Experimental drug could enhance multiple myeloma and myeloid leukemia therapies

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A pre-clinical study led by Virginia Commonwealth University Massey Cancer Center and Department of Internal Medicine researchers suggests that an experimental drug known as dinaciclib could improve the effectiveness of certain multiple myeloma and myeloid leukemia therapies. The study, recently published in the journal *Molecular Cancer Therapeutics*, showed that dinaciclib disrupted a cell survival mechanism known as the unfolded protein response (UPR). Without the UPR, multiple myeloma and myeloid leukemia cells were unable to combat damage caused by some anti-cancer agents.

"Although dinaciclib has shown promising pre-clinical activity against a variety of tumor cells, and is currently undergoing phase I/II clinical trials in several malignancies, the mechanisms responsible for its anti-tumor activity are not fully understood," says the study's lead investigator Steven Grant, M.D., associate director for translational research, co-leader of the Developmental Therapeutics research program and Shirley Carter Olsson and Sture Gordon Olsson Chair in Oncology Research at Massey. "Our research highlights a potentially new mechanism of dinaciclib action, and raises the possibility that this agent could be a useful addition to current multiple myeloma and myeloid leukemia therapies."

Dinaciclib is a member of a class of drugs known as cyclin-dependent kinase (CDK) inhibitors. CDKs regulate a series of events known as the cell cycle, or cell-division cycle, that lead to the division and duplication of cells. In many cancers, CDKs are overactive or CDK-inhibiting proteins are not functional, which results in the unregulated proliferation of cancer cells. Laboratory observations from this study suggest that two specific CDKs, CDK1 and CDK5, play key roles in regulating the UPR by helping to control the production and accumulation of a protein known as X-box binding pretein-1 (XBP-1).

The spliced form of XBP-1 (XBP-1s) helps regulate the expression of genes critical to cellular stress responses. External stressors, including certain anti-cancer agents, can cause mis-folded proteins to accumulate in the endoplasmic reticulum (ER), an interconnected network of sacs and tubules that manufacture, process and transport a variety of compounds important for cell survival. These stressors can also cause XBP-1s to accumulate in the cell's nucleus, which promotes the UPR and helps cells withstand the damaging effects of mis-folded proteins. The scientists discovered that dinaciclib, by interfering with UPR activation, caused multiple myeloma and myeloid leukemia cells to initiate a form of cell suicide known as apoptosis when exposed to agents that induced ER stress.

"These findings build on a long history of work in our laboratory investigating mechanisms by which cancer cells respond to environmental stresses," says Grant. "We intend to continue investigating ways in which dinaciclib and other CDK inhibitors might be used to disrupt the UPR and potentially improve the effectiveness of certain agents for the treatment of multiple myeloma or myeloid leukemia ."

More information: The full manuscript of the study is available online at: mct.aacrjournals.org/content/e … 3-0714.full.pdf+html

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