THE MANY FACES OF DEATH

Anastasis is not the only way to grant cells a stay of execution. Last year, in experiments involving gene silencing in cultured mammalian cells, immunologist and cell biologist Yinan Gong of the University of Pittsburgh Medical Center and his colleagues unexpectedly found that another form of programmed cell death, necroptosis, can also reverse.

In necroptosis—a programmed version of necrosis, a form of cell death linked with uncontrolled reactions to injuries or stress—a protein known as mixed lineage kinase-like (MLKL) opens holes in the plasma membrane, rupturing cells. Gong and his colleagues found that necroptosis does not always prove fatal. Instead, the ESCRT-III protein complex can isolate these holes onto bubbles in the plasma membrane. Shedding these bubbles then repairs the cells, a process the scientists dubbed "resuscitation."[10] The team hypothesizes that necroptosis happens when MLKL essentially overwhelms ESCRT-III.

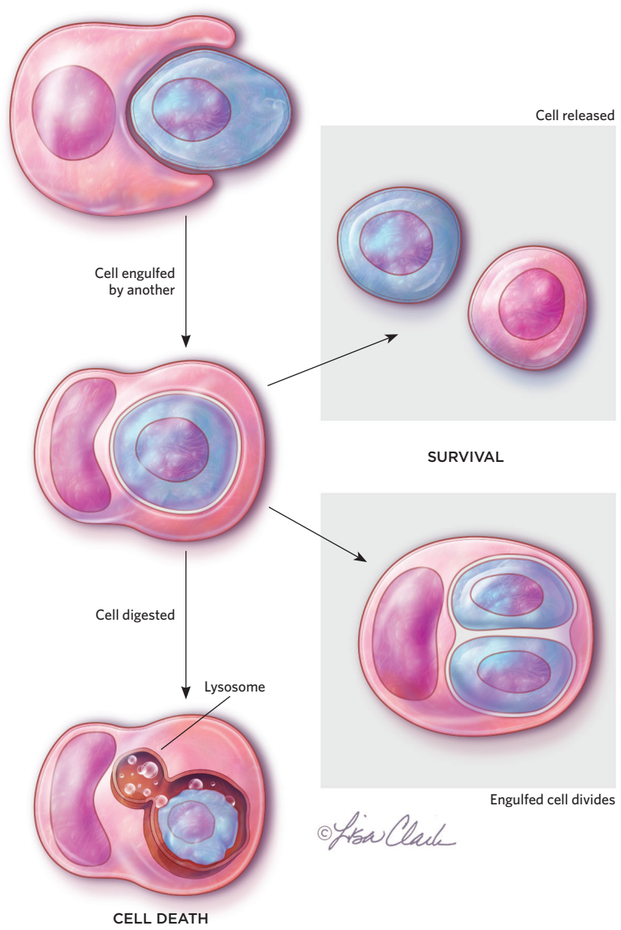
Other forms of cell death appear reversible, too. For example, in 2012, chemical biologist Scott Dixon of Stanford University found that ferroptosis, a form of cell death that is dependent on iron, can be reversed by treatment with lipophilic antioxidants or iron chelators. "Some people might assume that once a cell is exposed to a lethal stimulus, that's it, there is no chance of recovery," Dixon says. Now, research is showing "that a cell can be exposed to a stimulus that might be lethal, but within a period of time there is still a chance for an intervention to rescue the cell—not all hope is lost."

Even the striking form of cell death known as entosis, in which one cell swallows another alive, is reversible, with engulfed cells potentially emerging to continue living. "When a cell is engulfed, its nucleus can look fine, its plasma membrane can look fine, and with time-lapse video, we found it can get out and divide and do fine," says Mike Overholtzer, a cell biologist at Memorial Sloan Kettering Cancer Center in New York. "Cells can even divide while engulfed and emerge and be perfectly viable." He and his colleagues have found that entosis is prevalent in human cancers, and triggers for it include detachment from the extracellular matrix and glucose withdrawal,[11] but what determines an engulfed cell's fate is still unclear.

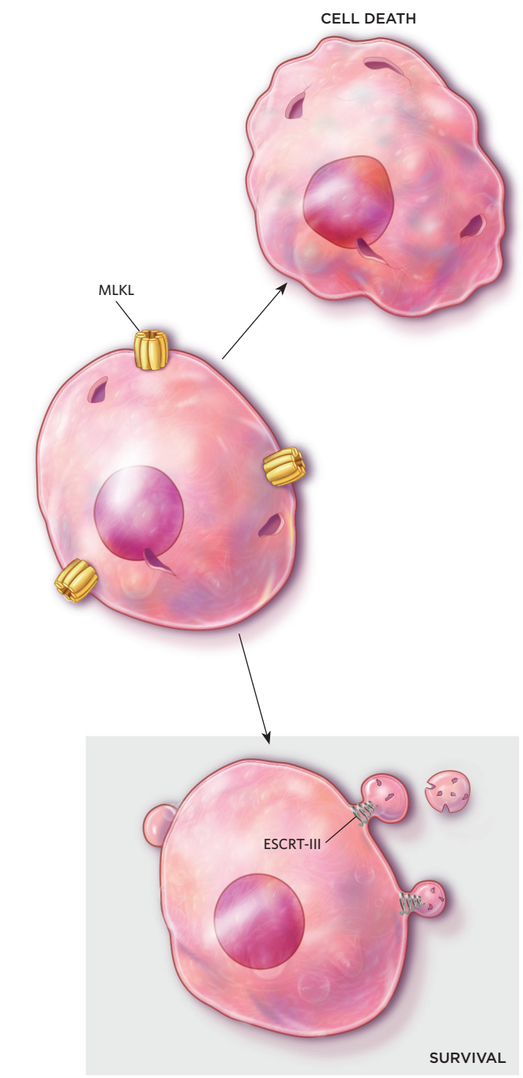
All in all, these findings suggest that these pathways might not always be dead ends. "With people, when a doctor needs to call a death, it's now well-defined—it's brain death. We know that when patients get to a certain point, they cannot come back," Gong says. "The question is still open as to what point a cell must reach before it does not come back."

OTHER FORMS OF CELL DEATH REVERSAL

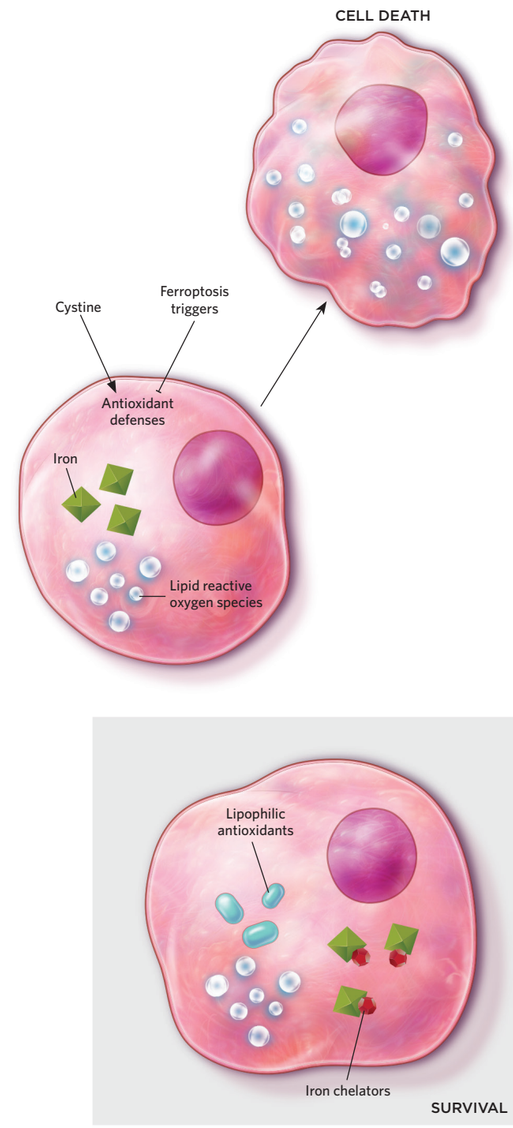
In addition to apoptosis, scientists have proposed more than 20 other regulated forms of cell death. Increasingly, researchers find some of these other kinds of cell death are also reversible.



ENTOSIS
In entosis, one cell engulfs another living cell, which is then killed and digested by lysosomes. Sometimes engulfed cells survive, even proliferating within their cellular captor or escaping altogether.



NECROPTOSIS
Necroptosis is a programmed version of necrosis, a form of cell death linked with uncontrolled reactions to injuries or stress. The process involves the protein MLKL poking holes in the plasma membrane, which causes the cells to rupture. However, the cell can blunt this process through the ESCRT-III protein complex, which isolates these holes onto bubbles in the plasma membrane. Shedding these bubbles then repairs the cells, a process scientists dubbed "resuscitation."



FERROPTOSIS
Ferroptosis is a regulated form of cell death that is dependent on iron. Cells initiate this pathway when normal uptake and metabolism of the amino acid cysteine (cystine is the oxidized dimer form of cysteine) is disturbed. Once triggered, ferroptosis will result in cell death in a few hours. However, researchers can administer lipophilic antioxidants or iron chelators to completely protect cells from succumbing to this form of cell death.