

Research first to combine targeted agents to kill multiple myeloma cells

February 10 2011

(PhysOrg.com) -- Scientists at Virginia Commonwealth University Massey Cancer Center have developed a novel treatment strategy for multiple myeloma that pairs two targeted agents to kill cancer cells. The study's findings, published in today's edition of the journal "Blood," are the first to demonstrate the synergistic, anti-myeloma effects of this combination regimen both in vitro and in vivo.

Multiple myeloma is a cancer involving antibody-producing cells in the bone marrow, and, in most cases, is incurable. Targeted therapies work by interfering with biological and biochemical functions critical for cancer cell survival and proliferation. The new treatment strategy from VCU Massey combines Src inhibitors, which block the activity of an important group of proteins that regulate cancer cell behavior, with Chk1 inhibitors, which interfere with cancer cells' ability to undergo cell cycle arrest and repair DNA damage.

"Chk1 inhibitors are currently used primarily in conjunction with conventional DNA-damaging chemotherapeutic agents," says the study's lead investigator Steven Grant, M.D., associate director for translational research, Shirley Carter and Sture Gordon Olsson Chair in Oncology Research and professor of internal medicine at VCU Massey Cancer Center. "By combining Chk1 inhibitors with another targeted agent, such as Src inhibitors, we were able to induce cell death in multiple myeloma cells while sparing healthy, normal cells."

When multiple myeloma cells are subjected to DNA-damaging agents,

or even when they are undergoing normal DNA replication, their DNA is subject to breakage. To survive, they must slow down their progression through the cell cycle in order to repair the DNA, or, if the damage is too severe, undergo a form of cell suicide.

Chk1 is an enzyme that allows cells to undergo cell cycle arrest, a process required to repair the DNA damage. When [cancer cells](#) are exposed to Chk1 inhibitors, they experience DNA damage and, as a consequence, launch another defense mechanism by activating a protein known as ERK1/2.

“The activation of ERK1/2 explains why multiple myeloma cells are able to survive the lethal effects of Chk1 inhibitors,” says Grant. “Therefore, we used Src inhibitors to block the activation of ERK1/2.” The results were more promising than even the researchers had hoped.

Grant’s team discovered that Src inhibitors not only blocked ERK1/2 activation, but also synergized with Chk1 inhibitors to trigger a dramatic increase in cell death. In addition, the combined treatment greatly reduced blood vessel formation, which plays an important role in the maintenance of many tumors, including multiple myeloma. Significantly, the treatment exerted virtually no effects on healthy, normal cells.

“We found tumors treated with the combined regimen were noticeably smaller and showed signs of a lack of blood supply when compared to tumors from the control group or those treated only with Chk1 inhibitors,” says Grant. “This study is not only the first to demonstrate that Src inhibitors can dramatically increase the effects of Chk1 inhibitors, but it is also the first to show that preventing blood vessel formation may contribute to the effectiveness of this combination strategy.”

This study builds upon more than seven years of research by Grant’s

team investigating cell signaling in relation to DNA damage repair and survival pathways involving Src and ERK1/2 proteins. The researchers are now developing more complex experiments as a prelude to clinical trials in multiple myeloma patients. “We’re hopeful the approach of combining targeted agents will open up the possibility of developing entirely new therapies for patients with [multiple myeloma](#) and potentially other blood cancers,” says Grant.

More information: The full journal article is available online at [bloodjournal.hematologylibrary ... ood-2010-06-291146v1](#)

Provided by Virginia Commonwealth University

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