

Potassium and Apoptosis

Scientists in the Laboratory of Signal Transduction at the NIEHS have broken new ground in the study of the effect of ions, particularly potassium (K^+), on apoptosis, or "programmed cell death." It is known that apoptosis plays an important role in the development of disease, but little is understood about how this mechanism works. In two papers soon to be published in the *Journal of Biological Chemistry*, investigators John Cidlowski, Carl Bortner, and Francis Hughes, Jr. explain that the loss of K^+ from a cell is a necessary precursor to apoptosis. This is a reversal in the understanding of the role of ion flux in apoptosis; it was thought previously that cell-size modulation and ion flux are secondary events in apoptosis. But these new findings indicate that ion efflux is actually a very early event in cell death.

All cells contain the genetically coded mechanism to begin the apoptotic process, a sort of cell "suicide." Several things happen to a cell during apoptosis. The most obvious and characteristic change is that the cell shrinks. Inside the shrunken cell, the activity levels of certain enzymes escalate, leading to a breakdown of the cell's DNA structure. At this point, the cell body begins to fragment, whereupon it is engulfed by surrounding phagocytic cells. The cascade of events leading to eventual cell death by apoptosis may be triggered by a number of chemical signals. For example, death may occur when a cell is no longer needed, such as when a human fetus loses the webbing between its fingers or when the endometrial lining of the uterus is sloughed off during menstruation, or when

DNA-level damage is detected in a cell, as may occur following infection with a virus.

Because apoptosis is an organism's way of maintaining healthy cell populations, the process, if unduly suppressed or stimulated, can lead to disease; in fact, the phenomenon of apoptosis is a key factor in the development of almost all diseases. For example, in such neurodegenerative diseases as Alzheimer's, heightened apoptosis leads to the premature and exaggerated loss of cells. Conversely, cancer may be the result of a failure in the apoptotic process, in which mutant cells are allowed to proliferate freely rather than being recognized as damaged and destroyed. It's believed that a process that plays such a central role in the development of disease could also play a central role in the prevention of disease. This is the concept behind chemotherapy, which triggers apoptosis by damaging cells, thereby causing the cancerous cells (albeit along with many healthy cells) to die. But chemotherapy and other such treatments don't always work because scientists haven't been sure how to control the apoptotic process. This may be about to change. In their *JBC* papers, the NIEHS scientists demonstrate that the loss of K^+ from a cell is an important signal requirement for apoptosis to begin, rather than a side-effect of the process, as was previously believed.

Much research into apoptosis has centered on the role that enzymes and tumor suppressor genes such as *p53* are thought to play. But because cell shrinkage is routinely regulated by ions and because enzyme activity is often influenced by ion levels, the

NIEHS investigators focused their examination on the effect of ionic changes on the activity of a cell's programmed apoptotic machinery. Specifically, they studied the effect of K^+ in relation to two of the enzymes whose activity level rises in the apoptotic cell: the internucleosomal DNA cleavage nuclease and caspase-3-like protease.

The relationship between cell shrinkage and fragmentation was studied using a combination of flow cytometry, inductively coupled plasma/mass spectrometry, and a fluorometric assay. While K^+ is the primary ion found inside a cell, the cell's external environment is rich in sodium; a constant cell size is maintained as long as the internal and external concentrations of these two ions remain fixed in relation to one another. But in apoptosis, the researchers found, K^+ flows steadily out of the cell, causing a loss in cell volume. And this shrinking of the cell appears to be closely linked to the activation of the enzymes that spur the degradation of the cell's DNA structure, resulting in cell death.

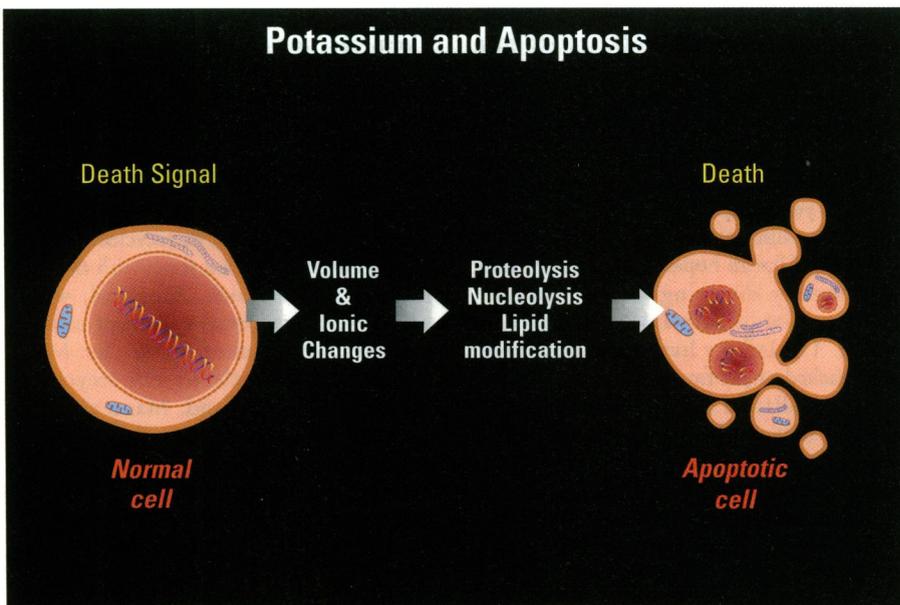
The discovery that K^+ efflux occurs very early in the process sheds light on the order of the chain of events involved in apoptosis, giving researchers a new way to look at how this process might be manipulated. Once a mechanism for voluntarily inducing or suppressing apoptosis is identified, a powerful tool will have been added to the arsenal against disease.

Well, Well, Well Water

A report recently issued by the General Accounting Office (GAO) suggests that many of the nation's private domestic wells are contaminated with excessive levels of nitrate and coliform bacteria. Entitled *Information on the Quality of Water Found at Community Water Systems and Private Wells*, the June 1997 report presents the results of an extensive investigation of private wells and community water supplies in the states of California, Illinois, Nebraska, New Hampshire, North Carolina, and Wisconsin.

According to Luther Atkins, the assistant director of the team that prepared the report in the resources, community, and economic development division at the GAO, the six states were selected based upon the amount of available data on private wells and the percentage of households that use well water for drinking purposes. "There's no single repository of data that speaks to contamination in private wells," Atkins says. "We had to depend on the states and other available studies . . . [and] we tried to get good geographical representation." Most of the data found by the GAO researchers were for total coliform bacteria and nitrate. The limited

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K^+ amikaze cells. NIEHS researchers have uncovered another clue in the mystery of apoptosis—the release of potassium (K^+) from a cell may cause cell shrinkage and spur the degradation of a cell's DNA, leading to cell death.