The most lethal cancer

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Inhibition of K-RAS–mediated Tumorigenesis and Metastasis by Blocking SIAH E3 Ligase–dependent Proteolysis in Pancreatic Cancer

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Blocking a molecular pathway stops deadly pancreatic cancer in its tracks

It's a target with a funny name—"seven-in-absentia homolog"—but if results from the laboratory of Amy Tang at the Mayo Clinic College of Medicine in Minnesota pan out, new drugs and new hope could emerge for patients with pancreatic cancer. Until now, they have had little of either. Pancreatic cancer is the most lethal form of human cancer known; the median survival time of pancreatic cancer patients is only six months, and the mortality rate is 95%.

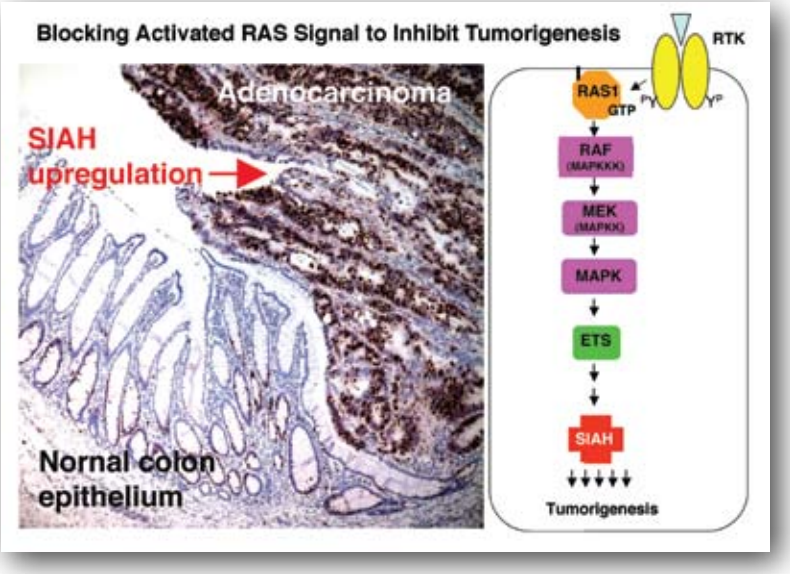
Tang and her colleagues believe that they have found a new therapeutic target for pancreatic cancer in the proteins produced by the human gene *SIAH* (seven-in-absentia homolog). That name in turn is derived from plain old "seven in absentia," or *SINA,* the whimsical name given to the gene when first discovered in the famous fruit fly, *Drosophila melanogaster.* In flies, *SINA* produces a family of RING domain E3 ubiquitin ligases. In all creatures, ubiquitin ligases turn cell pathways on or off by degrading proteins. In humans, the SIAH ubiquitin ligases sit smack in the middle of the molecular pathway that leads to pancreatic cancer, says Tang.

The key protein in the pathway regulating cell growth is K-RAS. When K-RAS becomes hyperactivated, it sets off a major signaling pathway that drives aggressive cellular transformation, oncogenesis, and metastasis in pancreatic cancers. Virtually all patients with pancreatic adenocarcinomas have mutations that hyperactivate K-RAS.

The Tang lab found that SIAH ubiquitin ligases were specifically and markedly upregulated in pancreatic cancers. The increased *SIAH* expression seemed to correlate with increased grades and aggressiveness of pancreatic cancer. Moreover, *SIAH* is normally required for mammalian K-RAS signal transduction.

By inhibiting *SIAH* function, the researchers abolished both tumorigenesis and metastasis of human pancreatic cancer cells growing in special mice (called nude because they are hairless) that have immune system deficits that prevent them from rejecting foreign tissue. The SIAH protein seems to work as a check-and-balance mechanism in the K-RAS pathway by chewing up and turning off proteins that regulate pancreatic cell growth, says Tang. "By attacking the SIAH-based protein degrading machinery, we block tumor formation in one of the most aggressive human cancers known."

SIAH is therefore an attractive new target for new anti-RAS and anticancer therapy in pancreatic cancer. "It is likely to move into the clinical setting for study as an interventional treatment in pancreatic cancer in human patients," Tang believes.



In pancreatic cancer (left), the ubiquitin ligase with the funny name of "seven-in-absentia homolog" or SIAH is the most downstream component in the long RAS metabolic pathway (right) that leads to tumor formation. Blocking SIAH blocks cancer progression. Anti-SIAH molecules have potential as new and effective agents against human pancreatic cancer, possibly in the near future.