

Theories of genes and cancer



**ASSIGN
BUSTER**

The Wind in the Trees

In the late 1950s, Peter Nowell and David Hungerford, two pathologists from Philadelphia had found an unusual chromosomal pattern in chronic myelogenous leukemia (CML) cells. In CML cells, Novell found that one copy of chromosome 22 had its head lopped off. Novell called this abnormality the Philadelphia chromosome after the place of discovery.

In 1973, a hematologist in Chicago named Janet Bowley followed this study, looking for the missing pieces of the Philadelphia chromosome. She found a pattern. The missing head of chromosome 22 had attached itself to the tip of chromosome 9. And a piece of chromosome 9 had attached itself to chromosome 22. This genetic event was called a translocation - the transposition of two pieces of chromosomes.

Bowley found this same translocation in the cells of every CML patient. Cancer was not disorganized chaos, but an organized chromosomal chaos resulting from specific, identical mutations. Chromosome translocation can create new genes called chimeras by fusing two genes formerly located on two different chromosomes. The CML translocation, Rowley postulated, had created such a chimera.

In 1969, Alfred Knudson, a geneticist at MD Anderson Cancer Center in Texas, wanted to capture a pattern of inheritance of cancer by studying retinoblastoma, an hereditary eye cancer. Retinoblstoma has two distinct variants, an inherited "familial" form and a sporadic form. Children who

suffer from the familial form may have strong family histories of the disease, and they typically develop tumors in both eyes. Children with the sporadic form never have a history in the family and always have a tumor in only one eye.

By studying cohorts of children with the two types of cancers, Knudson discovered the cohorts developed cancers at different “ speeds.” Inherited retinoblastoma cancer develops at early ages, typically between 2 to 6 months old. Sporadic retinoblastoma cancer develops at older ages, typically between ages 2 to 4 years old.

Humans inherit two copies of every gene, one from each parent. Knudson postulated that both copies of the Retinoblastoma (Rb) gene needed to be inactivated through mutation to develop retinoblastoma. Some children inherit one mutated version and one normal version of the Rb gene. The inherited mutation is “ the first hit.” These children are thus predisposed to the cancer, and only a single additional genetic mutation is needed for them to develop the cancer. So they develop cancer at earlier ages. Sporadic retinoblastoma develops at later ages because two independent mutations have to accumulate in the cell. Knudson called this the two-hit hypothesis of cancer. For certain cancer-causing genes, two mutational “ hits” are needed to produce cancer.

At first glance, Knudson’s two-hit theory seemed at odds with the src gene, which only required one activated copy to cause cancer. The answer is because the two genes perform two different functions. The src gene creates a hyperactive kinase that provokes perpetual cell division to cause cancer,

while the Rb gene performs the opposite function. It is a cancer suppressor gene, or an “ anti-oncogene.” It requires two mutation hits to inactivate such a gene.

A Risky Prediction

Risky prediction is a process scientists used to validate untested theories. For instance, the return of Halley’s comet in 1758 validated Newton’s law of gravity.

The first risky prediction involved Varmus and Bishop’s hypothesis on oncogenes. In the late 1970s, Varmus and Bishop had shown that the precursors of oncogenes, also called proto-oncogenes, already existed in all normal cells. They hypothesized that mutations in such proto-oncogenes caused cancer. To prove that they were right, we needed to the mutated versions of such proto-oncogenes inside the cancer cells.

How does one find such a gene? The MIT cancer biologist Robert Weinberg had an idea. If he transfers a fragment of the DNA containing the activated oncogene from the cancer cell into normal cells, then the activated oncogene should induce the normal cells to divide and proliferate, producing a foci out of the normal cells in the petri dish. By repeating this process and dividing the DNA fragments into smaller and smaller fragments, he should be able to isolate the culprit.

In the summer of 1979, a graduate student in Weinberg’s lab named Chiaho Shih went through the experiment using mouse cancer cells. He verified that

the method worked for mouse cancer cells. They then moved on to human cancer cells.

Three years later in 1982, Weinberg isolated a gene called ras from human cancer cells. The mutated ras gene encoded a hyperactive protein permanently locked “ on.” It was the long-sought “ native” human oncogene, captured out of a cancer cell.

Meanwhile, two other scientists, Mariano Barbacid, and Michael Wigler had also independently discovered the ras gene in 1982.

The second risky prediction the hypothesis that retinoblastoma was caused by the mutation of two copies of Rb genes. Thad Dryja, an ophthalmologist and geneticist, suspected that the mutation responsible was likely a deletion of the gene. To prove the hypothesis, Dryja wanted to prove that the two copies of the Rb gene were deleted from the cancer cells.

Week after week, Dryja extracted the chromosomes from his big collections of tumors and ran his probe set against the chromosomes. Eventually, he saw a blank space in his probes. A piece of DNA was missing in probe H3-8 of the tumor cells. Dryja took his probe to Steve Friend who had a collection of normal cells in Weinberg’s lab. Friend applied the H3-8 probe to normal cells and isolated the gene on that location. Both copies of the Rb genes were indeed deleted from the cancer cells.

The third risky prediction involved the hypothesis that activated oncogenes cause cancer. We already knew that (1) activated oncogenes were present in cancer cells, and (2) they could be isolated from the cancer cells. To prove “

causation”, we have to prove that activated oncogenes can create cancer in an animal.

In 1984, using transgenic mouse technology, Philip Leder’s team at Harvard created transgenic mice with an activated c-myc gene expressed in the breast cells. The mice developed small tumors in their breast late in life after pregnancy.

To test the roles of environmental stimuli and other oncogenes, Leder created a second OncoMouse with ras and myc expressed in breast cells. The mice developed tiny distinct tumors in their breasts in months, pregnancy not required. Scientists had created real, living tumors in an animal.

The Hallmarks of Cancer

Philip Leder’s experiment showed that scientists had created real tumors by manipulating two genes, ras and myc, in an animal. But activating two potent proto-oncogenes did not create the full syndrome of cancer in every cell of the mouse. It raised further questions about the genesis of cancer.

In 1988, using human specimens, a physician named Bert Vogelstein set out to describe the number of genetic changes required to start cancer.

Vogelstein studied how normal cells progress to cancer cells in colon cancer. He found a consistent pattern in his colon cancer samples. The genetic progression of cancer was a multi-step process. The transitions in the stages of cancer mirrored the transitions in genetic changes. Cancer cells did not activate or inactivate at random. Instead, the shift from a pre-malignant

state to an invasive cancer correlated with the activation and inactivation of genes in a strict and stereotypical sequence.

Cancer cells are caused by mutations of genes in their DNA. Besides uncontrolled growth, cancer cells also can resist death signals, grow their own blood vessels, and metastasize throughout the body.

In January 2000, Robert Weinberg and Douglas Hanahan wrote the seminal paper, “ The Hallmarks of Cancer” that gave the six essential changes in cell physiology that collectively cause cancer:

1. Self-sufficiency in growth signals – gas pedal stuck on
2. Insensitivity to growth-inhibitory signals- brakes don't work
3. Evading of programmed cell death (apoptosis) – won't die
4. Limitless replicative potential – uncontrolled growth
5. Sustained angiogenesis – having its own blood supply
6. Tissue invasion and metastasis