurons that do not get replaced. A neuron that must live as long as the organism that hosts it has virtually no other way to renew and maintain its operations. Cell biologists have also determined that autophagy acts as a defense against harmful viruses and bacteria. Any foreign object or organism that evades the extracellular immune system and makes its way through the cell membrane into the cytoplasm becomes a potential target for the autophagy system.

By the same token, when autophagy runs too slow, runs too fast or otherwise malfunctions, the consequences can be dire indeed. Many of the millions of people who suffer from Crohn's disease, a form of inflammatory bowel disease, may have defective autophagy systems that cannot keep the microbial flora in the gut from growing uncontrollably. A breakdown in the autophagy system in brain neurons has been linked to Alzheimer's disease, as well as to aging itself. Even a well-oiled autophagy system can be detrimental, enabling a cancer cell targeted by a blast of radiation or a toxic dose of chemotherapy to survive and repair itself, thereby perpetuating the cancer. Autophagy can sometimes act to eliminate a diseased cell for the greater good of the organism, but it can also become overzealous, consuming a cell even when the loss of that cell is not in the interest of the organism.

In the past decade investigators have been able to learn in great detail how the autophagy system works. Such insights are important not only because they enhance the basic understanding of how cells work, but also because they could lead to the design of drugs that might induce the system to ramp up or quiet down as needed. Controlling the rates of the process as well as the specific targets of its activities could have enormous therapeutic benefits and might even alleviate some of the decline in brain functioning people experience as they age.

### [Rescue Squad Turned Cleanup Crew](#)

Biologists apply the term "autophagy" to several related processes, but here we mean the kind of cleanup technically known as macroautophagy that has been most thoroughly studied so far. The process begins as various proteins and lipids, or fats, in the cytoplasm form sheets of double-layered membrane [see box on next two pages]. The sheets of membrane curl up on themselves into an open-ended globule that simply engulfs bits of cytoplasm along with whatever might be inside them. The globule, called a phagophore, then seals itself into a closed capsule known as an autophagosome. The autophagosome generally ferries its cargo to a lysosome, a kind of disposal plant, elsewhere within the cytoplasm. Typically the two organelles fuse into an "autolysosome," where the autophagosome gives up its cargo to the "digestive juices" of the lysosome. The useful molecular pieces that remain after digestion are recycled back into the cytoplasm.

In a general way, the process as an ongoing cellular activity has been recognized at least since the 1960s, when Christian de Duve of the Rockefeller University and others studied it under the electron microscope. Ten years ago one of us (Klionsky) and others (particularly Yoshinori Ohsumi of the National Institute for Basic Biology in Okazaki, Japan, and his co-workers) began

to study its molecular biology in yeast, which is far simpler than studying the same function in higher animals. That strategy has exposed many of the otherwise elusive details of the autophagic machinery because many of the proteins that take part in autophagy or regulate it are virtually identical to their counterparts in people, having remained little changed throughout evolution.

Autophagy itself may have evolved as a response to cell starvation or as a primitive immune defense, or both. To appreciate the need for a starvation response, think about what happens when an entire organism is deprived of food. If a person restricts food intake, the body does not immediately cease functioning and die; instead it starts to break down its own nutritional reserves. Fat cells can go first, but ultimately even muscle cells are broken up and fed to the metabolic fires to keep essential processes running.

Similarly, when cells starve they, too, break down parts of themselves to maintain their essential activities. Autophagosomes are active continuously, whether a cell is starving or not, engulfing bits of cytoplasm and so repeatedly renewing much of the cytoplasmic content. But several kinds of stress--starvation, the absence of growth factors or lack of oxygen, to name a few--signal the cell to speed up its assembly of autophagosomes. Hence, when nutrients are scarce, autophagy intensifies; autophagosomes scavenge the cytoplasm for proteins and organelles (regardless, it seems, of their functional status) that can be digested into nutrients and energy the cell can use.

If autophagy evolved, in part, as a response to starvation, its housekeeping function--even when nutrients abound--has long since become just as vital to the cell. Autophagosomes help to rid the cell of various kinds of unwanted denizens of the cytoplasm. Proteins, for instance, which carry out all the work of the cell, are sometimes put together incorrectly, and they can "wear out" with time. As a result, they may not function or, worse, may malfunction. If so, they must be culled before they cause a problem. Continuous autophagy keeps their concentrations at a low level.

Autophagosomes not only remove damaged proteins, but they also seek out and sequester damaged organelles many times the size of a protein. Mitochondria, for instance, are the organelles primarily responsible for generating energy within a cell, and they can send signals to other parts of the cell that initiate apoptosis, or cellular suicide.

Cells induce apoptosis for a variety of reasons, all more or less for the greater good of the organism. For example, the body continually generates more cells than it needs, and they must be eliminated. An aging cell that has ceased functioning efficiently may kill itself to make room for younger, more robust cells. A cell that switches from normal growth to cancerous proliferation can also be induced to commit suicide, making apoptosis one of the most important built-in barriers against cancer. Apoptosis depends on a complex series of cellular events, rigorously orchestrated by numerous protein signals, and so the death of the cell by apoptosis is considered to be a programmed event.

But a faulty mitochondrion can wreak havoc if it sets off apoptosis at the wrong time [see box on next page). Among the by-products of a functioning mitochondrion are reactive oxygen species (ROS)--oxygen ions and other oxygen-based molecular fragments. Working with such volatile chemicals often causes mitochondria to leak some of their contents, including the signaling

proteins that initiate apoptosis. In other words, a minor flaw in a small part of the cell can lead, inadvertently, to the death of the entire cell. The accidental cellular demise of a few skin cells might not be a big deal, but such a loss of memory neurons in the brain would definitely spell trouble.

Autophagy is a fail-safe against such a destructive mistake. Autophagosomes can remove damaged mitochondria and other kinds of organelles from the cytoplasm and ensure that they are destroyed by lysosomal enzymes in an autolysosome before they can induce an unscheduled programmed cell death--or, worse, the disorganized cellular demise known as necrosis.

Mitochondria can also release ROS into the cytoplasm, which, as the name "reactive oxygen species" implies, tend to react with many other molecules. In a healthy cell ROS levels are kept under control by antioxidant molecules that scavenge ROS. According to Shengkan V. Jin of the University of Medicine and Dentistry of New Jersey, however, when mitochondria become damaged, they can flood the cell with 10 times the usual release of ROS, much more than normal cellular detoxification systems can handle. The escape of such large amounts of ROS poses a cancer threat, because ROS that reach the nucleus may induce malignant changes in genes. Once again, autophagy can come to the rescue, removing the dysfunctional mitochondria from the cell. Eileen White of Rutgers University believes that autophagy also mitigates genome damage in cancer cells, thereby helping to prevent new tumors from forming.

### [Double-Edged Sword](#)

Soon after cell biologists unraveled the intricate molecular pathways of apoptosis, they recognized that cells can kill themselves by other means as well. Autophagy became a prime suspect. Current nomenclature reflects that history: apoptosis is also known as programmed cell death type I; autophagy is sometimes referred to as programmed cell death type II--although that designation remains controversial.

Autophagy could lead to cell death in two ways: the process might simply continue digesting the contents of the cytoplasm until the cell dies, or it may stimulate apoptosis. But why would a process that often prevents untimely cell death from accidental apoptosis sometimes be invoked to cause cell death itself? The puzzle may turn out to have a fascinating resolution. Apoptosis and autophagy may be closely interrelated and carefully balanced. For example, if organelle damage is too extensive for autophagy to bring under control, the cell must die for the sake of the entire organism. The cell may then rely on either of its suicide programs: it may allow autophagy to continue to the end, or it can signal for apoptosis, holding autophagy as a backup system if apoptosis is compromised. Two of the most intense and somewhat controversial areas of current investigation are how autophagy and apoptosis interconnect and whether autophagy on its own should be considered a pathway for cell death. Work at the molecular level may help resolve whether autophagy is primarily a pathway for cell survival or whether it can, in addition, act as an "angel of death." Recent studies by Beth Levine of the University of Texas Southwestern Medical Center at Dallas and Guido Kroemer of the French National Scientific Research Center (CNRS) have shown how the two processes can be coordinated. One of the proteins that signals for autophagy to begin, known as Beclin 1, binds with a protein that prevents apoptosis from starting, Bcl-2. Life-and-death decisions are made as bonds between the two kinds of proteins are

enhanced or broken. Levine's findings of that connection between autophagy and apoptosis have been further supported by the discovery that a fragment of a protein known as Atg5, which plays a leading role in the formation of autophagosomes, can make its way to mitochondria. Once there Atg5 can switch what was initially a purely autophagic response to an apoptotic one.

Every benefit seems to have its flaws, and autophagy is no exception. We noted earlier that cancer cells can sometimes invoke autophagy to save themselves. Anticancer treatments are often aimed at inducing malignant cells to commit suicide. Yet some cancer cells can defend against the treatments because autophagy jumps in to remove damaged mitochondria before they can trigger apoptosis. In fact, radiation and chemotherapy can actually induce higher-than-usual levels of autophagy.

Cancer cells can also take advantage of autophagy to avoid being starved. Few nutrients can reach the inside of a tumor, but as we mentioned earlier, a shortage of nutrients can trigger autophagy, prolonging the life of a cancer cell by enabling it to break down its own macromolecules for food. A straightforward treatment strategy might therefore be to suppress autophagy within a tumor or during radiation therapy or chemotherapy. Drugs for that purpose are in clinical trials. Unfortunately, as White points out, suppressing autophagy could boost the number of genetic mutations in cancer cells and so increase the chances of a relapse. It may take some fine-tuning to get the treatments right.

### [Preventing Neuron Breakdown](#)

Given the role of autophagy in keeping the cytoplasm clear of detritus and malfunctioning parts, it is hardly surprising that the process turns out to be particularly important to the well-being of long-lived cells such as neurons. Inefficient autophagy plays a pivotal role in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. All three cause slow but inexorable changes in the brain, but Alzheimer's, a form of dementia that afflicts 4.5 million people in the U.S. alone, is the most common.

One of the most frequent effects of normal aging is the accumulation of a brownish material called lipofuscin, a mix of lipids and proteins, in the bodies of brain cells. Superficially, the stuff can be likened to liver spots on aging skin. The accumulation of such material, according to Ralph A. Nixon of the Nathan S. Kline Institute for Psychiatric Research, is a sign that aging brain cells can no longer remove abnormally modified or damaged proteins fast enough to keep pace with their buildup. In Alzheimer's patients, a yellowish or brownish pigment called ceroid also builds up inside neurites, or projections from nerve cell bodies. The neurites swell where ceroid collects, and amyloid, or senile, plaques characteristic of the disease form on the outside of the swollen neurites.

So far investigators have not fully deciphered the exact ways senile plaques or their precursors lead to neuron damage. But the latest research shows, tellingly, that enzymes that help to deposit the plaques in certain early-onset forms of Alzheimer's are present on the membranes of autophagosomes. According to Nixon, such plaques may stem in part from incomplete autophagy and the consequent failure of the neurons to digest substances that would normally be swept up from their cytoplasm, broken down and recycled for parts. Supporting Nixon's

conclusion, electron micrographs of senile plaques in the brains of Alzheimer's patients show massive numbers of immature autophagosomes accumulating inside the parts of the neurons nearest the plaques. Precisely how the plaque material may collect on the outside of nerve cells has not been conclusively traced.

Given those results, it would seem that any means of promoting autophagy might slow the onset of the debilitating symptoms of Alzheimer's. Regretfully, however, no one yet knows whether activating autophagy in Alzheimer's patients would have any benefit, if the treatment cannot also ensure that autophagosomes fuse with lysosomes. But the good news is that such a treatment might be effective for Huntington's patients. A drug known as rapamycin, or sirolimus, which suppresses immunity and is used to block the rejection of organ transplants, particularly kidney transplants, turns out to induce autophagy as well. Rapamycin is now being tested for its effectiveness in stimulating autophagy to remove a kind of protein aggregate seen in Huntington's patients.

### [Getting Bugs Out of the System](#)

If an autophagosome can capture and destroy a leaky, cell-endangering mitochondrion, couldn't it do the same to unwanted parasites that invade the cellular interior--bacteria, protozoa and viruses that manage to get through the cell membrane? In fact, that hypothesis was recently verified experimentally. Taken together, studies by one of us (Deretic) and, nearly simultaneously, by two groups in Japan, one led by Tamotsu Yoshimori of Osaka University, the other by Chihiro Sasakawa of the University of Tokyo, have shown that autophagy can eliminate a diverse range of pathogens. The list includes *Mycobacterium tuberculosis*, the tuberculosis bacterium annually responsible for two million deaths worldwide; gut pathogens such as *Shigella* and *Salmonella*; group A streptococci; *Listeria*, which occurs in raw-milk cheeses; *Francisella tularensis*, which the Centers for Disease Control and Prevention has listed as a bioterrorism agent; and parasites such as *Toxoplasma gondii*, which is a major cause of illness in people with AIDS.

Yet just as cancer cells can exploit autophagy for their own survival, some microorganisms have evolved ways to subvert the process. For example, *Legionella pneumophila*, which causes Legionnaires' disease, is a bacterium, that readily gets inside a cell. But if *L. pneumophila* bacteria are engulfed by an autophagosome, they can delay or even prevent the autophagosome from fusing with a lysosome. Thus instead of serving as a vehicle that helps to rid the cell of a pathogen, the infected organelle becomes a niche where the bacteria can replicate, using the sequestered cytoplasm as a nutrient supply.

The very existence of such clever evolutionary tactics is good evidence that autophagy has long functioned as a major barrier to invasion by pathogens and their replication in human cells--a barrier that disease-causing agents must overcome to survive. Not surprisingly, HIV is another good example of a pathogen that can harness autophagy for its own purposes. Two groups in France, one led by Martine Biard-Piechaczyk of the Center for Studies of Pathogenic Agents and Biotechnologies for Health and the other by Patrice Codogno of INSERM, have jointly shown that HIV, which infects immune system cells known as CD4+ T cells, can increase cell death in uninfected "bystander" cells of the same kind. As HIV enters a cell, it sheds its outer envelope,

and the protein that makes up the envelope induces uncontrolled, excess autophagy and then apoptosis in cells that surround the HIV-infected cell. Thus by activating autophagy in "innocent" bystander cells, HIV further reduces the number of healthy CD4+ T cells in the body. Eventually the catastrophic loss of immune system cells brings about full-blown AIDS.

### The Immune Connection

Autophagy not only eliminates pathogens directly; investigators have also found that it takes part in immune responses [see box below]. For example, autophagosomes help to deliver pathogens or pathogen products to membrane molecules called toll-like receptors (TLRs), a subset of the regulators that control the so-called innate immune response. The role of autophagosomes in the process is to make a clever "topological" inversion. A pathogen in the cytoplasm can hide from TLRs because TLR binding sites for pathogens face away from the cytoplasm. The binding sites point either toward the space outside the cell or toward the inside of an endosome, or intracellular compartment. But autophagosomes can fix this topological problem by scooping up pathogens or their parts from the cytoplasm and delivering them to an endosome that embeds TLRs in its membrane. There the pathogen molecules meet TLRs at last. Their encounter signals the cell to produce chemicals called interferons, which act, for instance, to suppress the replication of the pathogen. This innate immune response is generated to combat infection as soon as it starts--no time is needed for the cell to build a highly specific response to the pathogen.

But autophagosomes can also help build that highly specific immune response, known as adaptive immunity. For example, when a virus invades the cytoplasm and tricks the cell into making viral protein, an autophagosome engulfs some of the viral protein and ushers it into another kind of endosome that embeds so-called MHC class II molecules in its membrane. Once inside that endosome, the viral protein is partly broken up, and a piece of it is loaded onto a part of an MHC class II molecule that faces the inside of the endosome. (Just as with the TLR, the MHC class II molecule would not meet properly with the pathogen molecule if the autophagosome did not bring the pathogen molecule inside the endosome.) Once the MHC class II molecule is bound to the pathogen fragment and the assemblage is transported to the surface of the cell, the immune system begins mounting an adaptive immune response, a slower but far more specific and more efficient response than innate immunity can muster.

### Long Life?

Remarkably, autophagy may also play a role in determining the human life span. Most people take it for granted that many diseases become more frequent with age, including cancer and the degeneration of neurons. The reason, in part, may be a decline in the efficiency of autophagy. According to Ana Maria Cuervo of the Albert Einstein College of Medicine, the current thinking is that cellular systems, including autophagy, undergo a steady loss of function with age. In particular, the systems that remove aberrant or dysfunctional proteins and organelles begin to work less efficiently, and the resulting buildup of damaged cellular components leads to disease.

If inefficient autophagy is to blame, Cuervo says, that could help explain why caloric restriction has been found to extend average life spans in several kinds of experimental animals. The less

food such animals eat (provided they get an adequate supply of essential nutrients), the longer they live, and the same may be the case for people. Recall that a restricted food supply--incipient starvation--speeds up autophagy. Hence, caloric restriction as one ages might offset the natural age-related decline of autophagy and so prolong the essential housekeeping function of the process in cells. Furthermore, Cuervo adds, recent research shows that if you can prevent the decline of autophagy in experimental animals, you can often avoid the usual age-related buildup of proteins damaged by reactions with oxygen compounds.

What was once seen primarily as a hedge against cellular starvation has come to be recognized as central to a broad range of factors affecting human health and disease. Research into autophagy is expanding in new and unexpected directions, generating an exponentially increasing body of scientific knowledge. But we have only begun. Learning to promote or inhibit autophagy at will holds great promise for the treatment of disease and perhaps even for slowing down the natural process of aging. But whether autophagy can be harnessed to benefit health, much less to become the elusive fountain of youth, will depend on gaining a fuller understanding of its mechanisms and of the intricate biochemical signals on which it depends.

### [MORE TO EXPLORE](#)

**Cell Suicide in Health and Disease.** Richard C. Duke, David M. Ojcius and John Ding-E Young in *Scientific American*, Vol. 275, pages 80-87; December 1996.

**Autophagy in Health and Disease: A Double-Edged Sword.** T. Shintani and D. J. Klionsky in *Science*, Vol. 306, pages 990-995; November 5, 2004.

**Autophagy in Immunity and Infection: A Novel Immune Effector.** Edited by Vojo Deretic. Wiley-VCH, 2006.

**Potential Therapeutic Applications of Autophagy.** D. C. Rubinsztein, J. E. Gestwicki, L. O. Murphy and D. J. Klionsky in *Nature Reviews Drug Discovery*, Vol. 6, pages 304-312; April 2007.

PHOTO (BLACK & WHITE): AUTOPHAGOSOME bounded by a double membrane has engulfed a mitochondrion, visible as the dark region inside the autophagosome. The image is magnified 35,000x.

PHOTO (COLOR)

PHOTO (COLOR)

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By Vojo Deretic and Daniel J. Klionsky

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Daniel J. Klionsky is Alexander G. Ruthven Professor of Life Sciences at the University of Michigan Life Sciences Institute. He is a former fellow of the John Simon Guggenheim Memorial Foundation, a National Science Foundation Distinguished Teaching Scholar and editor in chief of the journal *Autophagy*.

## **SURVIVING STARVATION**

Autophagosomes are constantly consuming parts of the cytoplasm, but nutrient scarcity boosts their baseline number. That increase speeds up the rate at which intracellular components, including intact proteins and other macro-molecules, are digested by autolysosomes into basic biochemical building blocks that are delivered to the cytoplasm as nutrients. The nutrient scarcity also signals the cell to reduce its functioning volume (schematically portrayed here as shrinkage). Without such literal "self-eating," the essential activities of the cell could not continue and the cell would die.

PHOTO (COLOR): Healthy cell

PHOTO (COLOR): Nutrient-deprived cell

LIVE OR LET DIE?

## **MAKING THE ULTIMATE DECISION**

The last act of a badly damaged cell can be to trigger its own death for the greater good of the organism. One suicidal pathway called apoptosis begins when mitochondria in the cytoplasm release signaling proteins. Some investigators have proposed that autophagy can act to save the cell from unnecessary apoptosis. Paradoxically, autophagy may also act as a second suicidal pathway when cell death is needed but apoptosis fails. Moreover, apoptosis and autophagy share certain kinds of signaling proteins, suggesting that the two processes engage in cross talk and may best be regarded as parts of a more comprehensive system within the cell.

**AUTOPHAGY AS SAFETY NET:** A damaged mitochondrion can send a spurious signal for the cell to begin apoptosis, even though the cellular damage is minimal. Autophagy can prevent the signal from causing unnecessary cell suicide.

**AUTOPHAGY AS "DECIDER":** In a badly damaged cell the system for triggering cell suicide responds dynamically to signals of stress. In the end, autophagy may throttle down, enabling the cell to survive; continue devouring the cell from the inside until it dies; signal for cell suicide by apoptosis (not shown); or, if apoptosis fails, serve as a suicidal backup to prevent the disorganized cell demise known as necrosis.

PHOTO (COLOR): 1 Signaling proteins that initiate apoptosis leak out of a damaged mitochondrion in the cytoplasm of an otherwise healthy cell

PHOTO (COLOR): 2 An autophagosome engulfs the damaged mitochondrion and the leaking signaling proteins, squelching the spurious signal

PHOTO (COLOR): 3 The autophagosome fuses with a lysosome and the toxic cargo is destroyed, saving the healthy cell

PHOTO (COLOR)

**AUTOPHAGY IN ALZHEIMER'S?**

**WHEN THE CLEANING STOPS**

In an aging brain neuron, autophagosomes can fail to complete their development, leading to a buildup of damaged proteins and consequent swelling in a neurite, or projection from the cell body of the neuron. The immature autophagosomes collect at the same site. Enzymes {yellow} that create protein fragments called amyloid beta seem to concentrate on the immature autophagosomes, and those fragments collect on the outer neurite surface {orange}. Aggregates of amyloid beta are the so-called senile plaques characteristic of neurons in the brains of Alzheimer's patients. Together those findings suggest that a breakdown in autophagy may contribute to Alzheimer's disease.

PHOTO (COLOR)

**CELL DEFENSE**

**REPELLING INVADERS**

Autophagy can mount several kinds of defenses against pathogens that enter the cytoplasm. The diagram shows how they can operate.

[PATHOGEN DEGRADATION](#)

Vesicle that buds off the cell membrane with an invading microorganism inside can be "swallowed whole" by an autophagosome and digested into harmless fragments by a lysosome

DIAGRAM: INNATE IMMUNE RESPONSE | 1: Virus that evades the first line of autophagosome defenses releases its nucleic acid (RNA, for instance)

DIAGRAM: INNATE IMMUNE RESPONSE | 2: An autophagosome delivers some of the viral RNA to an endosome, or compartment in the cell

DIAGRAM: INNATE IMMUNE RESPONSE | 3: Viral RNA in the endosome binds with a TLR, stimulating production of more autophagosomes and interferon (an "innate" response) that can interfere with viral replication

DIAGRAM: INNATE IMMUNE RESPONSE | 4: The cell translates some of the remaining viral RNA into viral protein

DIAGRAM: ADAPTIVE IMMUNE RESPONSE | 5: An autophagosome delivers viral protein to another kind of endosome, where the protein is broken up

DIAGRAM: ADAPTIVE IMMUNE RESPONSE | 6: A fragment of viral protein is loaded onto an MHC II molecule and presented at the cell surface, triggering a specific "adaptive" immune response against cells infected with the virus

DIAGRAM: PATHOGEN DEGRADATION