New Screening Approach Identified Potential Drug Combinations for Difficult-to-treat Forms of Melanoma

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- High-throughput screen identified several drug combinations effective in vitro.
- Some combinations were effective against cell lines resistant to single agent used clinically.

PHILADELPHIA — A novel approach to identifying potential anticancer drug combinations revealed that pairing cholesterol-reducing drugs called statins with cyclin-dependent kinase inhibitors might provide an effective approach to treating intractable melanomas driven by mutations in the NRAS and KRAS genes.

David F. Stern, Ph.D., professor of pathology at Yale University School of Medicine in New Haven, Conn., and colleagues reported these data in *Cancer Discovery*, a journal of the American Association for Cancer Research.

“The identification of gene mutations that drive specific subsets of cancers has had a major beneficial impact on treatments for these patients. But, such mutations can only be identified for some cancers. Some patients who have a specific cancer-driving genetic mutation never respond to the matching drug, while nearly all those who initially respond eventually become resistant to the effects of the drug and their cancers relapse,” said Stern.

For this reason, Stern and colleagues reasoned that using drug combinations may be necessary to address the problem of drug resistance and enable effective treatment of cancers driven by signaling molecules that currently cannot be targeted, such as RAS.

They developed an in vitro, high-throughput screen to test the effectiveness of anticancer drugs, alone and in pairs, against three types of melanoma cell lines: those driven by mutations in the RAS gene (representing approximately 20 percent of human melanomas), those driven by mutations in the BRAF gene (40 to 50 percent of melanomas) and those without mutations in either the RAS or BRAF genes.

Through analysis of 150 drugs as single agents, Stern and colleagues narrowed their pool to 40 drugs for combination testing. Melanoma cell lines driven by BRAF and RAS were sensitive to different combinations of drugs. Some combinations that killed BRAF-driven melanoma cell lines were also effective against BRAF-driven melanoma cell lines resistant to a single agent used to treat patients with

melanoma tumors characterized by BRAF gene mutations, and these combinations may prove to be helpful in preventing or managing resistance to these agents.

“Perhaps the most interesting observation was that several drug combinations that included a statin, a drug class used clinically to lower cholesterol, killed RAS-driven melanoma cell lines, given the lack of success in treating such cancers,” said Stern.

One statin combination that showed efficacy in vitro, simvastatin plus flavopiridol, an inhibitor of proteins called cyclin-dependent kinases that activate cell division, also worked in vivo substantially reducing the growth of a RAS-driven human melanoma cell line transplanted into mice.

“These agents may be extremely useful as partner agents in combination therapy. Since multiple cyclin-dependent kinase inhibitors are already in human clinical trials, there may be a short path to testing the combination of a statin plus a cyclin-dependent kinase inhibitor in patients with RAS-driven melanoma,” said Stern. “There is a great need for drugs to treat cancers driven by RAS. RAS proteins are inappropriately active in up to a third of all human cancers, including melanoma and lung and pancreatic cancers.”

“This brings up the important point that our high-throughput screening approach is applicable to other types of cancer, including lung and pancreatic cancer,” he added. “A major challenge is in picking the appropriate agents for combination screening, since with multiple doses per agent, the scale of a screen needed for all combinations grows rapidly. This requires careful evaluation of single agents, and analytical methods for choosing the best candidates for follow-up in combinations. For our work, the relatively small number of genetic subtypes was very important, so this system provides a great starting point for investigation of carcinomas (lung, pancreatic cancer, breast cancer), which are genetically more complex.”

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