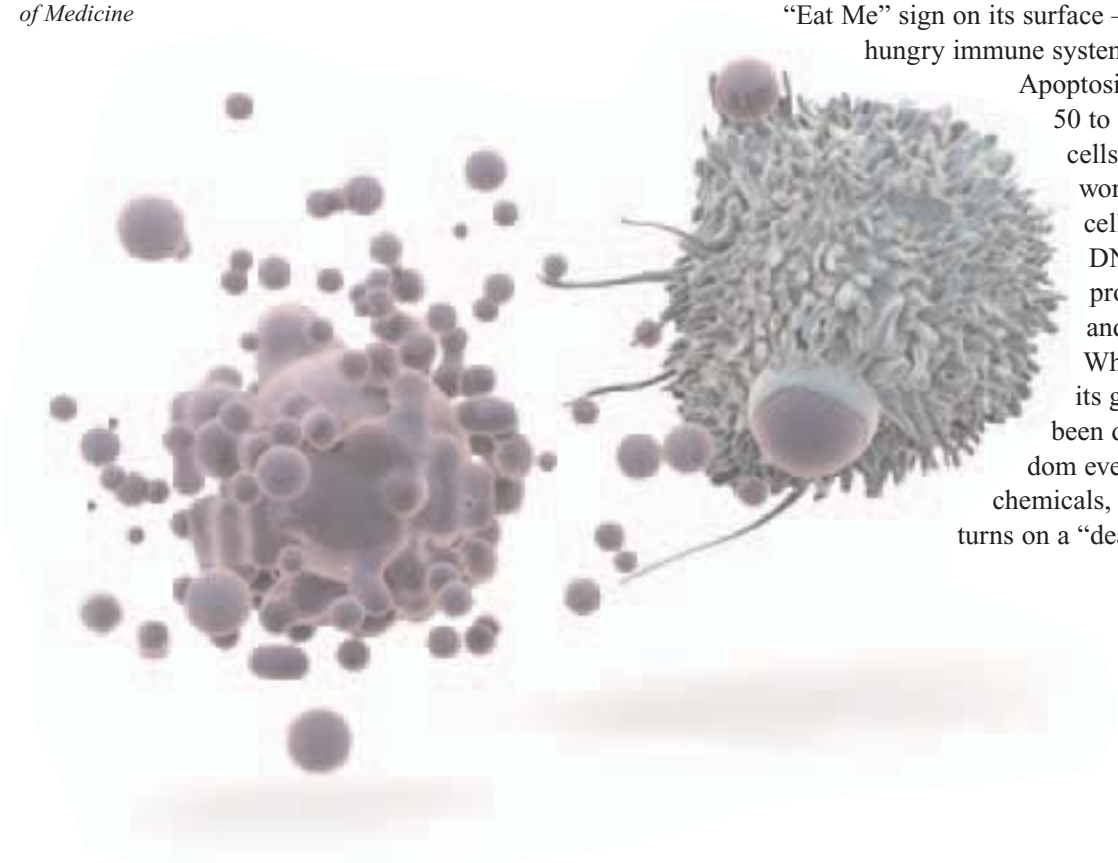
Making cancer cells die 'a good death'

Dana-Farber researchers are harnessing programmed cell death, or apoptosis, to attack tumors

By Richard Saltus

The final stage of apoptosis (natural cell death) involves a white blood cell called a macrophage (at right) consuming cell debris from the suicidal cell.

Image courtesy of U.S. National Library of Medicine



There comes a time in every cell's life to die for the body's greater good. When the orders do come – from outside the cell or within it – the cell obediently destroys itself, and the body disposes of the corpse without a trace.

Though some have called it "suicide without grief," the process of apoptosis, or "programmed cell death," is neither quick nor gentle. Over 24 to 48 hours, a poison cocktail released from within the cell chops up its DNA; the cell shrinks, is dismembered into neatly wrapped pieces, and – after posting a chemical "Eat Me" sign on its surface – is devoured by hungry immune system cells.

Apoptosis rids the body of 50 to 70 billion unwanted cells a day, including worn-out or obsolete cells and those with DNA damage that are prone to running amok and causing cancer. When a cell senses that its genetic blueprint has been damaged – by random events, radiation, or chemicals, for example – it turns on a "death program" of

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apoptotic events to cull itself from the body.

But this defensive purging can hit a snag, as Dana-Farber's Stanley Korsmeyer, MD, famously discovered about 15 years ago. If a surge of "survival" signals within a damaged cell outweighs its death signals, the cell may escape apoptosis and become the seed of a tumor. Genetic mutations in a cell's DNA, among other events, can turn on an excess of survival signals – just one more way in which cancer exploits natural processes to do its dirty work.

Before Korsmeyer made his discovery while based at Washington University in St. Louis, researchers likened the development of cancer to water flowing into a lake faster than it drained out. Triggered by abnormal genes called oncogenes, cells went into overdrive, proliferating abnormally and uncontrollably, forming tumors.

But this picture acquired a new dimension when Korsmeyer, who was studying a form of blood cancer called follicular lymphoma, showed that a broken chromosome caused overproduction of a cell survival factor known as Bcl-2. This protein protected cancerous cells from being shunted off for execution – and made the lymphoma harder to treat. "Bcl-2 was quite a shock and a surprise," he recalls. "We noticed that cells containing mutated Bcl-2 never died." Now the metaphorical lake was not only filling rapidly; its outlet was also blocked, speeding tumor growth.

"Stan's contribution was the realization that this was because Bcl-2 blocks apoptosis, a major insight that profoundly affected how we thought about cell death and survival," says Douglas Green, of the University of California, San Diego, a leading scientist in the field.

A new road to cancer

Korsmeyer's finding put apoptosis – or failed apoptosis, actually – squarely on the map as a fundamental process in initiating and maintaining cancer. The *Bcl-2* gene became the first in a new class of oncogenes (genes that cause cancer) that function by keeping cancer alive.

Since then, Korsmeyer, director of Dana-Farber's Molecular Oncology program since 1998, and others have made a string of discoveries about an entire family of molecules that regulate apoptosis – a word derived from Greek, meaning "falling leaves."

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An oncologist today can choose from at least 100 different cancer drugs, all of them aimed at killing dangerous cells or halting their growth without lethal harm to patients. Most current drugs aren't that selective, but they exploit a weakness of cancer cells – they're more vulnerable than normal ones to damage because their self-repair mechanisms aren't as effective.

Cancer drugs attack malignant cells in a number of ways. Among them:

- Blocking metabolic reactions on which the cell's life depends.
- Damaging the DNA in the cell, causing it to self-destruct by apoptosis (natural cell death).
- Shutting down the cell's ability to divide. Some compounds disrupt chemical reactions needed for DNA to copy itself, while others break the DNA strands. Still others, like taxanes (Taxol® and related drugs) and vincristine, "freeze" the miniature tubes forming the cell's framework so they can't disassemble themselves for cell division.
- Turning off overactive cell growth signals caused by genetic mutations. Among these "targeted" drugs are Gleevec®, Erbitux™, Herceptin®, and Rituxan®. Because they selectively pinpoint cancer cells (normal cells lack the growth-gene mutations), they have fewer toxic side effects than most conventional agents.
- Prodding the body's immune system to recognize and attack cancer cells. Experimental cancer vaccines are made with bits of the patient's own tumor, combined with compounds that trigger a strong immune response.
- Antiangiogenesis – slowing or halting a tumor's growth by disrupting the network of blood vessels that feeds it (see story, page 14). Antiangiogenic drugs include Avastin™, the first of its kind approved for commercial sale.

Despite this array of clever drug strategies, researchers are constantly hunting for new and better ones. Time will tell whether therapies based on the findings of Stanley Korsmeyer, MD,'s lab at Dana-Farber will add a new dimension to the fight against cancer, the nation's leading killer.

Bcl-2 was the founding member of a molecular family that includes several branches, some of them rivals. On one side are the survival-promoting Bcl-2 and its kin; opposing them are pro-apoptotic members such as BID, BAX, and BAK. At any given time, a cell's fate hangs in the balance of a life-or-death battle between pro-survival and pro-apoptotic signals.

Korsmeyer and his Dana-Farber colleagues have now launched the first efforts to treat cancer by tipping the balance in favor of cell death. To be specific, they hope to disable the survival molecules that have been holding their pro-death counterparts at bay. The idea is that the pent-up death signals will rush in and force the cancer cells to commit suicide.

"Cells are rigged to die," says Korsmeyer. "They have to have some intentional signaling, often in the form of growth factors, to keep them going. But when you take away the goodies – the survival factors – then the death program gets turned on."

In cancer, the death mechanism may be very active, but if survival signals hold the edge, they protect the cell from death. Yet this high stakes dynamic is something researchers believe they can exploit.

"There's reason to believe that cancer cells are dying to die," says Anthony Letai, MD, PhD, an Institute researcher formerly in Korsmeyer's lab and now heading his own. "They are on the threshold, generating death signals because cancer cells violate lots of normal rules, and these violations are punishable by death. One way cancer cells escape is through the presence of excess Bcl-2 or similar molecules that thwart apoptotic suicide."

Findings by Stanley Korsmeyer, MD, who joined Dana-Farber in 1998, changed scientific thinking about cell death and survival.

Releasing the brake

Letai compares a normal and a cancer cell to a pair of cars perched on the brink of a cliff. The Ford Taurus – a normal cell – is idling, with the driver's foot on the brake. The Chevy Corvette – the cancer cell – by contrast has its huge engine racing (pro-death signals) and only a heavy foot on the brake (Bcl-2 survival signals) keeps the vehicle still.

Now release the brakes on both cars. The Taurus continues to idle normally, but the Corvette with its pent-up energy shoots ahead – and over the cliff to destruction. Hence

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– Anthony Letai, MD, PhD

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the promise of drugs aimed at releasing the Bcl-2 brake in cancer cells by disabling it, sending the cancer into apoptosis, while normal cells would be much less affected.

Letai, Korsmeyer, and colleagues demonstrated the principle with experiments using mice genetically prone to leukemia. The rodents had been engineered so that the Bcl-2 proteins in their cells could be turned off when an antibiotic was added to their drinking water.

When the mice developed leukemia at five to seven weeks of age, half were given the antibiotic to shut down Bcl-2 activity. Within days, the lack of Bcl-2 caused the death of leukemia cells in the treated animals, and their blood counts returned to normal within 10 days. These mice far outlived their untreated counterparts, who died in just over 100 days. Some of the treated mice survived more than 200 days, and one more than a year.

Drugs that block Bcl-2 haven't reached human clinical trials, though Letai is collaborating with a drug company moving in that direction.

"What better way to kill cancer cells than targeting the molecules that directly control their survival?" he says. "I am confident that compounds like this will be an important class of arrows in our quiver to battle cancer – at least types of cancer in which Bcl-2 is blocking apoptosis."

Another Korsmeyer colleague, Loren Walensky, MD, PhD, has taken a different approach to anti-Bcl-2 drug development. In his work, he borrows a key portion from proteins in the Bcl-2 family that carries out apoptotic cell death. The so-called "BH3-only" protein segment, a string of amino acids nicknamed the "death domain," is critical to activating the cell death pathway.

As a step toward commandeering the natural death domain for use as an anti-survival drug, Walensky and colleagues made a synthetic copy and administered it to mice with leukemia. It required a neat biochemical trick to maintain the domain's Slinky-like coiled structure, but it worked. The artificial molecule blocked Bcl-2 family targets in the mice, and apoptosis killed the leukemia cells.

Research in high gear

Such an encouraging outcome has shifted Walensky and his colleagues into high gear in pursuit of this new drug approach. Many variations of the "death domain" coils exist, and, since some might perform better than others in different cancers, the researchers are hard at work to make and then test large panels of them. "The application of this chemical technology to Bcl-2 domains may lead to an arsenal of new compounds to use against different cancers," he says.

Walensky is gratified that the years spent studying apoptosis and the Bcl-2 family are beginning to bring potential cancer treatments into view. "The beauty of this approach is that you use what nature has already perfected – the pro-apoptotic signals and cell death machinery – to develop new treatments for cancer."

But apoptosis has a flip side. Too much programmed cell death can kill normal cells before their time, resulting in degenerative conditions like Alzheimer's disease and amyotrophic lateral sclerosis (ALS), infertility, and the destruction of pancreatic islet cells in diabetes. Nika Danial, PhD, also in the Korsmeyer lab, has found that the pro-death molecule BAD is involved in apoptosis of insulin-producing islet cells.

In a 2004 publication that gained wide attention, Danial reported that BAD unexpectedly bridges apoptosis and the conversion of glucose (sugar) to energy in the body. She says her work suggests that "controlling cellular metabolism may provide an effective therapeutic tool to manipulate the cell's death machinery to make cancer cells die a good death."

Research on apoptosis has exploded over the last 15 years, with the Korsmeyer lab contributing on many fronts. It's now perfectly reasonable to ask, as he did in the fall of 2004, "Can we exploit the inherent structure of these pro- and anti-death Bcl-2 family members to regulate human diseases?" The answers to that question should begin arriving soon. ■