New drug strategy attacks resistant leukemia and lymphoma

May 29 2012

Scientists at the Dana-Farber/Children's Hospital Cancer Center have developed an anti-cancer peptide that overcomes the stubborn resistance to chemotherapy and radiation often encountered in certain blood cancers when the disease recurs following initial treatment.

The strategy could pave the way for much needed new therapies to treat relapsed and refractory blood cancers, which are difficult to cure because their cells deploy strong protein "deflector shields" to neutralize the cell death signals that chemotherapy agents used against them initially, say the researchers.

The prototype compound, called a "stapled BIM BH3 peptide," is designed to disable the cancer's defenses by hitting a family of protein targets that regulate cell death.

In proof-of-concept studies in mice with transplanted, drug-resistant leukemia tumors, the compound alone suppressed cancer growth, and when paired with other drugs, showed synergistic anti-cancer activity, say researchers led by Loren Walensky, MD, PhD, of Dana-Farber/Children's Hospital Cancer Center.

Their paper has been posted online by the Journal of Clinical Investigation and will appear in the journal's June issue. Walensky is the senior author and James LaBelle, MD, PhD, is the first author.

A cell's "fate" – when and whether it lives or dies – depends on a tug-of-

war between pro-death and anti-death forces within the cell that serve as a check-and-balance system to maintain orderly growth. The system is regulated by the BCL-2 family of proteins, which contains both pro-death and pro-survival members.

When cells are no longer needed or are damaged beyond repair, the body activates pro-death BCL-2 proteins to shut down mitochondria – the power plants of the cell– resulting in an orchestrated cellular destruction known as apoptosis, or programmed cell death.

Many cell-killing cancer treatments work by triggering these "executioner proteins" to cause tumor cells to commit suicide in this fashion. But cancer cells can escape their death sentence – and even become immortal – by hyperactivating the survival arm of the family; these proteins intercept the executioner proteins and block their lethal mission.

"When cancers recur, they activate not just one type of survival protein, but many," explains Walensky, whose laboratory has extensively studied the cell-death system and makes compounds to manipulate it for research and therapeutic purposes.

"It's as if relapsed cancers 'learned' from their initial exposure to chemotherapy such that when they come back, they put up a variety of formidable barriers to apoptosis," he adds. "To reactivate cell death in refractory hematologic cancers, we need new pharmacologic strategies that broadly target these obstacles and substantially lower the apoptotic threshold."

When cancers specifically rely on one or two survival proteins, treating them with selective BCL-2 inhibitors can be very effective at eliminating the cancer cells' survival advantage. But relapsed cancers often evade such agents by deploying a battery of alternate survival proteins, so

what's needed, Walensky says, are "next-generation" compounds that can block a wider range of survival proteins without jeopardizing normal tissues.

In the current research, the scientists built a chemically-reinforced peptide containing the death-activating BH3 domain of an especially potent killer protein, BIM, which is able to tightly bind with and neutralize all of the BCL-2 family survival proteins. This 'stapled' peptide, which incorporates the natural structure and properties of BIM BH3, not only disables the survival proteins, but also directly activates pro-death BCL-2 family proteins in cancer cells, making them self-destruct. Importantly, non-cancerous cells and tissues were relatively unaffected by the treatment.

"The diversity of BCL-2 family survival proteins blunts the anti-tumor activity of essentially all cancer treatments to some degree," Walensky points out. "By using Nature's solution to broad targeting of the BCL-2 pathway with a stapled BIM BH3 peptide, our goal is to eliminate cancer's protective force field and enable the arsenal of cancer treatments to do their job."

Provided by Dana-Farber Cancer Institute