ONCOGENES AND CANCER

Cancer cells are characterized by uncontrolled and unorganized growth. Normal cells will grow in a single layer in a culture dish. They prefer to not be in contact and must be anchored to the medium or serum. In contrast, cancer cells tend to pile up on top of each other, and do not need to be anchored to the medium, and will form tumors in vivo.

In plants and animals, tumor viruses which invade those cells can cause the cells to become cancerous. While most viruses follow a lytic pathway, where they use the host cell to replicate themselves, and eventually lyse or kill the host cell, other viruses follow a lysogenic pathway, where at least part of the viral genome is actually incorporated into the host cell genome. This viral portion can then be passed along to future generations as the host cell replicates.

Specific genes called oncogenes in these viruses are responsible for the transformation of these normal host cells into cancer cells. The job of these oncogenes is to activate abnormally the replication and growth machinery of the host cells—remember that in normal resting cells, this machinery is not active.

Tumor viruses are of two types: DNA tumor viruses, that are usually relatively simple viruses containing only a few genes; and RNA tumor viruses, that are retroviruses, which contain a gene for the enzyme reverse transcriptase, as well as, in many cases, several other genes to facilitate transcription and post-translational processes.

All of the known and characterized oncogenes are actually derived during evolution from normal cellular genes. All of these genes encode proteins that are somehow related to the growth functions of a cell. At some evolutionary point, these genes were "captured" and incorporated into the viral genomes. This process, not as yet understood, is termed "transduction."

The vast majority of human cancers, however, are not linked to viral infection. Therefore, in most human cancers, there are no additional oncogenes incorporated into the cell. Rather, environmental factors cause damage to DNA, resulting in normal genes to be changed. If these changes occur in the gene sequences which control the expression of a given protein, excessive amounts of this protein begin to be produced in the cell. If this protein product is also involved in cellular growth, this can result in development of a cancerous cell. A normal cellular gene whose expression can be altered, and thereby cause the cell to become a cancer cell, is called a proto-oncogene.

For example, B cell tumors in humans often are the result of translocation of the highly-expressed immunoglobulin gene promoters to a different chromosome. The site of translocation is usually the same--they are incorporated into the same genetic locus—a target known as the "c-myc" proto-oncogene. The result is that this growth-related gene is put under the control of the immunoglobulin gene transcription factors, and is over-expressed. The B cell becomes cancerous.

For a second example, human myelogenous leukemia, is caused by a chromosomai change called the Philadelphia chromosome. In these patients, part of chromosome 9 is moved and attached to chromosome 22. On this section of chromosome 9 is a proto-oncogene known as "c -abl." When this proto-oncogene is inserted into chromosome 22, again always at the same locus, a large new gene is created, that when expressed, creates a "fusion protein." This protein, again apparently growth-related, caused the leukocyte to become a cancer cell.

In some cases, a proto-oncogene can be "activated" by a mutation which results in over-replication and duplication of the gene in a given segment of the chromosome. These multiple gene copies are then all expressed, resulting in over-production of the protein.

Other human proto-oncogenes can be activated by much simpler mechanisms. A human proto-oncogene called "c-ras" can undergo a single point mutation (a substitution of one DNA base), resulting in activation, and possible formation of a cancer cell. This proto-oncogene is thought to be responsible for certain bladder carcinomas.

The known human proto-oncogenes (as well as related viral oncogenes) fall into several distinct categories of genes, all of which, again, are somehow related to cellular growth.

a) Some proto-oncogenes encode growth factors. In most cases the cancer cells respond to these growth factors in addition to producing them. This results in an "autocrine stimulation" or growth of the cell line. Example: "v-cis" encodes a form of PDGF.

b) Some proto-oncogenes encode growth factor receptors. In many cases, these receptors are altered so as to not include their ligand-binding domains. The result is a receptor protein that is constantly turned "on" because it believes it always bound to its respective ligand. Example: the viral gene erbB encodes a form of the EGF receptor.

c) Many proto-oncogenes encode protein-tyrosine kinases, which are enzymes which are abundant on the inner surface of the cellular membrane. These signalling proteins are thought to play a major role in cellular growth. Proteins which have been phosphorylated on thier tyrosine residues are only abundant in reproducing and growing cells. They are thought to
activate intracellular signalling cascades, which result in several intracellular effects. Numerous examples of proto-oncogenes in this group are known, including "c-abl," the proto-oncogene on the Philadelphia chromosome mentioned above.

d) Other proto-oncogenes code for G proteins, which are molecular signals associated with the cellular membrane receptors, and also regulate a variety of intracellular signalling pathways. The proto-oncogene "c-ras" mentioned above belongs to this group.

e) Some proto-oncogenes encode transcription factors, which directly effect the expression of DNA in the nucleus. These proteins bind DNA and activate the transcription process. They act as nuclear signal transducers, or "third messengers," in the cell. An example: the proto-oncogene "c-myc" noted above.

More recent study into the activation of these proto-oncogenes and the neoplastic transition has resulted in the "Multiple-Hit" theory. In simple terms, this theory states that one proto-oncogene activation is not enough to make a cell a cancer cell. Rather, two subsequent hits or activations of two different proto-oncogenes are necessary for this transition to occur.

On the contrary, in other experiments, normal cells can be transformed into cancer cells by the incorporation of one activated proto-oncogene isolated from another cancer cell line, seemingly indicating that one proto-oncogene is enough to trigger the neoplastic transition. In such cases, it is possible that one proto-oncogene has already been activated in the "normal" cells. For example, many patients are known to have a predisposition for developing certain cancers. Retinoblastoma is much more common in certain families. These families have an inherited mutated gene known as the "Retinoblastoma Susceptibility Gene."

This susceptibility gene, as it turns out, does not actually encode a protein related to growth; nor is it a proto-oncogene at all. It is, however, a tumor suppressor gene, "anti-oncogene," or "recessive oncogene." The activity of these genes is difficult to measure--it is known that the gene products have anti-proliferative effects. The genes are only active when neither inherited allele is mutated, because the normal trait, as mentioned above, is recessive. The presence of one mutated gene from one parent results in the dominant trait being expressed, which is the "turning off" of this anti-proliferative gene, leaving the cell susceptible to becoming cancerous.

The development of human cancers, therefore, is almost certainly tied to the activation or inactivation of a combination of proto-oncogenes and/or anti-oncogenes. This is probably a step-wise process. An excellent example is the multiple-step development of colon cancer, where abnormal but benign growths called polyps can later undergo a neoplastic transition to become cancerous. Further research in this area continues to identify those genes which are responsible for the development of all types of human cancers, and this is creating a whole new target area for therapeutic agents which could potentially "turn off" the expression of these activated oncogenes.