Newly discovered kinase regulates cytoskeleton, and perhaps holds key to how cancer cells spread

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UCSD researchers say novel enzyme may provide new target for future anticancer therapies

Scientists at the University of California, San Diego have identified a previously unknown kinase that regulates cell proliferation, shape and migration, and may play a major role in the progression or metastasis of cancer cells.

The research will be published in the May 31 online Early Edition of the *Proceedings of the National Academy of Sciences.*

Richard L. Klemke, PhD, professor of pathology at the UCSD School of Medicine and the Moores Cancer Center, and colleagues say the new kinase or enzyme regulates the cytoskeleton – the internal framework of tiny filaments and microtubules in cells that gives them shape, coherence and the ability to move.

"This molecule may be an important new target for future anticancer therapies and a clinical biomarker that predicts whether a cancer is likely to spread," said Klemke.

Proper regulation of the cytoskeleton is important to many fundamental cellular functions, including axon/dendrite formation, migration, differentiation and proliferation. Conversely, deregulation of the cytoskeleton can contribute to a variety of human diseases, including cancer metastasis or the spread of tumors to other parts of the body.

The new kinase – called pseudopodium-enriched atypical kinase one or PEAK1 – plays a central role in the formation of cellular pseudopodia. Greek for "false foot," a pseudopodium is a highly specialized structure that protrudes from the surface of migrating cells. It attaches the leading, extending membrane of the cell to its underlying substrate, and then helps pull the cell forward. By endlessly repeating this process, a cell is able to move in a productive manner.

"Cancer cells capitalize on their innate ability to move in this fashion when they metastasize," said Jonathan A. Kelber, PhD, leading author on the paper and postdoctoral fellow in Klemke's lab. "Cancer cells detach from the primary tumor, invade the extracellular milieu and then enter the vascular system from which they can spread and seed new tumors in distant tissues."

Discovering PEAK1 provides researchers with a new player to study and investigate, one that may have significant influence in the biology of cells, particularly cancer cells. Evidence from mouse studies suggests PEAK1 is an important player during tumor growth, and Klemke's team has further demonstrated that PEAK1 levels are increased in primary and metastatic samples from human colon cancer patients. Whether PEAK1 is capable of transforming non-tumor cells into cancer cells remains to be determined.

"One exciting fact is that PEAK1 has kinase activity, which suggests you can design a small molecule drug that would specifically inhibit its activity," said Kelber. "But that work lies in the future. First, we need to fully identify the role of its kinase domain in tumor progression."

Co-authors of the paper with Klemke and Kelber are Yingchun Wang, formerly in the department of pathology and at the Moores Cancer Center, both at UC San Diego and currently at the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences in Beijing; Wei Wang and Jeanne M. Bristow in the department of pathology and at Moores at UCSD; Michael Bouvet in the department of surgery at UCSD and at Moores; Hop S. Tran Cao and Robert M. Hoffman in the department of surgery at UCSD; Greg T. Cantin and John R. Yates III in the department of chemical physiology at The Scripps Research Institute (TRSI); and Rui Lin and Thomas S. Edgington in the department of immunology at TRSI.

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