MedicalXpress

Team finds gene that promotes drug resistance in cancer

January 14 2013

Scientists from the University of Iowa and Brigham Young University (BYU) have identified a gene that may be a target for overcoming drug resistance in cancer. The finding could not only improve prognostic and diagnostic tools for evaluating cancer and monitoring patients' response to treatment but also could lead to new therapies directed at eradicating drug-resistant cancer cells.

Drug resistance is a common problem in many metastatic cancers. It leads to failure of chemotherapy treatments and is associated with poor patient outcomes, including rapid relapse and death.

The research team, including Fenghuang (Frank) Zhan, M.D., Ph.D., and Guido Tricot, M.D., Ph.D., from the UI, and David Bearss, Ph.D., from BYU, initially focused on identifying genes linked to the development of drug resistance in multiple myeloma, a bone marrow cancer that affects more than 20,000 Americans and causes almost 11,000 deaths annually.

Working with serial biopsied cells from 19 myeloma patients, the researchers analyzed genetic changes in the cells that occurred over the course of treatment with very intensive chemotherapy drugs. This approach identified a gene called NEK2 that is strongly associated with increased drug-resistance, faster cancer growth, and poorer survival for patients. The study was published Jan. 14 in the journal *Cancer Cell*.

Having established the relationship between high expression of the NEK2 gene and poor patient outcome in myeloma, the team then

examined the relationship in other common cancers—including breast, lung, and bladder cancer—by analyzing gene expression profiles from 2,500 patients' cells with eight different cancers in Zhan's lab.

"In all cases, an increase in the NEK2 gene was associated with rapid death of the patient," says Tricot, who is director of Holden Comprehensive Cancer Center's Bone Marrow Transplant and Myeloma Program at UI Hospitals and Clinics. "So this finding was not unique to myeloma; this is basically seen in every single cancer we looked at."

Taking the findings back to the lab, the team then examined the effect on cancer cells of either enhancing or blocking the expression of the NEK2 gene.

"Our studies show that over-expression of NEK2 in cancer cells significantly enhances the activity of drug efflux proteins to pump chemotherapy drugs out of cells, resulting in drug resistance. Furthermore, silencing NEK2 in cancer cells potently decreased drug resistance, induced cell-cycle arrest, cell death, and inhibited cancer cell growth in vitro and in vivo," says Zhan, UI professor of internal medicine.

The research team is now developing compounds to inhibit NEK2 by collaborating with David Bearss, Ph.D., associate professor of physiology and developmental biology at BYU, in the hope that these compounds may overcome drug resistance in cancer cells.

"We were able to show that if we inhibit NEK2, then we can actually restore sensitivity to drugs that we use right now," Bearss says.

Although development and clinical testing of such drugs for use in patients is not imminent, Tricot notes that the findings may have clinical use within the next several years.

"NEK2 expression may be a diagnostic or prognostic marker for drug-resistant cancer," he says. "If NEK2 is high, that would suggest that the prognosis is poorer and the patient might benefit from more aggressive treatment. The other potential use is for monitoring the cancer's response to therapy. If NEK2 levels increase, that would suggest development of increased drug resistance and might indicate that a change of treatment would be helpful."

Provided by University of Iowa