Cellular 'cannibalism' may be fundamental to development across evolution

14 November 2016

In living beings, from roundworms to humans, some cells may ball up unwanted contents on their surfaces for other cells to "eat." This is the finding of a study led by researchers at NYU Langone Medical Center and published online November 14 in *Nature Cell Biology*.

The results raise the possibility that cellular cannibalism may be more widespread than once thought, and may even shed light on certain brain disorders.

The work was done in the worm species *C. elegans*, which is famous for its role in past discoveries of vital mechanisms also at work in human cells. Specifically, the study found that, as an embryo develops into a worm, cells that pass on genes to the next generation (primordial germ cells or PGCs) form outer lobes, or "balls," that are digested by nearby cells that form the worm's gut.

By forming lobes destined to be clipped off and digested, germ cells may be discarding large amounts of material that would otherwise interfere with reproduction, say the study authors.

"These findings define a new way in which cells dramatically change their contents via cannibalism, and, in doing so, may reveal a new set of genetic causes for diseases when this mechanism goes awry," says Jeremy Nance, PhD, associate professor in the Department of Cell Biology at NYU Langone.

The study poses the question of whether this ability to quickly edit cell contents is vital to the function of many cell types in many organisms, including humans. A 2012 paper led by a separate research team, for instance, proposed that immune cells in the brain prune nerve connections by "eating" bulbs on nearby nerve cell extensions to edit brain circuitry. Some experts have asked whether some forms of autism may be caused by faulty cellular cannibalism. If these mechanisms exist, how widespread are they?

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In worms, as in humans, certain cells in a portion of the embryo, called the endoderm, migrate and become the cells that form the gut. In both species, cells that go on to form the sexual organs, and the cells that will become sperm and eggs, migrate alongside pre-gut cells to end up in their final location at the bottom of the gut.

It was while studying this partnership between co-migrating cell types that the research team first observed one cell type eating part of another. Researchers also found that the lobes put forth for removal by PGCs contained large numbers of mitochondria, the cell powerhouses that convert blood sugar into molecules that serve as cellular energy currency.

One theory for why this occurs is that mitochondria, as a side effect of making energy, also produce highly-reactive free radicals that can damage DNA in a process called oxidative stress. This is a problem for any cell, but more so for the gamete or germ cell, which carries the copy of genetic information that will serve as the template for the offspring. Any random change there could have devastating consequences, not just for one cell, but for future generations.

The study results raise the question of whether germ cells trade lower energy production, by getting rid of mitochondria via cell cannibalism, for greater DNA protection. Researchers will also seek to determine if genetic risk for some forms of sterility proceeds from the failure of cannibalistic mechanisms to protect gametes from oxidative stress.

Specifically, the research team found that lobe cannibalism is carefully choreographed by biochemical signals, with all lobes forming during

the same developmental time window and bitten off in a set order. Furthermore, progenitor gamete cells in worms always form lobes full of mitochondria, but the lobes are only cut off if partnering endodermal cells are present.

Moving forward, the research team will seek to identify the signals by which PGC lobes embed specifically into endodermal cells, and those that tell endodermal cells to eat lobes. The work may also help the field to determine whether similar cellular remodeling events shape brain circuitry, say the authors.

More information: Developmentally programmed germ cell remodelling by endodermal cell cannibalism, *Nature Cell Biology*, nature.com/articles/doi:10.1038/ncb3439

Provided by New York University School of Medicine