

Paradigms in oncology, old and new

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In the past decades, medicine has shifted from primarily a study in physiology to one in cellular and molecular biology. The consequent new understanding of the most basic antecedents of disease has revolutionized many specialties, and none more so than oncology. With this new knowledge naturally come new approaches to treatment. Beginning with this issue of *BUMC Proceedings*, I will occasionally review some of these molecular approaches and outline a sampling of current trials.

A key to understanding the new paradigm in cancer treatment is the realization that the old paradigm focused almost solely on interfering with the actual machinery of cell division, e.g., DNA replication or construction of the microtubule spindle array. While often effective, these therapies necessarily have certain limitations. The first is that cancer involves more than just abnormalities in cell growth. Malignant cells also display abnormal differentiation and show little respect for tissue boundaries. In fact, although abnormal cell proliferation is necessary, it alone is often insufficient for tumorigenesis. Therefore, therapies directed solely against cell division will have limited usefulness when the tumor is quiescent. The second limitation, of course, is that normal cells divide too. Every day, the epithelial lining of the skin and gastrointestinal tract and the hematopoietic stem cells of the bone marrow undergo perfectly normal cell division. Indiscriminate cytotoxicity directed against all mitotic cells thereby results in the most common toxic effects seen with chemotherapy, such as cytopenia, gastrointestinal symptoms, and hair loss.

The development of a more targeted approach requires better understanding of what makes cancer cells different from normal cells. We can still begin with the most obvious, cell growth. Under normal conditions, cell division occurs only in response to external signals that activate intracellular pathways, leading to the initiation of mitosis. These signals are generally transient, and further growth ceases once they are absent or countermanded by other inhibitory signals. Cell proliferation is thus tightly controlled and occurs only in response to specific needs. At the same time, other signaling pathways activated by injury or cell age induce a process of normal cell death, called apoptosis. Therefore, the normal number and location of cells in the body and its organs represent the balance between these 2 great machines of cell division and cell death. In some tissues, this cycle is very slow, while in others massive cell turnover occurs on an almost daily basis. Indeed, it has been estimated that each year, we produce and destroy our own body weight in cells.

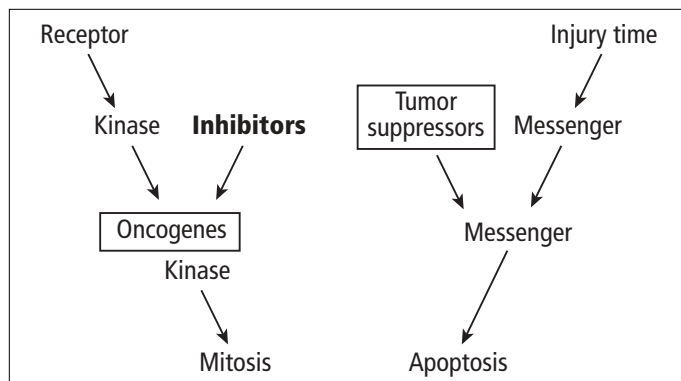


Figure 1. Balancing growth and death.

It follows, then, that any perturbation in this balance could lead to either inappropriate cell accumulation or loss. Such a perturbation can arise if mutations occur in the genes encoding any of the proteins in the signaling or control pathways of these 2 counterbalanced processes (Figure 1). For example, the growth-inducing pathways occasionally become biased to the “on” state as a result of genetic mutations, leading either to inappropriately activated growth-signaling proteins or inappropriately inactive growth-inhibitory proteins. The result is unrestrained growth of cells, the first step to malignant transformation, and so the mutated genes that produce these abnormal proteins are called oncogenes. The list of known oncogenes grows almost daily.

Methods for correcting the expression of these growth-encouraging proteins can be roughly divided into 2 classes: 1) small molecule inhibitors of the actual abnormal signaling activity and 2) manipulations of the mutated genetic machinery itself to suppress the production of the abnormal protein. Examples of the first class include tyrosine kinase inhibitors, selective estrogen receptor modulators, and farnesyltransferase inhibitors. The second method, that of actually altering production of the oncogene product, requires a more creative approach, since it entails suppressing the machinery of a very specific gene. However, these techniques, once developed, are applicable to a wider variety of targets than growth-signal molecules.

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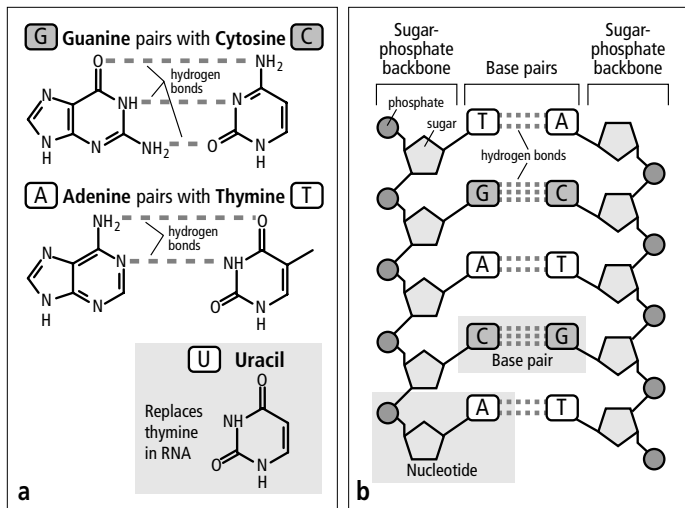


Figure 2. (a) Base pairing and (b) the structure of DNA.

SOME BASICS OF MOLECULAR BIOLOGY

Recall that the properties of each protein in the cell are determined by the quantity and linear sequence of its constituent amino acids. That information is encoded in the specific ordering of the nucleic acid molecules that make up the human genome. The entire genetic code is stored in linear polymers of DNA (Figure 2). These polymers normally exist as 2 strands, paired because of the affinity that each member of the 2 classes of nucleic acids that compose genetic material (purines and pyrimidines) have for each other. These affinities are quite specific; thymine matches best with adenine, while guanine pairs with cytosine in what are known as base pairs. Of the paired polymers, one is a “sense” or coding strand and the other is an “antisense” or complementary strand. Because of the sheer amount of DNA that must be stored within each cell, the DNA polymers are normally supercoiled and tightly packed with the help of certain DNA-binding proteins called histones. Therefore, in order to produce a particular protein, the region of DNA encompassing the gene of interest must be unraveled from its usual tightly packed and twisted shape so that the relevant sequences can be accessed. The specific sequence of DNA is then “transcribed” from the coding strand into a more useful single-stranded polymer of RNA that still retains all the information of the original DNA strand. Transcription of the “sense” strand occurs by utilizing the same base-pairing affinities of the RNA molecules to the corresponding DNA molecules that allowed the original pairing of the DNA strands.

Note that this primary RNA transcript therefore contains all the bases of the DNA strand (with uracil substituting for thymine). However, one of the remarkable findings in molecular biology has been the discovery that the vast majority of the genetic material that makes up the genome does not code for anything! These noncoding regions (introns) interspace between the real information (exons). Therefore, the primary RNA transcript requires extensive editing before an accurate blueprint for a protein can be produced (Figure 3). Enzymes (including RNA-based enzymes called ribozymes) perform much of this editing. Introns are excised and the remaining exons stitched back together to form a polymer containing the true blueprint or “message” to construct a protein. This edited RNA polymer (messenger RNA

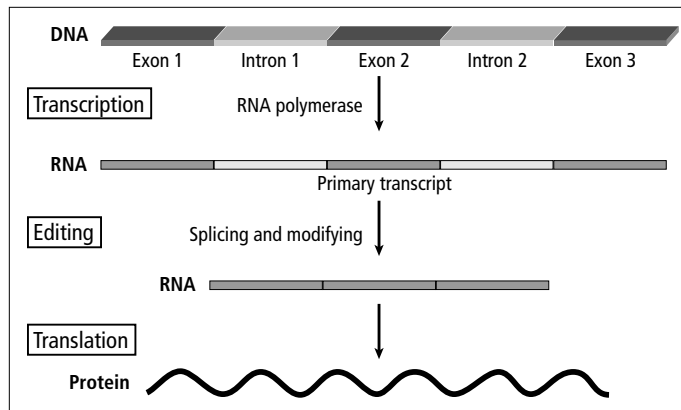


Figure 3. From gene to protein.

or mRNA) can then be translated into the appropriate amino acid combination to form the protein.

NEW APPROACHES

A glance at this process, then, points out certain areas where the production of a particular protein can be inhibited. The first, of course, would be at the DNA level. However, it has been difficult to design techniques that can specifically prevent activation of a single gene. This may be due to our limited understanding of this process, but preventing gene activation might not be desirable in any event. Often, whole “gene cassettes” are activated by a single signal. Inhibition of this entire cassette could lead to loss of specificity, as many genes would be affected.

Given this, the next obvious step is the processing of RNA. Here, several approaches are possible, all of which take advantage of the forces of base pairing. In one method, previously constructed sequences of nucleic acids complementary to known regions of a particular RNA are introduced. This technique, called antisense technology, will be discussed in the next article in the series. Another method is to manipulate the editing of primary RNA into mRNA by the introduction of specific ribozymes. Both of these methods are highly specific for a unique mRNA molecule and so are highly targeted.

Other gene therapy approaches seek to capitalize on the genetic defects of cancer cells in order to target cytotoxic therapy. For example, approximately 50% of human tumors demonstrate some defect in the tumor suppressor pathway p53. Therefore, the introduction of intact p53 genes into the tumor cells may restore their ability to abort neoplastic transformation. Or, even more directly, replicating viruses normally inhibited by the p53 system can be delivered with the result that replication and cytotoxicity occur only in the p53-defective tumor cells. Viruses have been extensively explored as gene delivery vehicles in a variety of genetic diseases, including cancer. Adenoviruses have been used most commonly, but adeno-associated viruses, reoviruses, and retroviruses are also being studied. Genes delivered by this technique fall into 2 categories: those missing due to genetic mutations associated with many cancers and those endowing certain properties to the tumor cells, such as enhanced sensitivity to radiation or chemotherapy or increased immune antigenicity.

The development of molecular therapeutics will accelerate as new avenues for research are pointed out by findings of current trials. We are indeed on the brink of a new world in oncology.