

Targeted therapy reactivates 'guardian of the genome' in resistant cancer

November 15 2010

A study demonstrating pharmacological rescue of a key tumor suppressor may lead to new therapeutic strategies for human cancer and significantly broaden the types of tumors that respond to targeted therapy, including those that have been resistant to current treatments. The research, published by Cell Press in the Nov. 16 issue of the journal *Cancer Cell*, focuses on cancers exhibiting inhibition of p53, a protein that is critical for initiating cell death pathways in abnormal cells.

It is common for [cancer cells](#) to find some way to disarm p53, also known as "guardian of the genome" due to its action in preventing defective cells from dividing. "The critical importance of the protective function of p53 is underscored by the diversity of molecular strategies employed by cancer cells to subvert p53 activity, such as overexpression of antagonistic proteins like HDM2 and HDMX," explains senior study author Dr. Loren D. Walensky from Harvard Medical School.

"Restoration of p53 activity remains an important goal in the quest for more effective [cancer therapeutics](#)."

Previous work demonstrated that selective inhibition of HDM2 restored p53 function in cancer cells. However, these results were often compromised by expression of HDMX. In an earlier study, Dr. Walensky and colleagues described the generation of "stapled" peptides designed to resemble the section of p53 that interacts with HDM2. When biochemical and structural studies revealed that HDM2 and HDMX engage the same region of p53, the researchers examined whether the most effective engineered HDM2 inhibitor (SAH-p53-8) could also

interfere with HDMX and how this interaction might influence the p53 activity.

The SAH-p53-8 compound was even more effective at targeting HDMX and effectively blocked formation of the inhibitory p53-HDMX complex, thereby restoring the [p53 pathway](#) and reducing tumor cell viability. Importantly, when SAH-p53-8 was delivered intravenously to mice with HDMX-expressing cancer, p53 activity was increased and tumor growth was suppressed.

"We found that targeting HDMX overcame HDMX-mediated p53 suppression and resistance to selective HDM2 inhibition, while dual targeting of HDM2 and HDMX maximized therapeutic reactivation of the p53 [tumor suppressor](#) pathway in cancers that express both protein antagonists and retain functional p53," concludes Dr. Walensky.

"Importantly, monitoring cellular levels of p53-HDMX complex may be useful for predicting cancer cell susceptibility to HDMX inhibition and determining the efficacy of HDM2 inhibitor-mediated p53 restoration, which forms the basis for enhancing the therapeutic impact of dual HDM2/HDMX targeting in resistant cancers."

Provided by Cell Press

Citation: Targeted therapy reactivates 'guardian of the genome' in resistant cancer (2010, November 15) retrieved 18 April 2024 from <https://medicalxpress.com/news/2010-11-therapy-reactivates-guardian-genome-resistant.html>

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