MedicalXpress

Scientists defeat hurdle to eradicating inactive multiple myeloma cells

November 14 2011, By John Wallace

Researchers at Virginia Commonwealth University Massey Cancer Center have developed a novel treatment strategy for multiple myeloma that delivers a deadly one-two blow to kill even the most inactive, or cytokinetically quiescent, cells. Because multiple myeloma can rest in a non-proliferative state for extended periods of time, this discovery may help to overcome a major hurdle to treating this fatal disease.

Recently published in the journal "Blood," a study by a team of researchers led by Steven Grant, M.D., Shirley Carter Olsson and Sture Gordon Olsson Chair in Oncology Research, associate director for translational research and program co-leader of Developmental Therapeutics at VCU Massey Cancer Center, shows that combining the clinically relevant MEK1/2 inhibitor AZD6244 and the Chk1 inhibitor AZD7762 effectively induces apoptosis, a form of cell suicide, in actively cycling as well as quiescent multiple myeloma cells. Chk1 inhibitors prevent cells from arresting in stages of the cell cycle that facilitate the repair of DNA damage. However, these agents may also interfere with multiple other Chk1-related survival functions. MEK1/2 inhibitors prevent cells from activating a variety of proteins responsible for promoting various DNA repair mechanisms, among numerous other actions. The combination of drugs did not appear to harm normal, healthy bone marrow tissue.

"We believe Chk1 inhibitors by themselves may not always be effective against multiple myeloma because they target the cell cycle process, but multiple myeloma cells are frequently not actively cycling," says Grant.

“Nevertheless, Chk1 inhibitors may still induce limited DNA injury in non-cycling cells, which have alternative ways to repair the damage. By introducing a MEK1/2 inhibitor, we may have disabled compensatory DNA repair pathways, thereby leaving cells, including those that are not cycling, with few options besides apoptosis.”

All cells progress through a cycle that leads to DNA replication and cell division. Each phase of the cycle is responsible for different biological functions. In the first phase, known as G0, cells rest after progressing through mitosis, the final phase of the cell cycle that separates a cell’s chromosomes in the nucleus into two daughter nuclei. Cells in the G0 phase and early G1 phase are in a regenerative state, repairing damage to their DNA. Chk1 inhibitors promote DNA damage by allowing cells to enter the cell cycle inappropriately, where they die. Historically, dormant cells such as multiple myeloma cells have been less susceptible to Chk1 inhibitor strategies, such as those that combine conventional DNA-damaging chemotherapies.

MEK1/2 inhibitors interfere with a signaling cascade known as the Ras/Raf/MEK/ERK pathway. This pathway, one of the most commonly dysregulated pathways in cancer, is comprised of a chain of cellular proteins that act like on/off switches for a variety of biological processes mediating cell survival and cell cycle progression, among others. One important survival mechanism is responsible for regulating a pro-apoptotic protein known as Bim. By inhibiting the Ras/Raf/MEK/ERK pathway, MEK1/2 inhibitors allow Bim to accumulate in cells. This lowers the threshold for apoptosis in cells and appears to serve as a particularly effective “death trigger” that promotes elimination of cells containing DNA damage.

“A multi-institutional phase II clinical trial evaluating AZD6244 in patients with refractory multiple myeloma has recently been initiated. Since this agent is already being evaluated in a clinical setting, we are

hoping this will accelerate the translational research process and our study will provide the foundation needed for successor trials combining this agent with clinically relevant Chk1 inhibitors like AZD7762," says Grant.

The full research manuscript is available online here.

Provided by Virginia Commonwealth University