Shifting Focus from Oncogenes to Genetic Instability, a Defect Common to All Cancers

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Professor Wallace McKeehan spent the last twelve years of his scientific career trying to develop cancerous tumors using growth-promoting genes in specially designed laboratory animals. This spring he heralds a new phase in his research with three scientific papers that focus instead on tumor suppression. Discovering why he made this about-face explains much about cancer research today.

Since 1993, McKeehan has led the Center for Cancer Biology and Nutrition at the Institute of Biosciences and Technology in Houston, located in the renowned Texas Medical Center. The institute is part of The Texas A&M University System Health Science Center. McKeehan himself is known worldwide for his research into cell-to-cell communication. When that process goes wrong, cells grow wildly.

“In my laboratory, we manipulated the FGF cell signaling system, trying to produce cancer in prostates,” McKeehan explains. “However, we could bring the cells to the very brink of cancer, but we could not cause malignancy. Our mice would have benign hyperplasia in their prostates but not cancer. We could not turn off the naturally-occurring tumor suppressors that prevented the genetic flexibility needed for cells to evolve into tumors.” Dauntless, McKeehan pressed on. He took this failure and turned it on its head.
“Until recently, most cancer research has concentrated on understanding what happens when single genetic mutations collect,” he continues, “but different cancers seldom exhibit the same set of mutations. We scientists have studied single genetic mutations because they have been easy to research, but now we are turning to the property that is common to all cancers—genetic instability that allows them to constantly adapt and evolve in the body.”

This is where tumor suppressors that prevent genetic instability come in, the process that was keeping McKeehan’s lab mice from developing rampant cancer in their prostates. It is now as important for him to understand what keeps cancer and genetic instability from occurring as it was previously to try to induce cancer in his mice with growth factors.

“A beautiful and elaborate process in our bodies works hard to ensure that when our cells divide, they do so properly. It’s fortunate that our tumor suppressors act so ably to keep gross error and genetic instability from happening because this is probably the common cause of all human cancers. It is what allows cancer cells to adapt continuously to their environment and escape therapy. If we can understand what happens at the instant of cell division—or mitosis—when gross genetic error and genetic instability are averted—then we can go a long way towards understanding and then stopping cancer in its tracks.”

Quickly, McKeehan sketches the important process of cell division—giving a shorthand course in Mitosis 101.

When cells divide, they must do so correctly. Exactly half of the chromosomes must go into one new cell and half into the other. If done wrong, then one cell ends up with too much
and the other with too little. This is what is known as aneuploidy, or gross genetic error, which occurs during the division of one cell and gives rise to genetic instability, which leads to cancer.

A network of quality control regulates this process to insure chromosomes are evenly divided. If not, the error is recognized and the cell and its genome destroyed to prevent cancer. McKeehan’s three new research papers point to a potentially novel form of cell death that recognizes when the machinery called microtubules that separates the chromosomes evenly are defective and improper distribution threatens.

Microtubules are part of the cell’s structure that are tubular in shape, and they are capable of growing and shrinking in order to divide chromosomes evenly. The dividing cell sometimes pauses to see if all its dividing chromosomes are lining up evenly, which is called a checkpoint. If that process fails, then the microtubules freeze up, disastrous error threatens and the cell must die if cancer is to be prevented. Mitochondria, which normally serve as the cell’s power factories, are involved in killing the cell, if required. The mitochondria sit in wait, aligned along the microtubules, ready to rush into action if the checkpoint fails.

McKeehan’s research team is comprised of Dr. Leyuan Liu and several Ph.D. students. His team has found new molecules that partner to recognize when the checkpoint fails, causing the microtubules to freeze and then causing the mitochondria to mass around the defective cell. Thus the threat of cancer is removed. McKeehan’s discovery brings us closer to understanding this fascinating process. Once fully understood, the process can be mimicked and used to stop cancer.

Humanity’s goal of finding a cure for cancer may not be a pipedream after all.

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