Imaging studies reveal order in programmed cell death

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(PhysOrg.com) -- Every day, about 10 billion cells in a human body commit suicide. Cells infected by virus, that are transformed or otherwise dysfunctional altruistically sacrifice themselves for the greater good. Now, new imaging experiments have revealed a previously unseen order to this process, showing closely related cells dying in synchrony as a wave of destruction sweeps across their mitochondria, snuffing out the main source of energy that keeps cells alive.

In experiments published recently in The Journal of Cell Science and Biophysical Journal, researchers in Sanford M. Simon's Laboratory of Cellular Biophysics at Rockefeller University photographed the deaths of individual cells, showing an orderly series of events in the staged shut-down of the cell. The experiments revealed that the likelihood of death, as well as the timing, depends on how closely cells are related, not on their proximity to one another or their stage in the cell cycle. The findings rule out, for instance, the hypothesis that cells die in a localized cascade accelerated by the secretion of toxic molecules from dying cells nearby.

"What we saw is that, regardless of their location, only the sister cells remained linked in the timing of their deaths," says Simon. "It suggests that there is not some nonspecific toxic effect here, but that the variability is in the molecular makeup of the cells — the variability in the population."

Apoptosis is crucial not just in the routine maintenance of life but also in

early development — when some cells, such as those that would otherwise form webbing between human fingers, are programmed to die — and in the tuning and trimming of the nervous system. “I like to think of it as sculpting, chipping away pieces at a time to create the form,” Simon says. A better understanding of apoptosis could help explain certain developmental disorders. What’s more, cell death, or the lack thereof, is important in the pathology of some cancers, in which mutant cells fail to die and grow out of control, forming tumors and spreading throughout the body. One potential therapeutic goal would be to learn how to trigger cell death in targeted populations, like tumors.

Investigating the population dynamics of cell death led to the examination, on a much faster timescale, of what was happening inside individual cells during apoptosis. Using single-cell microscopy and fluorescent tags that probe for cell function or for proteins that leave the mitochondria during apoptosis, graduate fellow Patrick Bhola and Postdoctoral Associate Alexa Mattheyses took pictures as the proteins dispersed through the membrane of one mitochondrion and the process spread in a wave to the other mitochondria in a cell. Some scientists had assumed that this happened simultaneously to all mitochondria throughout the cell. “This spatial coordination means that there is an upstream signal for release that is spatially localized within individual cells,” says Mattheyses.

“The idea in general was to look at individual events in the cells and see if we could get any insights that we could not get looking macroscopically at whole populations of them,” Simon says. Simon’s close-up, observational approach has recently yielded new insights into how cells import and export protein cargoes across the cell membrane and how individual HIV particles are born, among other things. Now the microscopy techniques are enabling a deeper understanding of apoptosis, says Bhola. “It’s one of those things where if you can’t see what’s going on, you tend to assume it’s random or all at once,” he says. “But when

you get a good look, you find it happens in a very organized fashion."

More information:

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-- Journal of Cell Science 122: 4296-4302 (November 3, 2009)
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