A Synergetic Combination for KRAS-Driven Cancers

Can a new approach to drug combination therapy eradicate KRAS-mutant cancers?

A major challenge in cancer involves the most commonly mutated oncogene, KRAS, which produces a small protein that activates other proteins that drive cancer. Some 90 percent of pancreatic cancers, 40 percent of colorectal cancers and 20 percent of cancers overall have mutations in KRAS. Yet KRAS has proven difficult to target with small molecule drugs. The most effective candidates inhibit MEK, a signaling pathway activated by KRAS mutations. Although MEK inhibition can slow the growth of KRAS cancers, it does not kill them. Researchers have undertaken genetic screens to find additional genes whose disruption is specifically toxic to KRAS-mutant cancers.

Jeffrey Engelman, MD, PhD, director of the Center for Thoracic Cancers at Massachusetts General Hospital Cancer Center, undertook an alternate strategy. He hypothesized that another gene works in conjunction with MEK, one that on its own may not drive cancer and thus would not be identified in traditional genetic screens. His team performed an unbiased screen that identified a novel target, BCL-XL. The team is now ushering a combination of MEK and BCL-XL inhibition to clinical trial. The study appeared in the January 14, 2013 issue of *Cancer Cell*.[1]

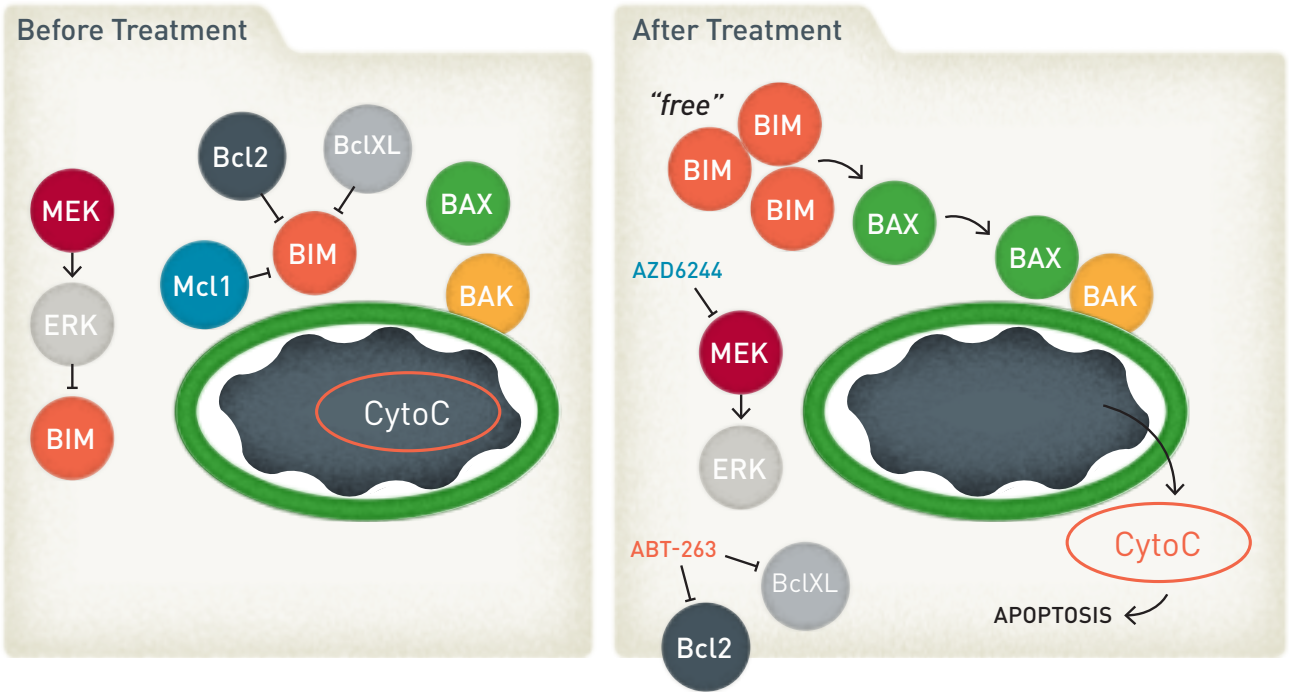
MEK ELUDES CELL DEATH SIGNALS FOLLOWING INHIBITION

Dr. Engelman's team used a large library of RNA molecules, each of which may disrupt a different gene in a different cell. They tested the RNAs in cancer cells with and without the KRAS mutation. Half of each type was grown in the presence of a MEK inhibitor (selumetinib). Any KRAS cell that died when bathed in a MEK inhibitor had a deactivated gene that normally operates with MEK to evade cell death. By searching for the cell in which the disrupted gene had the most potent effect in combination with the MEK inhibitor, the researchers identified that "co-conspirator" gene as BCL-XL.

MEK inhibition initially upregulates the protein BIM, which primes the KRAS cancer cells *(continued on page 6)*

A New Route to Apoptosis

Mechanisms underlying the cell death induced by combined MEK inhibition (AZD6244) and BCL-XL inhibition (ABT-263).



(continued from page 5) for death. Dr. Engelman discovered that BCL-XL binds to and inhibits BIM, thus allowing cells to override the cell death pathway. By inhibiting BCL-XL along with MEK, the upregulated BIM leads to cell death.

SYNERGETIC INHIBITION

Dr. Engelman's team tested a combination of selumetinib with an investigational BCL-XL inhibitor (navitoclax, or ABT-263). In both cell cultures and mice, the combined inhibition caused a dramatic increase in tumor cell death, and was much more lethal to KRAS cells than inhibiting just one or the other. In genetically engineered mouse models of human KRAS-mutant cancer, the combined therapy caused significant tumor regression.

However, the experiments showed a differential effect among cells that had epithelial versus mesenchymal phenotypes. Cells in the epithelial state demonstrated a more robust response than those in the mesenchymal state. Given the large body of research finding that cells transitioning from an epithelial to a mesenchymal state (EMT) are evolving to become more invasive and drug resistant, this result suggests that mesenchymal status may predict patient prognosis and drug response. (For more on Mass General Cancer Center's investigation of EMT, see page 3.)

Dr. Engelman has received approval to test the combination in a clinical trial, which should begin this year. Researchers will collect data on patients' epithelial-mesenchymal status to study whether it correlates with patient response.

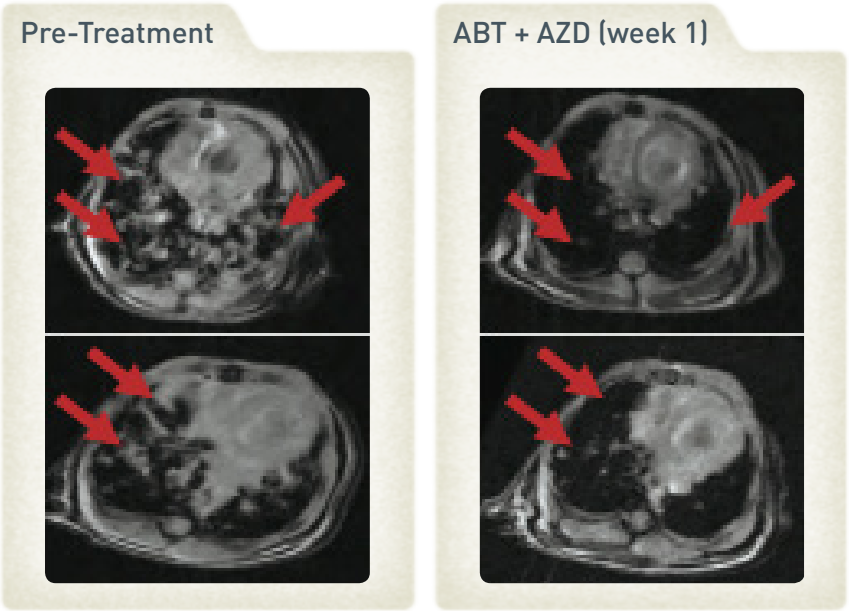
TAKING THE BCL-XL FINDING FURTHER

A study by Dr. Engelman's team in the January 2014 issue of *Cancer Discovery* found a similar lethal combination by inhibiting both BCL-XL and mTOR, a master regulator of numerous cell growth signals.[2] Here, the team screened more than 600 colorectal cancer cell lines with 130 drugs to determine which ones made the cells more sensitive to BCL-XL inhibition with navitoclax. The researchers found that an inhibitor of mTOR, AZD8055, worked synergetically with BCL-XL inhibition in colorectal cancers driven by KRAS or BRAF, an oncogene driving 5 percent to 15 percent of colorectal cancers. However, the combination was not effective in non-small-cell lung cancers with KRAS mutations.

Each of the two approaches—using RNA and drug screens—has advantages and limitations. The first strategy casts a wide net to find novel targets. However, some of those hits may be difficult to target with drugs because they lack an accessible binding site. The second approach restricts the number of targets being explored, but because it uses existing or investigational drugs, it may accelerate the translation from bench to patient bedside. Together, the strategies may provide the synergy needed to treat KRAS-mutant cancers. "There hasn't been a single agent that is effective against KRAS," says Dr. Engelman. "These combinations are the next best approach." ■

Combined Drug Treatment

Lung tumors in mice treated with a combination of a MEK inhibitor and a BCL-XL inhibitor led to a dramatic increase in tumor cell death after one week of treatment.



[1] Corcoran, Ryan B, Katherine A Cheng, Aaron N Hata, Anthony C Faber, Hiromichi Ebi, Erin M Coffee, Patricia Greninger, et al. "Synthetic Lethal Interaction of Combined BCL-XL and MEK Inhibition Promotes Tumor Regressions in KRAS Mutant Cancer Models." *Cancer Cell* 23, no. 1 (Jan. 14, 2013): 121–128.

[2] Faber, Anthony C, Erin M Coffee, Carlotta Costa, Anahita Dastur, Hiromichi Ebi, Aaron N Hata, Alan T Yeo, et al. "mTOR Inhibition Specifically Sensitizes Colorectal Cancers with KRAS or BRAF Mutations to BCL-2/BCL-XL Inhibition by Suppressing MCL-1." *Cancer Discovery* 4, no. 1 (Jan. 2014): 42–52.

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