Tapping into TASP1

By Kai-Jye Lou, Staff Writer

Researchers from Washington University in St. Louis and colleagues from other U.S. institutions have identified a potent small molecule inhibitor of taspase-1. The group now plans to use the small molecule as a scaffold to design drug-like inhibitors of the cancer-associated enzyme.

Taspase-1 (TASP1) is a protease linked to proliferation and apoptosis in multiple cancer types including glioblastoma and melanoma.2,3

Previously, James Hsieh and collaborators at Stanford University used the structural data of the TASP1 active site to help rationally design peptide-based inhibitors.4 However, the resulting compounds lacked potency and were unlikely to be useful in vivo because TASP1 acts on intracellular targets.

At the time, Hsieh was an assistant professor of medicine at Washington University in St. Louis. He is now a laboratory head in the human oncology and pathogenesis program at Memorial Sloan-Kettering Cancer Center.

Hsieh and collaborators have now switched gears and used a cell-based, dual-fluorescence functional assay to screen a library of synthetic compounds from the National Cancer Institute (NCI) for molecules that target TASP1. The best hit was the arsenic acid compound NSC48300, which inhibited TASP1 with an IC50 of about 7.5 μM.

NSC48300 did not compete with any substrates of TASP1, indicating that the compound is allosterically inhibiting the enzyme's activity. Thus, the data suggest the possibility of developing TASP1 inhibitors that do not target the enzyme's active site.

In mouse models of TASP1-overexpressing human breast cancer and glioma, NSC48300 decreased tumor growth compared with vehicle.

Results were published in Cancer Research.

The team included researchers from the Washington University in St. Louis, Memorial Sloan-Kettering, the Rosalind Franklin University of Medicine and Science, the Dana-Farber Cancer Institute and NCI. Hsieh carried out the study while at Washington University in St. Louis.

Gearing up for drug discovery

Although NSC48300 is a clear step in the right direction, the compound itself is unlikely to advance into the clinic.

“This series of preclinical studies has demonstrated the feasibility of targeting taspase-1 to treat cancer.” —James Hsieh, Memorial Sloan-Kettering Cancer Center

“First, we are working with the Chemical Biology Consortium through NCI to develop more potent, more specific and less toxic compounds than NSC48300. Second, we would like to identify the most appropriate types of cancers to treat. Third, we would like to develop a probe that can be easily utilized to examine the activity of taspase-1 and the efficacy of taspase-1 inhibitors. And fourth, we need to understand whether taspase-1 inhibitors can synergize with other anticancer drugs,” he said.

In addition, Hsieh noted that the group is working with collaborators at Columbia University to cocrystallize NSC48300 and TASP1 to better understand the compound’s mechanism of action.

Roland Stauber, professor of molecular and cellular oncology at the Johannes Gutenberg University Mainz, said that “characterizing the active form of taspase-1 in vivo will be important for the rational design of strong taspase-1 inhibitors.”

Stauber and colleagues developed the first cell-based assays to dissect the function of TASP1 and also used them to identify two small molecules that partially inhibited the enzyme's activity.6

He went on to point out that the existing crystal structure for TASP1 (ref. 7) might not accurately mirror the form of the protease that should be targeted for therapeutic applications. Indeed, he thinks the rational design of potent TASP1 inhibitors has been challenging in part because the structure of the active protease in vivo is still unclear.

Stauber also wanted to see additional studies directly linking TASP1 to various types of cancer, including breast and brain cancer, as well as additional in vivo data showing that NSC48300 is indeed a specific TASP1 inhibitor.

Washington University in St. Louis has filed a patent application covering TASP1 inhibitors and their uses. The work is available for licensing.

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REFERENCES
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- National Cancer Institute, Frederick, Md.
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