

Homeless cells find temporary lodging -- and their demise

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Sometimes healthy cells commit suicide. In the 1970s, scientists showed that a type of programmed cell death called apoptosis plays a key role in development, and the 2002 Nobel Prize in Physiology or Medicine recognized their work. As apoptotic cells degrade, they display standard characteristics, including irregular bulges in the membrane and nuclear fragmentation.

Now, Harvard Medical School researchers have uncovered a new type of death devoid of these features. In the Nov. 30 issue of *Cell*, they report a bizarre cell-in-cell invasion and death process, which they name entosis, after the Greek word for “within.”

“We watched homeless cells, free of their normal attachments, bore into their neighbors and die inside compartments called vacuoles,” says Michael Overholtzer, a postdoctoral researcher in Joan Brugge’s lab.

“We’re not sure if entosis evolved to play a particular role or if it’s simply an aberration of a normal process,” adds Brugge, who is Chair of the Department of Cell Biology.

Overholtzer discovered entosis while working with human breast cells that normally form sheets of tissue. When these cells become detached from their protein-rich beds, they generally die through apoptosis. But Overholtzer noticed that they behave oddly long before displaying apoptotic features. In fact, many of these homeless cells actually nest inside their neighbors.

Further experimentation revealed that the cells actively invade neighboring cells. While some of the intruders—which initially appear healthy—later exit their hosts unharmed, most die inside vacuoles.

But Overholtzer didn't realize the implications of his initial observation until he crossed paths with Brigham and Women's Hospital pathologist Andrea Richardson. She informed him that the scientific literature is full of "cell-in-cell" references in the context of cancer.

"Although these structures have been described by pathologists for decades, nobody knew how they formed," says Brugge.

Overholtzer conducted additional experiments with his non-cancerous cell line. In collaboration with Guillaume Normand of Associate Professor of Cell Biology Randall King's lab, he tracked the cells over time and was shocked to see that some of them actively bored into their neighbors. Furthermore, the invaders appeared to be healthy.

The fate of the internalized cells was even more surprising. While most of them eventually died, some exited their hosts and swam off unharmed. Still others divided inside their vacuoles, producing daughter cells—and additional proof of the invaders' viability. Overholtzer stained the suspended cells for a protein associated with apoptosis to confirm that it was not playing a role.

"Pathologists have speculated for years that some internalized cells are alive and our data suggests they were right," says Overholtzer.

Next, he looked at other human cell lines. A variety of them displayed entosis when tested, including four of nine tumor lines. Cancerous MCF7 cells proved particularly prone to invasions with a whopping 30 percent of them housing "neighbors." These hospitable hosts invited additional experiments.

After 24 hours, 12 percent of MCF7 cells displayed massive cellular and nuclear degradation lacking apoptotic hallmarks. All of these cells were nestled inside vacuoles, and stains implicated acidification in their death.

He still doesn't know which cell orders the killing, but it appears the houseguest forces its way into the host. The initial contacts between MCF7 cells resemble the junctions established during a normal epithelial process that occurs when cells press against each other to form dense sheets. In suspension, epithelial cells may hijack this process to push into neighboring cells or to pull the membrane of a neighboring cell around them.

“The simplest explanation is that entosis is an aberration of normal epithelial processes,” Overholtzer says. “The invasion could occur when you get unequal contractile forces between two unanchored cells.”

But he and Brugge haven't ruled out other possibilities. Perhaps entosis represents a new type of programmed cell death that evolved for a particular purpose.

“It's very difficult to know whether this is a cellular program with a normal role in development,” says Brugge.

Regardless of its origins, entosis shows up in the clinic. Overholtzer collaborated with Edmund Cibas at Brigham and Women's Hospital and Stuart Schnitt at Beth Israel Deaconess Medical Center to obtain fluid exudates (derived from the circulatory system) and primary tumor tissue from breast cancer patients. Seven of eight exudates and 11 of 20 primary breast carcinomas displayed some cell internalization.

The next step is to determine if entosis helps or hurts cancer cells.

“Our first instinct is that entosis inhibits tumor progression by killing

‘homeless’ cancer cells before they colonize distant sites, and we’re working on ways to model this,” says Overholtzer. “One could also imagine that entosis promotes tumor progression by providing nutrients for some cells from their neighbors, but we do not yet have evidence for this.”

Source: Harvard Medical School

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