Scientists pinpoint protein that could improve small cell lung cancer therapies

Approximately 15 percent of all lung cancers are small cell lung cancers (SCLC), which grow rapidly and often develop resistance to chemotherapy. However, researchers at Virginia Commonwealth University Massey Cancer Center have revealed new insights into the mechanisms leading to this resistance that may lead to improved therapies.

Chemotherapies work primarily by mediating B-cell lymphoma 2 (Bcl-2) family proteins, which are responsible for regulating cell death. Depending on their function, this family of proteins can trigger a form of cell suicide known as apoptosis or they can activate mechanisms that prevent apoptosis and promote cell survival. Recently, drugs have been developed that block the function of pro-survival Bcl-2 family proteins. One of these drugs known as ABT-737, and its orally available derivative ABT-263 (currently being tested in clinical trials), has been shown to kill SCLC cells and potentially increase the effectiveness of chemotherapies that affect Bcl-2 family proteins. However, the effectiveness of ABT-737 varies greatly in a broad range of SCLC cells.

In a recent study published in Nature Publishing Group's journal *Cell Death & Disease*, Massey researchers Hisashi Harada, Ph.D., and Geoffrey Krystal, M.D., Ph.D., discovered that the expression of a protein called Noxa is critical to the effectiveness of ABT-737 because it helps regulate the function of MCL-1, another pro-survival Bcl-2 family protein. Through experiments with cultured SCLC cells, the researchers found that Noxa recruits MCL-1 to the mitochondria, the cell's power producer, which degrades MCL-1 and makes the cancer cells more sensitive to ABT-737.

"Essentially, we discovered how ABT-737 works and why some small cell lung cancer cells are not as affected by it," says Harada, member of the Cancer Cell Signaling research program at Massey and assistant professor in the Philips Institute of Oral and Craniofacial Molecular Biology at the VCU School of Dentistry. "By targeting Noxa, which breaks down MCL-1, we could potentially develop novel small cell lung cancer therapies and help overcome resistance to conventional chemotherapies."

Previous research has shown that Bcl-2 pro-survival family members, like BCL-2 and MCL-1, are over-expressed in SCLC. However, until recently the precise role of these proteins in SCLC biology and therapeutic resistance was poorly understood. When ABT-737 was discovered, it was able to block BCL-2 and another pro-survival protein known as BCL-X_L, but not MCL-1. The current research points to the pro-survival functions of MCL-1 as the cause of ABT-737's varied effectiveness.

"Now that we have uncovered Noxa and MCL-1 as potential targets, we can work to better define the mechanisms that help regulate their expression," says Krystal, member of the Developmental Therapeutics research program at Massey and professor of microbiology and immunology in the VCU School of Medicine. "Moving forward, we plan to conduct additional studies to further define these mechanisms in order to better sensitize small cell lung cancer cells to drugs like ABT-737."

Harada and Krystal collaborated on this research with Nobuyuki Tanaka, M.D., Ph.D., professor at the Nippon Medical School in Japan; Wataru Nakajima, Ph.D., Virginia Commonwealth University post-doctoral fellow; and Mark Hicks, research assistant.

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The full manuscript of this study is available online at:
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