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Live and Let Die: Cells' Life and Death Decisions Laid Bare

When cells experience the stress of disease, injury, or development gone awry, they are faced with the decision to soldier on or to commit suicide in the larger interest of the health of the organism.

Now, a team of researchers led by Peter Walter, a Howard Hughes Medical Institute investigator at the University of California, San Francisco (UCSF), has teased out new details about how cells decide their fates when the endoplasmic reticulum, a key quality control center found in all eukaryotic cells, experiences stress. They report their findings in the November 9, 2007, issue of the journal *Science*. HHMI investigator Kevan Shokat at UCSF collaborated on the research with Walter's group.

The new research reported in *Science* reveals a critical way “cells restructure themselves in order to meet changing needs. If the changes cannot be made, the fidelity of their processes is compromised,” said Walter.

"How does a cell make a life or death decision? At first, it tries to fix (the problem). At some point, however, it needs to make decision. If the choice is apoptosis, it's bad for the cell, but it's good for the organism."

- Peter Walter

The research reveals the intimate details of a signaling pathway regulated by the endoplasmic reticulum that is essential for the health of a cell. The finding is important because it unmasks molecular leverage points that may one day have implications for treating a range of human diseases, including cancer, diabetes, proteinopathies and viral infections.

The endoplasmic reticulum is a maze of tubes and sacs within a cell that ensures that proteins are folded properly. Ensuring the quality of folded proteins is essential because proteins are the cell's key messengers and

sensors. If the system is out of whack, it can impede the signals sent or received by cells and compromise the health of the organism.

In short, all the proteins a cell makes must pass through the endoplasmic reticulum on their journey to the cell's surface where they are either secreted to signal other cells or embedded as conduits and sensors in the cell membrane. Only properly folded proteins are allowed through the endoplasmic reticulum. Those that don't pass muster are degraded.

But when a cell is under stress, its protein folding capabilities can be compromised and the level of misfolded proteins can jump, which ratchets up the pressure on the endoplasmic reticulum. In response to stress, the endoplasmic reticulum jump-starts a set of three signaling pathways, known collectively as the unfolded protein response (UPR), that either promote cell survival by reducing protein misfolding, or trigger cell death if the stress on the endoplasmic reticulum isn't alleviated.

“The unfolded protein response adjusts the amount of endoplasmic reticulum in the cell so it can handle the flux in unfolded proteins,” Walter said.

The paradox of the system, Walter explained, is that the signaling pathways simultaneously kick in protective and toxic responses, setting the table for either cell rescue or cell death. The puzzle, he said, is how those pathways coordinate a response to stress and arrive at a tipping point that determines the fate of the cell.

Working with embryonic human kidney cells in culture, Walter's team elicited stress responses by exposing the cells to a drug. As expected, the group observed the activation of all three signaling branches of the UPR. An unexpected observation, however, was that the activity of the individual signaling pathways varied significantly with time, suggesting that varied time courses of the different UPR signaling branches was the key to cell life or death.

To test the idea, Walter's group created cells with an extra copy of the gene that regulates one of the UPR signaling branches: “That allows us to manipulate the timing of one of the pathways with a designer drug, which was developed in Kevan Shokat's lab at UCSF,” said Walter.

By sustaining the activity of the UPR signaling pathway known as IRE1, the cells endured prolonged stress and survived. This finding demonstrated that when that pathway winds down under normal circumstances, cell death is the outcome, said Walter.

To test the idea further, Walter's group used a rat model of retinitis pigmentosa, a heritable disease that can cause blindness when photoreceptor cells in the eye die due to misfolded rhodopsin molecules. “We looked (in the rat model) to see if something similar happened with respect to timing” of the

pathway, Walter said. “And we indeed found that was the case.”

Although more work is required to ferret out all the subtle complexities of the UPR signaling pathways, said Walter, the new findings reported by his group ultimately promise a detailed understanding of a key cellular process.

“How does a cell make a life or death decision? At first, it tries to fix it, said Walter. “At some point, however, it needs to make decision. If the choice is apoptosis, it's bad for the cell, but it's good for the organism.”