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THE MOLECULAR BASIS OF CANCER

BY FRANK GORGA

After cardiovascular diseases, cancer is the second leading cause of death in America. Since 1990 over half a million Americans have died each year of some form of cancer, and the number and rate is still increasing. In 1970 approximately 17 percent of all deaths were attributed to cancer, while by 1995 the figure had risen to 24 percent. In her chilling book on the meaning of illness in America, *Illness as Metaphor*, Susan Sontag described cancer as the sickness of the American 20th century. Learning about cancer has become more than a useful chore for those who suffer from the disease or wish to cope with the diseases of family members and loved ones. It is increasingly a matter of cultural literacy to come to understand the workings of a disease whose consequences seem to spare none of us. In the following essay, Frank Gorga, Assistant Professor of Chemistry, summarizes some of the most recent scientific thinking on the basic nature of cancer.

INTRODUCTION

Approximately three decades of intensive research have led to an explosion in our knowledge of the molecular and cellular basis of cancer. Perhaps the most fundamental result of this research effort is the realization that cancer is a “genetic” disease. I use the term “genetic” in a broad fashion. “Genetic disease” is generally taken to mean an inherited or inheritable condition. In a broader sense a genetic disease results from changes to an organism’s genetic material (i.e. its DNA). The expression of oncogenes (literally “cancer genes”) within cells is a crucial event in the early stages of tumor formation. Oncogenes can arise in cells via two mechanisms: infection of cells by tumor viruses and conversion (mutation) of cellular protooncogenes to oncogenes. These discoveries and their implications for the prevention, detection and treatment of cancer are discussed below.

BASIC TUMOR BIOLOGY

Tumors are masses of cells that have escaped the normal mechanisms that strictly regulate and limit the growth of most cells in an animal. The formation of a clinically recognizable tumor is a multi-step process. Tumors are thought to originate via the oncogenic transformation of a single cell. Once a cell is

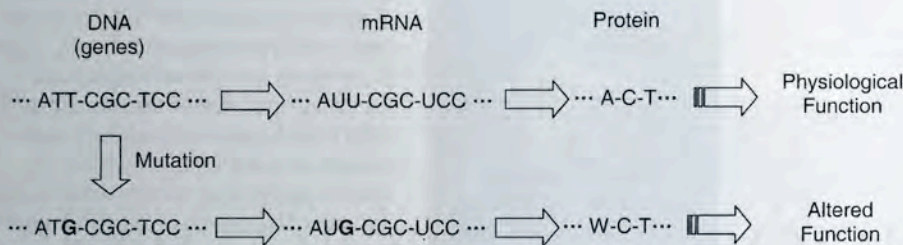
transformed it has gained the ability to grow uncontrollably and microscopic patches of transformed cells (cancer *in situ*, to the pathologists) form. In order to progress to a clinically significant (macroscopic) tumor the transformed cells must be able to avoid the immune system. In some cases, the ability to cause angiogenesis (i.e. to stimulate the growth of blood vessels) is also important in progression to a clinically significant tumor. Relatively late in their existence, some tumors gain the ability to escape from the site of their initial derivation and invade other areas of the body. This is the process of metastasis.

Each of these processes, oncogenic transformation, ability to escape recognition by the immune system, angiogenesis and development of metastatic potential, are associated with genetic changes. Herein, we will concentrate on the genetic changes associated with oncogenic transformation.

THE GENETIC BASIS OF TUMORS

The earliest evidence for the genetic basis of tumors is probably the discovery in 1911 by Peyton Rous that sarcomas (solid tumors) in chickens could be transmitted between animals using a “cell-free filtrate.” The active agent in this “cell-free filtrate” was found to be a virus called, aptly, Rous sarcoma virus. If one takes the view that a virus is a small “package of genes” with the ability to infect an appropriate host cell and thereby add the viral genes to the host cell, then one arrives at the simple conclusion that tumors can be caused by the addition (and, presumably, subsequent expression) of genetic material (i.e. viral DNA) to cells.

In the years since Rous’ work numerous other tumor viruses, infecting various animals, have been discovered. The significance of “tumor viruses” to human disease went unappreciated and, in fact, was hotly debated for a number of years. The moral and ethical difficulty in performing the experiment of infecting a human with a tumor-causing agent makes it impossible to directly “prove” that a specific virus causes tumors in humans. However, molecular epidemiological studies that demonstrate the presence of a specific viral DNA in the same tumor type from



THE CENTRAL DOGMA OF BIOLOGY

Genetic information is stored as the sequence of bases in deoxyribonucleic acid (DNA) within the nucleus of each cell. The expression of genetic information begins with the synthesis of a messenger RNA molecule (mRNA) whose sequences of bases coincide with that of the gene. Proteins are synthesized by “reading” the bases three at a time and “translating” the mRNA molecule into the amino acid sequence of the encoded protein. The expression of genes is under very tight temporal and spatial control. Changes in the expression of genes result in changes in the functioning of cells, and ultimately in physiologic changes. Alteration of the bases within a gene (mutations) result in changes to the encoded protein and, ultimately, in changes in function.

many individuals provide circumstantial evidence that some human tumors are the result of viral infection. This type of correlation has, perhaps, been most clearly shown in the case of human papilloma virus and cervical carcinoma as well as Epstein Barr virus and Burkett's lymphoma.

There are a large number of human and animal tumors that are not associated with viral infection. The evidence that these tumors also have a genetic basis comes from three lines of inquiry. First, was the realization by Bruce Ames and others that many (most) carcinogens are also mutagens. That is, agents (including chemicals and radiation) that are known to cause cancer are also able to cause damage to DNA. The fact that damage to DNA can cause cancer led investigators to (cautiously) propose that the mutation of normal cellular genes might play a role in causing tumors. Further evidence supporting this hypothesis comes from applying the tools of molecular genetics to tumor biology.

Secondly, during the 1970's and '80's, virologists studying Rous sarcoma virus were able to show that a single viral gene among the roughly half dozen total was responsible for tumorigenesis by these viruses. This oncogene

(i.e. “cancer causing gene”) was named *src* (short for “sarcoma”). In 1981, Michael Bishop and Harold Varmus made the surprising discovery that normal (i.e. non-tumor) cells contained a gene that was related to the viral *src* gene. This normal cellular gene, called cellular *src* (*c-src*), is a member of a family of genes called protooncogenes.

Lastly, in 1978, Robert Weinberg and coworkers demonstrated that there were oncogenes present in tumors of non-viral origin. This question was answered by a simple, elegant gene transfer experiment in which DNA isolated from tumor cells was used to convert oncogenically transformed normal cells in culture (see side bar “Gene Transfer”). This experiment clearly demonstrated the presence of oncogenes in the large majority of tumors.

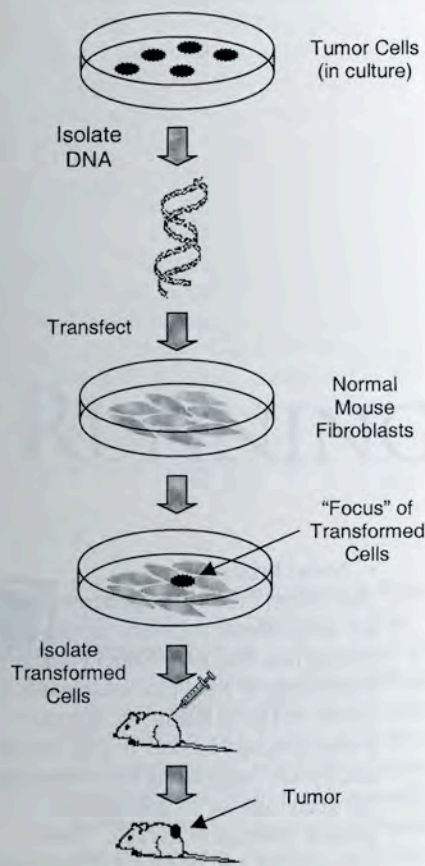
Thus, our current understanding is that tumor formation is initiated by the expression of an oncogene within a cell. This expression can be brought about in two ways. Infection with a tumor virus and subsequent expression of viral genes, including the viral oncogene, is the cause of relatively few tumors. Most tumors are caused by the conversion (via mutation) of a subset of normal cellular genes, the protooncogenes, into oncogenes.

THE BIOLOGICAL ROLE OF PROTOONCOGENE PRODUCTS

The discovery of protooncogenes in normal cells raises questions regarding their role in normal cellular processes. Are protooncogenes silently sitting within normal cells “waiting” to cause cancer, or do these genes play a role in normal physiological processes? The fact that the protein products of protooncogenes are expressed in (at least some) normal cells argues strongly for the latter. Research into the detailed functioning of many individual protooncogenes has invariably described a role for the gene and its product in some physiological process. The processes in which protooncogenes are involved is quite varied; however, most protooncogenes have been found to be involved (not surprisingly) in the mechanisms that govern the growth and differentiation of cells. The biochemical function of protooncogene products is even more varied. Protooncogenes encoding protein products that serve as circulating growth factors and as cell surface receptors for these growth factors have been discovered. Many protooncogene products have been found to serve as components of the intracellular signal transduction pathways that serve to transmit the “signal” generated by growth factors from the cell surface to the nucleus in order to effect the changes in gene expression needed for cellular division.

IMPLICATIONS FOR THE DIAGNOSIS AND PREVENTION OF CANCER

The discovery of protooncogenes and their mutation to oncogenic forms has caused a profound change in the way we think about cancer prevention and diagnosis. The fact that the ultimate cause of cancer is genetic change (mutation) suggests that prevention of cancer is “simply” a matter of eliminating our exposure to mutagens (agents that cause mutation). However, it is impossible to exist without some exposure to mutagens. Mutagens, including cosmic and other radiation, as well as some mutagenic chemicals, are present in the natural environment.



DEMONSTRATION OF ONCOGENES BY GENE TRANSFER
DNA, isolated from tumor cells (growing in culture), is mixed with calcium phosphate and added to normal mouse cells under conditions where the DNA can enter the cells (this process is called transfection). If an oncogene is present in the DNA, a small number of the normal cells will become oncogenically transformed (i.e. "tumor-like"). If these transformed cells are isolated and injected into a mouse, they grow to form a tumor.

Eliminating exposure to these agents is physically impossible. Thus, oncogenic mutation and cancer must be considered to be a (partially) natural phenomenon. The "best" we can hope for is to minimize, taking into account the economic and social costs, our exposure to mutagens that result from human activity and thus minimize the frequency of oncogenic mutations.

The discovery of oncogenic mutations also helps to explain the observation that incidence of cancer, in general, rises with age. Simply, given a constant (or nearly constant) rate of mutation, the longer people live the greater the chance that they will suffer an oncogenic mutation somewhere in their bodies.

The existence of oncogenic mutations opens new possibilities in the detection of cancer. Currently, most cancers are detected indirectly by the symptoms they cause. Thus, tumors must be large enough to "cause problems" before they are detected. However, the earlier a tumor is detected, the smaller it is, and the less likely it will have spread to other tissues (metastasize); thus the more "curable" the tumor is. If one can design specific molecular-level probes for oncogenes or their products, it should be possible to devise a diagnostic test that may allow earlier and more accurate detection of tumors. One (somewhat controversial) example of this idea is the test for prostate-specific antigen (PSA) used in the screening of men for prostate tumors.

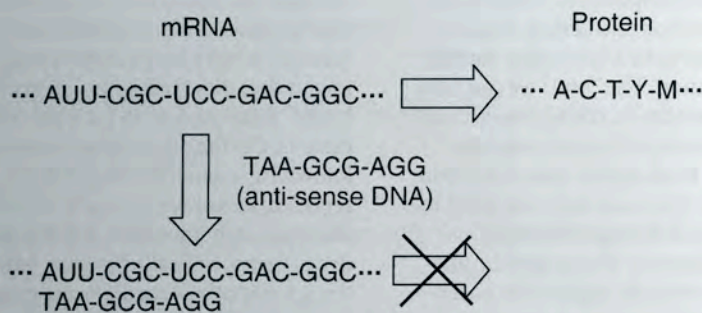
IMPLICATIONS FOR ANTI-TUMOR THERAPY

The discovery of protooncogenes and their varied functions has also dramatically changed our view of anti-tumor therapy. Most current anti-tumor therapies (including chemotherapeutic drugs and radiation treatments) are not "anti-tumor" *per se*. These treatments target rapidly growing cells and thus affect a number of normal tissues in addition to tumors, thereby causing the side effects associated with anti-tumor therapy (see side bar "Anti-tumor Therapy"). Discovery of oncogenes and the gaining of detailed information about the biochemical activity of their products is both discouraging and

encouraging in terms of anti-tumor therapy. The (relatively) large number of oncogenes underscores the fact that "cancer" is not a single disease and means that there will be no "magic bullet" that will cure all (or even most) tumors. On the other hand, each known oncogene, and its product, represents a known potential target for anti-tumor therapy. Development of drugs that specifically interfere with the activity of a particular oncogene product should allow more effective treatment of the tumors caused by expression of that particular oncogene, including a large decrease in the side effects of the anti-tumor therapy. In addition, "anti-sense" therapy designed to specifically disrupt the expression of oncogenes represents a powerful new, although unproven, approach to anti-tumor therapy.

SIDE EFFECTS OF ANTI-TUMOR THERAPY

Anti-tumor radiation treatment and most current chemotherapy drugs work by interfering with DNA replication or some other aspect of cellular division. Thus these agents do not specifically target tumor cells; rather they kill both tumor cells and normal cells that happen to grow rapidly. One consequence of this lack of specificity is the side effects of cancer treatment. Although most cells in the adult body do not grow, or do so slowly, there are tissues whose function requires the regular replenishment of cells. These tissues contain populations of cells that grow rapidly during the course of normal functioning. Many of the side effects of anti-tumor therapy, including loss of hair, nausea and immunosuppression, are directly attributable to disruption of rapidly growing cell populations in hair follicles, the intestines, and bone marrow, respectively.



ANTI-SENSE TECHNOLOGY

Much of nucleic acid structure and function is based on base-pairing interactions between the building blocks (bases) of DNA and RNA. These complementary interactions are specific in that within a DNA molecule adenine (A) always pairs with thymidine (T) and guanine (G) always pairs with cytidine (C). In RNA, thymidine is replaced with uracil (U), which also pairs with adenine, but the "rules" of bases pairing are otherwise the same. Anti-sense technology is a method for disrupting the expression of a specific protein within cells. This technology involves the introduction (into a cell) of an anti-sense DNA that is complementary to the mRNA that encodes the protein of interest. This anti-sense DNA binds specifically to the mRNA (via specific base pairing) and inhibits its translation into protein. Thus, this technology allows the specific disruption of the production of a single protein within cells. Although anti-sense technology is currently useful in the lab, the technology for delivery of anti-sense DNA's in whole organisms is still under development. Once the technology is fully developed, disruption of oncogene expression using this technique should be an effective anti-tumor therapy.

CONCLUSION

That three decades of intensive research in oncology and related basic sciences has not led to a cure for cancer may seem disappointing to the general public; it has, however, led scientists to a much better understanding of the "problem" of cancer. The discovery of the genetic basis for tumorigenesis, along with the advent of "biotechnology" holds great promise that the next thirty years will bring both more effective anti-tumor therapies and greatly improved diagnosis of tumors.

SOURCES OF FURTHER INFORMATION

- Cancer Net (<http://cancernet.nci.nih.gov/>) This web site (maintained by the National Cancer Institute) has information on cancer at all levels. Material appropriate for patients (and other non-specialists) is maintained, as well as specialized information for health professionals and basic researchers.
- Scientific American, September 1996 (<http://www.sciam.com/0996issue/0996currentissue.html>) This special issue of Scientific American titled "What You Need To Know About Cancer" has numerous articles dealing, in more detail, with many of the issues covered herein.

• Nobel Prizes

Two Nobel Prizes have been awarded for work related to tumor viruses and oncogenes. The 1975 Nobel Prize in Physiology or Medicine was awarded jointly to David Baltimore, Renato Dulbecco and Howard Temin "for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell." More information can be found at the Nobel Foundation's web site (<http://www.nobel.se/laureates/medicine-1975.html>). In 1989, the Nobel Prize for Physiology or Medicine was awarded jointly to J. Michael Bishop and Harold Varmus, "for their discovery of the cellular origin of retroviral oncogenes" (<http://www.nobel.se/laureates/medicine-1989.html>). Bishop's (Biosci Rep. 10(6): 473-491, 1990) and Varmus' (Biosci Rep. 10(5): 413-430, 1990) acceptance speeches were published in Bioscience Reports.

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