

# Alter Ego

*One protein encourages prostate cancer and another stifles it. Both are encoded by the same gene.*

SOME GENES ARE LIKE STORIES THAT LET READERS CHOOSE BETWEEN several endings. Take the gene *KLF6*, for instance. The way a person's cells read *KLF6* can result in a protein that drives growth or one that slows it. That decision makes a difference in prostate cancer, according to research by Goutham Narla, a recent winner of an HHMI Early Career Physician-Scientist Award. ¶ Ten years ago, when Narla was an HHMI medical research fellow, he made a discovery that helped characterize

*KLF6* as a tumor suppressor gene that is blocked in prostate cancer. The work was an outgrowth of research on the liver; Narla trained, as a medical student and then as an M.D./Ph.D. student, in the laboratory of Scott L. Friedman, a physician-scientist at New York's Mount Sinai School of Medicine who studies liver disease.

With Friedman and colleagues, Narla, who launched his own lab at Mount Sinai in 2006, recently revealed that *KLF6* also encodes a protein that drives cancer development and progression. On the basis of this discovery, they've proposed ways to predict a man's risk of developing prostate cancer and whether the disease, once diagnosed, is likely to recur. In 2008, they designed what may one day be a new treatment for the most aggressive forms of the disease.

In 1998, Friedman was studying a class of cells (hepatic stellate cells) involved in liver healing. His lab group had found that when these cells reproduced, *KLF6* was

active. Although every cell in the body expressed *KLF6*, Friedman wanted to know the gene's role in the liver. As an HHMI medical fellow, Narla engineered mice with overactive *KLF6* in the liver.

The mice were unusually small—with small livers. At the time, “we thought, maybe this gene actually tells cells to stop growing,” Narla recalls. He tested the idea and discovered that *KLF6* engages well-known cellular machinery for growth suppression—specifically, tumor suppression.

Narla scoured the literature and found that many patients' prostate tumors have DNA damage in a region of the chromo-

some that includes *KLF6*. He dissected human prostate tumors and confirmed that most lacked one copy of *KLF6* or had mutations in the gene. Moreover, when he activated *KLF6* in cultured tumor cells, the cells grew more slowly.

In human and mouse tumors, he found four versions of *KLF6* messenger RNA (mRNA). Cells read the gene like a choose-your-own-adventure story, skipping some parts and transcribing the others into mRNA.

Protein made from the shortest version, called *KLF6-SV1*, drives cellular changes that speed the spread of tumor cells in mice.

In 2005, the team studied the DNA of more than 3,400 men and found that some have a hereditary variation in *KLF6* that changes how cells read the gene. As a result, they make more *KLF6-SV1* and



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GOUTHAM NARLA



less full-length mRNA. A man born with the variation is twice as likely to develop prostate cancer as someone without it. “He makes a little more *KLF6-SV1*, and over his lifetime that drives the process of cancer development forward,” Narla says.

Genetic testing for this variation may predict a man’s chance of developing prostate cancer.

The researchers also found, in 2008, that patients whose tumors had high concentrations of *KLF6-SV1* had a greater chance of disease recurrence. This finding may lead to a test on a patient’s tumor biopsy that could inform treatment decisions.

Narla and colleagues also managed to reverse the effects of *KLF6-SV1* in the lab. After inducing prostate-derived tumors in mice, they injected the tumors with small RNA segments, called siRNA, that attach specifically to *KLF6-SV1* and prevent it from being translated into protein. The tumors regressed. These siRNA also killed prostate cancer cells in culture. The study was published in the *Journal of Clinical Investigation* in August 2008.

“It was really Goutham’s work that led us into an understanding of [the gene’s] role in cancer,” says Friedman, who adds that he’s gratified to see his student emerging as

an independent scientist. The early career physician-scientist award, part of HHMI’s effort to support young scientists working to translate scientific discoveries into better treatments for patients, will provide five years of funding to Narla’s lab.

Narla believes he’s finally getting close to his goal of helping patients. “As a clinician I was struggling to find a way to apply this information to the patients we see every day with metastatic cancer. When we identified *KLF6-SV1* and were able to actually target it and see tumors shrink, I was extraordinarily excited.” ■

—OLGA KUCHMENT