Researcher investigate 2-drug synergy to treat drug-resistant chronic myeloid leukemia

October 24 2012

(Medical Xpress)—An interdisciplinary team of researchers has dissected a case of synergy in drug-resistant chronic myeloid leukemia to understand the mechanism by which two drugs, danusertib and bosutinib, work together to overcome resistance in the BCR-ABL gatekeeper mutation-specific disease. The team includes a researcher at Moffitt Cancer Center and colleagues at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences in Austria and the Massachusetts Institute of Technology. The goal is to address an unmet medical need because this BCR-ABL mutation confers resistance to all currently approved kinase inhibitors for chronic myeloid leukemia.

The study appeared in the Sept. 30 online version of *Nature Chemical Biology*.

"Treatment of chronic myeloid leukemia rapidly improved after the introduction of the first BCR-ABL inhibitor, Gleevec (imatinib)," said study co-author Uwe Rix, Ph.D., an assistant member of the Moffitt's Drug Discovery Department and Experimental Therapeutics Program. "However, it soon became apparent that a broad spectrum of possible resistance mechanisms necessitated second- and third-generation BCR-ABL inhibitors. Although these are mostly very successful, none of the currently approved options has been effective in patients with chronic myeloid leukemia who harbor the BCR-ABL gatekeeper mutation."

The researchers investigated the molecular mechanisms and logic underlying the synergistic interaction between danusertib and bosutinib, which is specific for BCR-ABL gatekeeper mutation-transformed cells. They applied a novel systems pharmacology approach involving a combination of different proteomics and gene expression profiling methods.

"We found previously unappreciated features of both agents," Rix said. "The synergy did not correlate with direct inhibition of BCR-ABL. Instead, our observations converged on the downstream MAPK signaling cascade as the predominantly affected pathway in the synergistic inhibition of BCR-ABL."

The researchers said the combination of both compounds impaired the activity of c-MYC, a gene regulator that codes a transcription factor playing a well-established but a not well understood role in a broad spectrum of human cancers.

"In the context of chronic myeloid leukemia, c-MYC is required for BCR-ABL-mediated transformation," Rix explained. "What is intriguing is that chronic myeloid leukemia cells with the BCR-ABL gatekeeper mutation seem to be more dependent on the MAPK/c-MYC signaling axis than BCR-ABL wild-type cells. Thus, challenging c-MYC with drugs appears promising in these resistant cells, but steps have only recently been made."

The researchers concluded that they have unraveled the action and impact of a "new synergistic drug interaction between danusertib and bosutinib in a clinically relevant, highly drug-resistant disease setting" by revealing a "non-obvious synergistic mechanism elicited by several off targets of the two small molecules."

"We believe this strategy of gaining a functional understanding of drug

synergy may serve as a model for further mode-of-action studies," they concluded.

More information: www.nature.com/nchembio/journa … df/nchembio.1085.pdf

Provided by H. Lee Moffitt Cancer Center & Research Institute