Taking down autophagy

By Joanne Kotz, Senior Editor

Researchers at **Harvard Medical School** and the **Shanghai Institute of Organic Chemistry** have identified a small molecule called spautin-1 that blocked the prosurvival autophagy pathway in cancer cells.¹ Based on the findings, **Harvard University**, **Roche** and China's **BioBay** have partnered to develop spautin-1 derivatives and test them in preclinical models of breast and ovarian cancer.

Autophagy occurs during cellular starvation or stress and is a process by which a cell generates building blocks by degrading its own proteins and organelles in the lysosome. In the nutrient-deficient environment of the tumor, autophagy can serve as an alternative energy source that helps the malignant cells survive.

"Autophagy has been recognized as an important mechanism for mediating cancer cell survival, for instance by sustaining tumor cells under stress and also by mediating resistance to anticancer therapy," said Junying Yuan, a professor in the Department of Cell Biology at Harvard Medical School and colead author of the study.

The challenge has been a dearth of druggable targets in the pathway.

"Research on autophagy inhibition has been hampered due to the lack of high-quality tool compounds with well-established mechanisms of action," said Anders Åberg, CEO of **Sprint Bioscience AB**, which is focused on autophagy, cancer cell metabolism and cachexia. The company has a discovery-stage program targeting phosphoinositide 3-kinase class 3 (Vps34), a kinase that regulates autophagy.

To identify new inhibitors, a team led by Yuan and Dawei Ma, a professor at the Shanghai Institute of Organic Chemistry, screened a library of bioactive compounds for small molecules that decreased autophagy in human glioblastoma cells. The researchers optimized the top hit and named it spautin-1 (specific and potent autophagy inhibitor-1).

In breast cancer cell lines grown in nutrient-limiting conditions, spautin-1 reduced induction of the prosurvival autophagy pathway and increased apoptotic cell death compared with vehicle.

Next, the team studied the molecule's mechanism of action.

In human glioblastoma cells, spautin-1 reduced levels of Vps34 and other proteins in the Vps34 complex.

The team speculated that spautin-1 could be lowering levels of the Vps34 complex by inhibiting a deubiquitinating enzyme. An *in*

vitro assay showed that spautin-1 inhibited the two deubiquitinating enzymes that regulate the Vps34 complex—ubiquitin specific peptidase 10 (USP10) and USP13.

USP10 deubiquitinates p53, a tumor suppressor in which gain-of-function missense mutations can be tumorigenic. Indeed, spautin-1 decreased cellular p53 levels compared with vehicle. Yuan told *SciBX* that the molecule similarly reduces levels of mutant p53 in cancer cells.

According to Yuan, spautin-1's ability to block autophagy and reduce the levels of p53, which is commonly mutated in human cancers, could both be useful mechanisms in treating cancer.

"Reducing the accumulation of mutant p53 may be an important therapeutic goal" in mutant p53-driven cancers, she said.

Data were published in *Cell*.

Multiple mechanisms

The next step will be to test spautin-1 in preclinical cancer models.

"Lowering mutant p53 activity could be of great interest because of the potential to reduce the invasive properties of a tumor driven by a gain-of-function p53 mutant protein," said David Lane, chief scientist at the **Agency for Science, Technology and Research** (A*STAR).

Lane wants the authors to test whether spautin-1 lowers signaling through the mutant p53 pathway in cancer cells and in tumors or if the molecule just affects mutant p53 expression.

"The danger of a p53 stability inhibitor is that it would promote tumor formation in the long term," he said.

Yuan countered that while long-term loss of wild-type p53 is tumorigenic, there is no evidence that short-term reduction of p53, such as would occur during treatment, can lead to the formation of cancers.

According to Åberg, another option would be to test the compound in models of autophagy-driven cancer indications, such as pancreatic cancer.

"An efficient autophagy inhibitor could potentiate existing treatment regimens by erasing a residual cancer cell population after primary chemotherapy or irradiation," he told *SciBX*.

Partner plan

Yuan told *SciBX* that Harvard, Roche and BioBay will develop spautin-1 derivatives and first test them in mouse models of cancers that have missense mutations in p53, including breast and ovarian cancer.

BioBay, a biotechnology company cluster in China, will contribute medicinal chemistry and preclinical development expertise. Roche will provide access to its drug discovery, development and commercialization capabilities. Yuan's team will test the molecules in cancer models and continue to explore the mechanism of action of spautins.

Spautin-1 and its role in cancer cell survival is "clearly of interest to Roche," said pharma spokesperson Peter Sandbach. "This is very early research, so it's difficult to make specific predictions about what might result from this particular project."

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**—Anders Åberg,
Sprint Bioscience AB**

Sandbach expects the collaboration with Harvard and BioBay eventually will include multiple projects originating from Harvard.

“We’ll be identifying a range of further projects within our focus technology and disease areas with an emphasis on areas within the strategic remit of our own research organization in China,” he said.

Sandbach said that future projects could be in oncology, virology, metabolic diseases, CNS and inflammation. “Alternatively, projects could involve technologies or technology platforms that may cross multiple areas,” he added.

Financial details of the partnership were not disclosed.

Yuan said Harvard has filed patent applications covering new targets, methods of screening and treatment, and composition of matter for the results reported in the paper.

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