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Cannibalistic signals help mammalian embryos develop normally

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A cannibalistic process called autophagy spurs dying embryonic stem cells to send "eat me" and "come get me" signals to have their corpses purged, a last gasp that paves the way for normal mammalian development, UT Southwestern Medical Center researchers have found.

Autophagy is the way cells devour their own unwanted or damaged parts. It was known to be active in cell death that occurs during normal embryonic development, but its precise role was unclear.

Some thought it might contribute to cell death or actually help keep cells alive.

The novel role autophagy plays in removing cells that die during normal embryonic development is described in a study appearing online today in *Cell*. Mouse embryos lacking autophagy have cells that can't make the chemical signals needed for their removal by healthy cells. If dead cells build up, it can result in abnormal development and inflammation and also trigger autoimmune disease.

"The activation of autophagy in cells destined to die may serve to clear dead cells and prevent detrimental inflammation during normal development or when cell death occurs in certain diseases," said Dr. Beth Levine, professor of internal medicine and microbiology and chief of the division of infectious diseases at UT Southwestern. "Our findings also suggest that defects in autophagy might trigger autoimmune diseases and, if so, reversing the defects could potentially help treat such

diseases."

To determine autophagy's role in development, Dr. Levine, the Cell study's senior author, and her research team examined autophagy in mouse embryonic stem cells during cavitation. In this earliest wave of programmed cell death that occurs during mammalian development, cells form a ball, known as an embryonic body, and cells in the center die and are removed, leaving a gap.

But in mouse embryonic bodies lacking the autophagy genes atg5 or beclin1, cells died normally but remained in the center. The embryonic bodies then failed to develop normally.

Researchers took this a step further and studied actual mice that lacked the autophagy genes in their lung and retinal tissues, finding that healthy cells engulfed fewer than 25 percent of dead cells during embryonic development, compared to 75 percent in normal mice.

"Without autophagy, the dead cells just don't get engulfed very efficiently," Dr. Levine said. "If you don't have rapid removal of dead cells, you get a lot of unwanted inflammation."

But why do the dead cells in normal embryos disappear?

Through the study, Dr. Levine and the researchers demonstrated it is due to autophagy's ability in dying cells to prompt signals for engulfment by healthy cells. Engulfment depends on signals from the dying cells. An "eat me" signal is made when the chemical phosphatidylserine is exposed on the outside of cell's membrane. A "come get me" signal is made through the secretion of another chemical, lysophosphatidylcholine.

The autophagy-deficient mouse embryonic bodies failed to develop normally because their cells didn't expose phosphatidylserine and

secreted low levels of lysophosphatidylcholine, the study shows.

"In other words, they didn't generate either of these two needed signals," Dr. Levine said.

The researchers also found that the cells of the autophagy-deficient mouse embryos had low levels of ATP, a vital energy source for many cellular functions. Autophagy is known to generate amino and fatty acids utilized in ATP production.

Treatment with an alternative fuel, methylpyruvate, restored normal levels of ATP in autophagy-deficient mouse embryonic bodies and bypassed the bodies' failure to prompt signals needed for the healthy cells to engulf the dead ones, Dr. Levine said.

"This study shows that autophagy-induced signals are essential for normal development," she said. "It also raises the possibility that defects in autophagy might spur inflammation in human conditions with cell death, such as neurodegenerative diseases or chemotherapy-treatment of cancer."

Source: UT Southwestern Medical Center

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