New combination therapy developed for multiple myeloma

Each year, more than 25,000 Americans are diagnosed with multiple myeloma, a form of blood cancer that often develops resistance to therapies. However, researchers at Virginia Commonwealth University Massey Cancer Center are reporting promising results from laboratory experiments testing a new combination therapy that could potentially overcome the resistance hurdle.

While several drugs are effective against multiple myeloma, including the proteasome inhibitor bortezomib, multiple myeloma cells are often able to survive by increasing the production of a protein known as Mcl-1. Mcl-1 regulates a number of processes that promote cell survival and has been implicated in resistance to anti-myeloma drugs that were initially effective. However, a team of researchers led by Xin-Yan Pei, M.D., Ph.D., and Steven Grant, M.D., recently published the findings of a study in the journal PLoS ONE demonstrating that a novel drug combination both reduces Mcl-1 expression and disrupts its interactions with other proteins to effectively kill multiple myeloma cells. The therapy combines a type of drug known as a Chk1 inhibitor with another called a MEK inhibitor. Chk1 inhibitors prevent cells from arresting in stages of the cell cycle that facilitate the repair of DNA damage, while MEK inhibitors prevent cells from activating a variety of proteins that regulate DNA repair processes while promoting the accumulation of pro-death proteins.

“This research builds on our previous studies that showed exposing multiple myeloma and leukemia cells to Chk1 inhibitors activated a protective response through the Ras/MEK/ERK signaling pathway,” says Pei, instructor in the Department of Internal Medicine at the VCU School of Medicine. “By combining a Chk1 inhibitor with a MEK inhibitor, we have developed one of only a limited number of strategies shown to circumvent therapeutic resistance caused by high expressions of Mcl-1.”

In laboratory experiments, the scientists enforced overexpression of Mcl-1 in human multiple myeloma cells. They found that this caused the cells to become highly resistant to bortezomib, but it failed to protect them from the Chk1/MEK inhibitor regimen. Additionally, the combination therapy was able to completely overcome resistance due to microenvironmental factors associated with increased expression of Mcl-1. A cell’s microenvironment consists of surrounding cells and the fluids in which they reside, and the communication between cancer cells and their surrounding cells can significantly impact resistance. Mcl-1 plays a key role in this communication by facilitating events that promote cancer cell survival.

“Not only was the combination therapy effective against multiple myeloma cells, it notably did not harm normal bone marrow cells, raising the possibility of therapeutic selectivity,” says Grant, the study’s lead investigator and Shirley Carter Olsson and Sture Gordon Olsson Chair in Cancer Research, associate director for translational research and program co-leader of Developmental Therapeutics at VCU Massey Cancer Center. “We are hopeful that this research will lead to better therapies for multiple myeloma, and help make current therapies more effective by overcoming resistance caused by Mcl-1.”

The researchers have started initial discussions with clinical investigators and drug manufacturers with hopes of developing a clinical trial testing a combination of Chk1 and MEK inhibitors in patients with refractory multiple myeloma. It is too early to estimate when the trial will open.

In addition to Pei, Grant collaborated on this study with Yun Dai, MD., Ph.D., Shuang Chen, M.D., Ph.D, Leena E. Youssefian, Weslie W. Bodie, Yukie Takabatake, Jessica Felthousen, Jorge A. Almenara, Ph.D., Lora B. Kramer, Liang Zhou, and Michael Sanderson, all from the Division of Hematology, Oncology and Palliative Care at the VCU School of Medicine, and Robert Orlowski, M.D., Ph.D., from M.D. Anderson Cancer Center.

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The full manuscript of this study is available online at:
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0089064