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Blocking molecular pathway with whimsical name possible therapeutic target for pancreatic cancer

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A possible new therapeutic target for pancreatic cancer, the most lethal form of human cancer, has been identified in the proteins whose DNA recipe comes from gene, "Seven-In-Absentia," according to researchers at the American Society for Cell Biology (ASCB) 48th Annual Meeting, Dec. 13-17, 2008 in San Francisco.

In their studies with the fruit fly, Drosophila melanogaster, at the Mayo Clinic College of Medicine in Minnesota, scientists found a link between the "Seven-In-Absentia" or SINA gene and the aggressive cellular transformation, oncogenesis and metastasis that characterize pancreatic cancer.

Scientists already knew that a mutation in the K-RAS gene underlies the abnormal, excessive cell growth of pancreatic cancer.

Because the mutated form of this growth-promoting gene is hyperactivated, a major signaling pathway that drives cell growth is in over-drive in most patients with this cancer.

The "Seven-In-Absentia-Homolog" (SIAH) protein seems to work as a check and balance mechanism in the K-RAS pathway by chewing up and turning off the excessive growth-promoting proteins produced by the hyperactive, mutated form of the gene, says Amy Tang whose Mayo lab conducted the research.

"By attacking the SIAH-based protein degrading machinery, we block tumor formation in one of the most aggressive human cancers cells known," she reports.

Because of these results, SIAH may be an attractive new target for novel anti-RAS and anti-cancer therapy in pancreatic cancer, the median survival of which is only six months, and the mortality rate is 95 percent.

By inhibiting SIAH function, Tang and her colleagues were able to completely abolish both tumorigenesis and metastasis of human pancreatic cancer cells that were growing in "nude" mice that have immune system deficits that prevent them from rejecting foreign tissue.

"It is likely to move into the clinical setting for study as an interventional treatment in pancreatic cancer in human patients," Tang says, referring to the SIAH inhibition.

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, Tang explains.

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.

Source: American Society for Cell Biology