Medical Xpress

Researchers shed light on mechanism of action used by anti-cancer drug

June 11 2007

Virginia Commonwealth University Massey Cancer Center researchers have uncovered a new mechanism of action of the anti-cancer drug sorafenib, which could stimulate the development of novel regimens in which it is combined with other molecularly targeted agents for patients with blood cancers and solid tumors.

In the new study, led by Steven Grant, M.D., Massey's associate director for translational research and co-leader of the cancer center's cancer cell biology program, VCU researchers identified a mechanism by which sorafenib inhibits protein translation, and which may be involved in reducing expression of pro-survival factors, such as Mcl-1, and other proteins. The findings were published online in the journal *Molecular and Cellular Biology* on June 4.

According to Grant, sorafenib, or Nexavar which is manufactured by Bayer Pharmaceuticals, has recently been approved for the treatment of patients with renal cell cancer, the most common form of kidney cancer in adults. It was originally developed as an inhibitor of the oncogene, Raf, which is frequently mutated in numerous cancers, including leukemia. Oncogenes are typically responsible for promoting tumor growth.

Previous findings by Grant's team, reported in the Journal of Biologic Chemistry, showed that in human leukemia cells, sorafenib lethality was less a consequence of Raf inhibition, but rather reflected interference with the synthesis of Mcl-1. They found that sorafenib interfered with

Mcl-1 translation, a process in which proteins are synthesized from their constituent amino acids. However, the mechanism by which protein translation was inhibited by sorafenib remained largely unknown.

In the present work, Grant and his team found that in human leukemia cells, sorafenib induces a process known as endoplasmic reticulum (ER) stress, which results from accumulation of misfolded proteins in the ER. The ER is a subcellular structure which plays a key role in cellular protein disposition. When stressed in this way, the cell responds to the protein load by reducing protein synthesis, increasing levels of protein chaperones, and by accelerating protein degradation. However, according to Grant, when ER stress exceeds a certain threshold, the ER stress response is converted from an adaptive to a pro-death response.

The team observed that exposure of cells to sorafenib resulted in the pronounced phosphorylation of a protein known as eIF2á, a process that serves as a critical brake on protein translation in cells subjected to ER stress. Interestingly, they also found that sorafenib, by virtue of its ability to inhibit Raf, also prevented an increase in expression of a chaperone protein known as Grp78, which is classically induced in the ER stress response, and which helps to resolve stresses associated with increased protein loads. The net effect of these actions was to induce a shutdown of protein synthesis accompanied by a dramatic increase in cell death.

“The notion that sorafenib acts by inhibiting protein synthesis and reducing expression of Mcl-1 suggests that this agent might be logically combined with other targeted agents whose antitumor activity is limited by Mcl-1 expression,” Grant said. Several such targeted agents are currently undergoing clinical evaluation in patients with various malignancies.

Source: Virginia Commonwealth University

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