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Team finds new target for melanoma treatment

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Scientists at Sanford-Burnham Medical Research Institute (Sanford-Burnham) today announced the discovery that a gene encoding an enzyme, phosphoinositide-dependent kinase-1 (PDK1), plays an essential role in the development and progression of melanoma. The finding offers a new approach to treating this life-threatening disease.

The team of researchers, led by Ze'ev Ronai, Ph.D., professor and scientific director of Sanford-Burnham Medical Research Institute in La Jolla (San Diego, Calif.), used genetic mouse melanoma models to show the importance of the PDK1 gene in melanoma. Specifically, mice lacking the PDK1 gene in their melanocytes (cells that transform to become melanoma) had smaller melanoma tumors, a significant loss of metastasis, and a prolonged survival time. In some cases, the median survival time was increased by more than 50 percent. Further, by treating mice with the PDK1 gene with an inhibitor of PDK1 (PDK1i), the scientists were able to delay the development of melanoma and inhibit metastasis. The published results are available online in the advanced online publication of *Oncogene*.

"We have shown that PDK1 is required for melanoma metastasis, and that by inactivating the PDK1 enzyme we can delay the onset of melanoma lesions and almost completely abolish metastasis," Ronai said. Prior to this study, it was known that PDK1 activity played an important role in normal cell processes such as cell metabolism, protein translation, and cell survival. PDK1 activity was also known to be associated with specific tumor types. For example, inactivation of PDK1 activity has

been shown to inhibit pancreatic cancer. This study provides the first genetic evidence for the importance of PDK1 in melanoma.

David Fisher, M.D., Ph.D., professor and chairman of the Edward Wigglesworth Department of Dermatology, director of the Melanoma Program, and director of Cutaneous Biology at Massachusetts General Hospital, Harvard Medical School, commented, "The study by Ronai and colleagues is novel and important for melanoma therapeutics because it identifies a new and tractable treatment approach. The investigators achieved impressive results which validate PDK1 as a new treatment target for melanoma."

"This collaboration between Sanford-Burnham and Yale researchers shows unequivocally that melanoma cells require PDK1 for both development and metastasis. The team also demonstrates that a molecular inhibitor is capable of duplicating the effects of the genetic approaches suggesting that the cancer field should invest more efforts into PDK1 targets," said Meenhard Herlynn D.V.M., D.Sc., director of Melanoma Research and leader, Molecular and Cellular Oncogenesis program at the Wistar Institute in Philadelphia, Pa.

Melanoma, Disease Progression, and Treatment

Although less common than other types of cancer, melanoma is the most deadly form of skin cancer. In the United States, over 70,000 new cases are diagnosed per year and 9,000 deaths are attributed to the disease. Metastatic melanoma is a progressive form of melanoma that happens when cancerous cells from the original tumor break off, circulate, and form new tumors in other parts of the body, leading to life-threatening disease.

Recently, advances in the treatment of melanoma that activate the immune system by targeting the molecules CTLA4 and PD1, and

targeting kinases such as BRAF, have shown promise. Although these drugs have led to improved patient survival, they do not cure melanoma. Therefore, additional therapies are needed. Recently, it has been shown that a combination of targeted therapies can be more effective.

"It is important now to demonstrate the impact of PDK1 inhibition in combination with other therapies currently used in melanoma, including BRAFi or immunological targets (PD1/CTL4A), on melanoma development and metastasis. A number of PDKi are available and others are in development, offering an important addition to the currently available combination therapies. Ultimately, our goal is to see if inhibition of PDK1 will contribute to better outcomes for patients with melanoma," Ronai said.

About Protein Kinases

In many cancers, pathogenic kinases work together to disrupt the cell cycle, leading to uncontrolled cell growth and tumor formation.

Protein-kinase inhibitors block the actions of pathogenic kinases and inhibit uncontrolled cell proliferation. For this reason, cancer-specific protein-kinase inhibitors either individually or more recently as combinations of inhibitors with pharmacologic immunological modulators—"cocktails"—are being tested and used to treat cancers.

Provided by Sanford-Burnham Medical Research Institute

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