



Molecular Switch for Prostate Cancer May Yield Road Map of Cancer Machinery and Targets for Drugs

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Molecular biologists from Texas A&M's Institute of Biosciences and Technology and Duke University have teamed up to pinpoint a genetic switch in prostate cancer cells that may trigger a quiescent tumor to erupt into an invasive, deadly cancer that spreads throughout the body. The discovery of this single genetic switch could open a research pathway leading to a road map of the complex changes prostate cancer cells undergo in their progression to a deadly form. Such a road map would yield not only molecular markers allowing physicians to better pinpoint the stage of a prostate cancer, but also new drugs to kill cancer cells or preventive strategies to hold them in a harmless state at earlier stages.

The scientists are Dunn Professor of Biochemistry and Biophysics [Wallace McKeehan](#) of Texas A&M University's Institute of Biosciences and Technology and Russ Carstens and [Mariano Garcia-Blanco](#) of the [Duke Medical Center Department of Pharmacology and Cancer Biology](#). They published their findings in a paper in the April issue of *Molecular and Cellular Biology*. The research combines Dr. McKeehan's expertise of working with prostate cancer cells and manipulating them genetically outside the body and the Duke scientists' expertise in molecular genetics.

Prostate cancers are distinguished by their tendency to linger at a relatively benign stage for many years, but to suddenly transform into a deadly form that spreads throughout the body. The scientists discovered the molecular basis for a genetic switch that governs whether a cancer cell generates one or another form of a protein receptor molecule called FGFR2 (Fibroblast Growth Factor Receptor 2) displayed on the surface of the cell.

In a report just four months earlier in the December issue of *Cancer Research*, Dr. McKeehan showed that by inserting the gene for the FGFR2 molecule into malignant rat prostate cells that had lost the gene, this caused them to again respond to neighboring cells when they were placed under the skin of male rats. These receptors are molecular locks into which a protein called a growth factor from another cell in the prostate fits to direct proper cell behavior. As long as the FGF-R2 receptor is of one type -- called IIIb - the cancer cell is well-behaved and controlled by a protein messenger which comes from neighboring prostate cells, called stroma cells.

Those stroma cells, in turn, are controlled by the male hormone androgen. Dr. McKeehan first observed this phenomenon in model rat prostate tumors. Now he has teamed up with the Duke group who investigated the mechanism at a molecular level.

When the cancer cell abruptly switches over to making another receptor type, called IIIc, it becomes a rogue that frees itself from the controlling influence of neighboring cells, becomes "androgen-independent" and spreads throughout the body.

The three scientists discovered the switch as a short stretch of RNA nestled in the string of

"messenger RNA," a molecule which constitutes the blueprint for the receptor and which moves out of the cell's nucleus to the protein-making machinery, where it governs production of FGF-R2. The scientists found that this string of messenger RNA actually includes the code for producing both IIIb and IIIc, with the genetic switch sitting between the two lengths of RNA code. That switch acts as the dotted line for molecular "scissors" to cut out one part of the RNA and leave the other which determines which form of FGF-R2 is the result.

Dr. McKeehan explains that this phenomenon is called "alternative splicing," which is similar to the process of editing film. An editor starting from the raw footage can decide to cut one scene and not another, possibly producing two very different films.

The researchers cautioned that they do not know yet whether this switch in the receptor is critical for either androgen independence or metastasis, or whether it's just a marker. But even if it is a marker, it could still be useful as a very early signal of a turning point in aggressiveness of the tumor. The researchers contend that this finding is important because of our lack of knowledge about what causes prostate cancers to re-occur as highly metastatic and malignant forms after surgery.

Dr. McKeehan pointed out that the molecular findings are unique because genetic mistakes in genes often cause defective messenger RNA or its lack of expression, not in alternative splicing the RNA into one form or another that is otherwise normal. Dr. McKeehan pointed out that both research groups will follow this initial clue to understand how the RNA switch itself is controlled, and ultimately to broadly map the deadly machinery of prostate cancer.

Dr. McKeehan added, "By extension of these studies, we hope to find many more targets for anti-cancer drugs to selectively kill these aggressive tumors before they are severe enough to cause symptoms. Discovery of new markers that allow physicians to tell whether a particular individual needs immediate treatment because of presence of a tumor that will become aggressive or should do nothing will help in making treatment decisions."

He added that molecular switches as those described may be targets for preventive agents in the diet that are being investigated by joint projects between the Center for Cancer Biology and Nutrition in the Institute of Biotechnology and Sciences in the Texas Medical Center and the Texas Agricultural Experiment Station and Citrus Center at Weslaco and Kingsville, Texas.