UC San Diego Health

Researchers Identify New Drug Targets for Cancer

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Solving a 100-year-old genetic puzzle, researchers at the University of California, San Diego (UCSD) School of Medicine and the Ludwig Institute for Cancer Research have determined that the same genetic mechanism that drives tumor growth can also act as a tumor suppressor. Their findings could lead to new drug targets for cancer therapies.

In a study published in the January 1 issue of *Cancer Cell*, Don Cleveland, Ph.D., UCSD Professor of Medicine, Neurosciences and Cellular and Molecular Medicine and member of the Ludwig Institute for Cancer Research, looked at a common characteristic of cancer cells called aneuploidy. Aneuploidy – the occurrence of one or more extra or missing chromosomes – was first proposed as the cause of cancerous tumors nearly a century ago by German biologist Theodor Boveri, but his hypothesis had remained unproven.

"We questioned whether the wrong number of chromosomes contributed to tumor growth, or was a consequences of the accrued damage in cancerous cells," said Cleveland.

To find out, researchers in the Cleveland lab created and analyzed mouse models with cells having a highly variable number of chromosomes to discover if such aneuploidy made the mice more tumor-prone.

"We found that, with age, having cells which inherited the wrong composition of chromosomes resulted in a larger number of spontaneous tumors," said Cleveland. But the more unexpected feature of their findings was discovered when the research team added other genetic errors to mice with a high rate of aneuploidy – tumor development was slowed.

The UCSD researchers also studied mice that were missing a tumor suppressor gene, which is a gene that acts to prevent cell growth. If a mutation occurs in this gene, it makes the individual – or in this case, the mouse – more susceptible to the development of cancer in the tissue in which the mutation occurs.

"When we created mice missing a tumor suppressor gene that also had a high rate of aneuploidy, tumor development was actually sharply delayed," said Cleveland, adding that in tumors, "there is always a balance between uncontrolled growth and death."

The researchers hope that, in the future, they can develop what they are calling "aneuploidy therapy." Drugs that inhibit accurate delivery of the right number of chromosomes to each new cell, resulting in aneuploidy, would be used to destroy tumors caused by mutations in the tumor suppressors.

"This study opens up a whole series of potential therapeutic targets for cancer," said Beth A.A. Weaver, of the Ludwig Institute for Cancer Research and UCSD Department of Cellular and Molecular Medicine, the study's first author. "By increasing the level of genetic damage, we can kill those tumor cells."

Other contributors include Alain D. Silk, Ludwig Institute for Cancer Research and UCSD Department of Cellular and Molecular Medicine; Cristina Montagna, UCSD Departments of Pathology and Molecular Genetics; Pascal Verdier-Pinard, Departments of Molecular Pharmacology and OB/GYN and Women's Health, Albert Einstein College of Medicine, Bronx, NY.

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