New strategy directly activates cellular 'death protein'

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Researchers at Dana-Farber/Children's Hospital Cancer Center have devised a strategy to directly activate a natural "death" protein, triggering the self-destruction of cells. They say the development could represent a new paradigm for designing cancer drugs.

In an article published as an advanced online publication by *Nature* Chemical Biology, scientists led by Loren Walensky, MD, PhD, report they identified a prototype compound that "flips a switch" to directly activate one of the most powerful death proteins, known as BAX, triggering apoptosis, or self-destruction of unwanted cells.

"Having identified the 'on switch' for the BAX protein several years ago, we now have a small molecule that can directly turn this death protein on," says Walensky, senior author of the report. The first author, Evripidis Gavathiotis, PhD, carried out the work in Walensky's laboratory; currently he is an assistant professor at Albert Einstein College of Medicine in New York.

The development exploited the discovery by Walensky's team of a distinctive groove, or "trigger site," on the BAX protein that converts it from a quiescent form to an active one. When activated, BAX damages the cell's mitochondria, releasing signals that break the cell apart and digest its pieces. This process of programmed cell death is part of a natural check-and-balance mechanism to control cellular life and death.

In search of molecular compounds that could fit snugly into the trigger

site and jump-start BAX, the investigators used computer-based screening to sift through 750,000 small molecules from commercially available libraries.

The search paid off with the identification of a small-molecule compound named BAM7 (BAX Activator Molecule 7), which selectively bound to BAX and flipped its "on switch," turning it into an active death protein.

"A small molecule has never been identified before to directly activate BAX and induce cell death in precisely this way," explains Gavathiotis. "Because BAX is a critical control point for regulating cell death, being able to target it selectively opens the door to a new therapeutic strategy for cancer and perhaps other diseases of cellular excess."

But wouldn't switching on cell-death proteins in a patient kill normal cells as well? The researchers say that other compounds now in clinical trials that target the apoptosis pathway haven't shown such side effects. Gavathiotis suggests that there are sufficient extra survival proteins in normal cells to protect them against pro-death BAX. Cancer cells, however, are under stress and their survival mechanism is stretched to the limit, so that an attack by BAX pushes the cells over the brink into self-destruction.

The Walensky group has previously developed other compounds designed to spur apoptosis of cancer cells. These agents do so either by blocking "anti-death" proteins, deployed by cancer cells to prevent BAX and other death molecules from carrying out their assignment, or by blocking both "anti-death" proteins and activating "pro-death proteins" simultaneously. BAM7 is the first compound that avoids combat with cancer cell's survival proteins and binds directly and selectively to BAX to turn on cell death.

"We find that small molecule targeting of the BAX trigger site is achievable and could lead to a new generation of apoptotic modulators that directly activate BCL-2 executioner proteins in cancer and other diseases driven by pathologic apoptotic blockades," write the authors.

Walensky and his colleagues continue to work on BAM7, which is a prototype of drugs that might one day be approved for cancer treatment. Several biotechnology companies have already expressed interest in developing the compound, he says.

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