Cancer, metastasis, clonality, carcinogen, mutagens, malfunction of genes, aneuploidy, gene amplification, chromosomal translocation, oncogene, proto-oncogene, familial cancer, tumor suppressor gene, gain of function (genetic dominance), loss of function (genetic recessiveness), tumor progression

2. Lecture Notes

Cancer is a formidable adversary

In developed nations, cancer accounts for one-quarter or more of all deaths. The disease will soon be the leading cause of death in the USA, and it is an ever-increasing global burden of suffering and mortality.
Recent research has produced a unifying paradigm for the fundamental malady of cancer

Cancer is not one disease but more than one-hundred, arising from numerous causes and in the numerous tissues of our bodies. It was once thought that we would have to solve the puzzle of cancer one form at a time. But recent decades have produced a unifying theme: whatever the causes, all cancers arise from the malfunction of genes. This lecture outlines five major lines of enquiry that led us to this genetic paradigm for cancer.

First, the properties of a cancer cell are heritable

The properties of cancer cells are faithfully transmitted from one cancer cell to its daughters, and so on, ad infinitum. In other words, the properties are heritable. Rudolph Virchow may have been the first person to call attention to this feature, by pointing to the similarities between cells in the initial (or “primary”) tumor and metastatic cancer cells that had spread to distant sites in the body. Eventually, it became apparent that cancer cells are typically capable of indefinite (so-called “immortal”) reproduction, in contrast to normal cells, whose reproductive life-span is typically limited. Through endless rounds of cell division, however, cancer cells retain their malevolent behavior.

Second, many causes of cancer (“carcinogens”) damage DNA, causing mutations

The possibility that external agents might cause cancer was recognized as early as the 18th century. This was eventually proved by demonstrating the ability of chemicals and X-rays to elicit cancer in rodents. Soon thereafter, it was discovered that X-rays cause mutations. Eventually, tests with bacteria demonstrated that many (but not all) carcinogens are mutagenic, and it became apparent that mutations represent damage to DNA.

Third, cancer cells contain abnormalities of chromosomes

Chromosomes are the structural housing for DNA in cells. Cancer cells can contain a variety of chromosomal abnormalities. These include: a decrease or increase in number - - a condition known as “aneuploidy” (the normal number of chromosomes is
known as “euploidy”); loss or amplification of focal regions within individual chromosomes; and exchange of regions between chromosomes known as “translocations.” It seemed likely that these abnormalities would affect the structure and/or function of genes.

Fourth, cancer-causing genes (or “oncogenes”) found in retroviruses are derived from the genes of normal cells.

Retroviruses are a distinctive family of viruses that use reverse transcription (copying RNA into DNA) to replicate their genome. Some of these viruses have genes that can cause cancer (“viral oncogenes”). The description of viral oncogenes provided the first definitive evidence that genes can have a direct role in cancer. But the significance of retroviral oncogenes became even larger with the discovery that they were acquired from the DNA of normal cells. Their ability to cause cancer is due either to excessive expression in the context of viral infection or to mutations acquired during the piracy from normal cells. The cellular genes capable of giving rise to viral oncogenes are known by the generic term “proto-oncogenes.”

The discovery of proto-oncogenes raised the possibility that all cancer might involve the malfunction of these genes, no matter what the cause. That idea was quickly given credence with the demonstration that a variety of proto-oncogenes are affected by genetic anomalies in the cells of human cancers, including gene amplification, chromosomal translocations and point mutations within the body of the gene. Each of these anomalies creates a dominant malfunction of the affected gene that over-rides the function of its normal counterpart. By now, several hundred proto-oncogenes have been described in the human genome.

Fifth, the study of inherited cancer uncovered a second sort of cancer gene known as “tumor suppressors.”

Between five and ten percent of human cancer is inherited in a dominant fashion, appearing in every generation of a family lineage. The nature of this inheritance was first elucidated for retinoblastoma, a relatively rare tumor of children that occurs in the retina of the eye. Inheritance of retinoblastoma is associated with a specific deletion within the structure of human chromosome 13. The deletion creates a recessive predisposition to retinoblastoma: both copies of the gene must be disabled before the deficiency can take effect. The inherited predisposition to cancer arises because
Inheritance of one disabled copy creates a head-start towards achieving a complete deficiency in the gene. Numerous other such genes have now been discovered, although many have been implicated only in sporadic, as opposed to inherited cancers. In sporadic tumors, both copies of the recessive gene become defective subsequent to conception or birth, generally in a somatic rather than a germinal cell. As a class, these genes are known as “tumor suppressor” genes. The schemes for congenital and sporadic tumors is explained with diagrams in the lecture.

The two sorts of cancer genes have reciprocal roles in cancer

The malfunction of proto-oncogenes acts as a jammed accelerator, driving the cancer cell in a relentless manner. Only one of the two copies of a proto-oncogene needs to malfunction in order to cause trouble. In genetic terms, it represents a dominant “gain of function.” In contrast, tumor suppressor genes represent brakes on cellular behavior, and their malady in cancer cells represents a recessive “loss of function.” In general, both copies of a genetic brake must be lost or inactivated before a contribution to tumorigenesis can occur, although there may be occasional exceptions to this.

The genesis of cancer requires the accumulation of multiple genetic maladies over the course of time.

Most if not all cancers display malfunction of both proto-oncogenes and tumor suppressor genes, in combinations that vary from one cancer to another, and more dramatically, from one type of cancer to another. These malfunctions accumulate over time in a process known as “tumor progression,” a sort of cellular evolution in miniature. The rarity of each step in this progression accounts for the fact that cancer is mainly a disease of older individuals. The various genetic malfunctions cooperate to create the malevolent behavior of cancer cells. If we are to fully understand the cancer cell, we must decipher exactly how each malfunction contributes to the disease. The genetic paradigm for cancer has opened new and promising avenues to virtually every aspect of the challenges posed by cancer. Part 2 of this lecture series illustrates that promise.
3. Recommended Reading


4. Review Questions

1. What was the first and most elementary indication that cancer might represent a malady of genes?

2. What was the first indication that external agents might cause human cancer?

3. How was the role of external agents in cancer first proven?

4. What experiment first linked an external agent to genetic damage?

5. Why do the abnormalities of chromosomes in cancer cells support the idea that genetic malfunction is responsible for cancer?

6. What was the experiment that first linked genes to cancer in a direct manner?

7. Why was the discovery of proto-oncogenes so important to our understanding of cancer?

8. Are the genes responsible for inheritance of human cancer distinct from all other cancer genes?
9. Why does the general incidence of cancer increase with age?

10. Is the genetic paradigm merely a fundamental discovery, without practical significance? Explain your answer.

5. Answers to Review Questions

1. The stable heritability of the cellular phenotype.

2. The association between cancer and exposure to noxious agents, particularly in the workplace.

3. By the exposure of rodents to chemicals and radiation.

4. The induction of mutations in fruits flies by X-rays.

5. Chromosomes house the DNA of cells. Their abnormalities could affect the structure and/or function of genes.

6. The demonstration that mutations in the oncogene (v-src) of Rous Sarcoma Virus could cause the cancerous phenotype of infected cells to become dependent upon temperature, i.e., “conditional.”

7. It demonstrated the existence of normal genes that could be converted to cancer genes by genetic malfunction. Pursuit of this insight settled the long-standing dispute over the role of genes in cancer. The genetic paradigm for cancer was born.

8. No. The heritability of cancer is due to a deficiency in one or another tumor suppressor gene, and deficiencies affecting the same genes occur in sporadic cancer as well.

9. The genesis of cancer requires the accumulation of distinct genetic malfunctions. These are each rare and, thus, the genesis of a tumorigenic combination is increasingly likely as time passes.

10. No. The description of the genetic maladies in cancer cells offers new insight into the causes of cancer, new ways to detect cancer and predict its outcome, and new approaches to treatment of the disease.
6. Discussion Questions

1. Cancer will soon become the leading cause of death in developed nations. What are some possible explanations for this, and which are likely to be correct (more than one may apply)?

2. What are the implications of the fact that most cancers appear to be clonal in origin?

3. Human DNA incurs countless mutations every day of life. What forces might constrain this from producing a catastrophic incidence of cancer?

4. What are some ways that chromosomal damage might create genetic malfunction?

5. What is a conditional mutation and how might it affect gene function?

6. Why do cells have proto-oncogenes? Did evolution create these genes as a restriction on life span?

7. The heritable genetic deficiency in the case of a tumor suppressor gene such as RB1 is recessive: both copies of the gene must be defective before a tumorigenic effect occurs. Yet the inherited disease occurs in every generation, in what is nominally a dominant pattern (see the family tree for RB1 in the lecture). How can this be explained?

8. What sort of genetic malfunction might represent the most efficient way to initiate tumorigeneis?

9. Explain why a combination of genetic malfunctions might be required to produce cancer.

10. What might prevent either a dominant oncogene or a recessive defect in a tumor suppressor gene from being an inherited cause of cancer?

7. Answers to Discussion Questions

1. The identification and recording of cause of death has gradually improved, allowing the recognition and recording of cancers that were previously overlooked. Almost certainly true, but grossly insufficient as an explanation for the rise of cancer as a cause of death. b.) There is an epidemic of cancer associated with developed economies and life styles. There is no evidence for an epidemic of cancer, other than the prevalence of cancers caused by tobacco smoke - - lung cancer was once considered a rare disease, now it is a major cause of death. Other societal factors
can influence the incidence of cancer, witness the rise in obesity, which is in turn a risk factor for a variety of cancers (perhaps 10% of all cancer). c.) Other causes of death have diminished. This is the principal explanation. Deaths from infections and cardiovascular disease have declined, leaving cancer near the top of the deadly heap. Only cardiovascular disease ranks higher, and deaths from this cause are declining steadily due to preventive measures and therapeutic interventions. d.) People are living longer than in the past. This is certainly true, but it is not nearly as important as (c). e.) Other imaginative answers are conceivable, although unlikely to be applicable.

2. Clonality indicates that the cancer had its origin in a single cell, and that each step in tumor progression in turn represented the emergence of a new clone. The end product is a population of malignant cells that is still clonal in nature, but far removed from the cell that initiated the process. This process is diagrammed in the lecture. The scheme appears to be generally applicable to tumorigenesis, although exceptions have been found. In truth, as tumor progression wears on, diverse clones of cells can emerge, each of which is capable of sustaining itself. As a result, an advanced tumor may contain cells derived from multiple clones. But one of these clones usually predominates, and all the clones derived from that initial cell with which the genesis of the tumor began. The cellular heterogeneity of individual tumors can make it difficult to predict the properties of the tumor from an analysis of the bulk tumor.

3. Multiple forces combine to protect against cancer. These include an elaborate set of mechanisms to repair damaged DNA; machinery designed explicitly to protect the ends of chromosomal DNA; the ability of cells to commit suicide in the face of catastrophic damage to DNA; and the ability of the immune system to recognize and destroy at least some types of cancer cells. Other answers are conceivable.

4. An increase in chromosome number can produce an increase in the amount of gene products (protein or RNA), which overwhelm the regulatory devices of the cells - - a genetic gain of function, a jammed accelerator. b.) Gene amplification can achieve the same outcome as an increase in chromosomal number, but in a more focal manner. c.) A loss of one or more chromosomes can deplete the cell of one or more tumor suppressor genes, reducing the braking capacity of the cell. c.) Limited deletions within chromosomes can achieve the same outcome in a more focal manner. d.) Chromosomal translocations can change the regulation of a gene by moving it into a new chromosomal environment, alter protein structure by deleting a
portion of the coding element, fuse two genes together to create a dangerous mongrel, or give rise to internal deletions of the sort described by (c).

5. A conditional mutation typically affects the protein product of the gene, making its function dependent upon a specific condition, such as temperature. In the case of the v-src oncogene of Rous Sarcoma Virus, transformation to cancerous behavior is sensitive to temperature: the gene product no longer functions at the temperature at which the virus normally infects cells, but can function at a lower temperature. The usual explanation for temperature-dependent behavior is that the mutation causes the protein to assume an inactive form or to be unstable at the “restrictive” temperature.

6. Proto-oncogenes have normal and vital function in cells, selected by evolution. The genes become dangerous oncogenes only when their function is jammed in an active state by one means or another. Paradoxically, by current evolutionary theory, there should be little if any selective pressure against cancer, because the disease occurs mainly after the reproductive period of human life. In this view, Nature had no motive to create a predisposition to cancer.

7. Inheritance of a defect in one copy of a gene creates a head start towards achieving a complete deficiency in the gene. Somatic mutation after conception need disable only one copy of the gene, not two, thus increasing the likelihood of a complete deficiency in the gene. These circumstances create the illusion of dominant behavior, but the gene is functionally recessive. This answer is illustrated by two slides in the lecture.

8. Any malfunction that destabilizes the genome. The most obvious example would be an impairment of DNA repair. Such a “mutator phenotype” hastens tumorigenesis by increasing the frequency of lasting mutations throughout the genome.

9. Cancer is a complex phenotype, with virtually every aspect of cellular function permuted. Different malfunctions would be required to cripple DNA repair, unleash cellular proliferation, confer the properties required for metastasis, etc.

10. In either instance, the malfunctions may be lethal to the embryo.
8. Explain or Teach These Concepts to a Friend

1. What are the properties of the cancer cell that account for metastasis?

2. Describe examples of how the genetic paradigm might assist in the search for the causes of cancer and in the development of new therapies for the disease.

3. How might the cancer genome participate in the apparent immune response to cancer?

4. What mechanisms might account for chromosomal translocation?

5. A variety of viruses have been implicated as causes of human cancer, including cancer of the cervix, liver and immune cells. How does the genetic paradigm for cancer apply to the mechanisms of tumorigenesis by these viruses? Choose two specific examples as case studies.

9. Research the Literature on Your Own

1. The frequency of cancer generally increases with age.

2. Although there are numerous causes of cancer, most if not all cancers arise from genetic malfunction.

3. There are two sorts of cancer genes, dominant and recessive.

4. Cancer typically arises from a single cell, yet the cellular properties of the full-blown cancer will differ greatly from those of the original initiating cell.