

Genes and Cancer

Cancer is really many diseases, all characterized by a lack of controlled cell division.

What kind of evidence suggests that genes play a role in cancer?

- 1) Specific types of cancers seem to run in families.
- 2) Chemicals, radiation and other mutagenic agents are also carcinogens- meaning they can cause cancer. In other words, things that damage DNA can also cause cancer.

In some families, the inherited predisposition for cancer can be attributed to inability to repair damage caused by mutagens.

Xeroderma pigmentosum in humans leads to a high risk of skin cancer due to the inability to repair thymine dimers caused by UV light. There are several genes involved, but each specific defect is inherited as a recessive trait.

OMIM: <http://www.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id=278700>

Other examples include Blooms syndrome where the ability to repair crosslinked DNA that is caused by compounds such as mitomycin C. Patients have lots of broken chromosomes and a very high risk of leukemia.

OMIM: <http://www.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id=210900>

In the case of ataxia telangiectasia which also leads to high risk of cancer, patients are unable to repair DNA damage caused by radiation.

OMIM: <http://www.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id=208900>

These examples also infer that mutations in other genes can cause cancer. Each case where DNA repair is defective is inherited as a simple recessive trait, at least so far as cancer risk is concerned.

There are also examples of dominant mutations that lead to cancer as well. One example is Familial adenomatous polyposis (FAP); an inherited tendency to develop polyps in the colon. Over time, unless they are removed periodically, one of the polyps is likely to become cancerous.

OMIM: <http://www.ncbi.nlm.nih.gov/80/entrez/dispomim.cgi?id=175100>

In these cases, as in all others we look at, it seems that at least 2 things must go wrong before cancer develops.

Are there cancers that do not seem to involve gene defects?

Cancers in birds and rodents often seem to be associated with virus infections. Way back in 1910, Francis Peyton Rous showed that chickens injected with a filtered extract from chicken tumors would also develop tumors. The causal agent was eventually proven to be a virus that is now called Rous Sarcoma Virus or RSV, since it causes tumors called sarcomas. Only after many decades and the advent of recombinant DNA technology was it possible to appreciate some of the details of how RSV is implicated in cancer ;

RSV is a "**retrovirus**" meaning that the virus is multiplied and packaged as an RNA in its transmissible form. One of the proteins coded by the virus is "**reverse transcriptase**", an enzyme that can make DNA from RNA. The DNA copies can sometimes be inserted into a chromosome of the host, where they are called a provirus. So long as the insertion does not disrupt an important gene and the virus is not expressed, it may be replicated as part of the host DNA and passed without noticeable effects through mitosis and meiosis.

Normal retroviruses have a typical structure that is very simple:

LTR gag pol env LTR

LTR stands for long terminal repeats, which seem to be able to fold into 'hairpins' that are important in the ability to insert into host DNA. *Gag* is a gene for spikes on the coat of the virus and *env* is a gene for making coat protein. *Pol* is the gene that codes

for the reverse transcriptase. As it turns out, the copies of a retrovirus that cause tumors are somewhat abnormal; they often have an **oncogene** (a tumor inducing gene) in place of a part of the *env* gene. When these genes were discovered they were

termed *v-onc* genes for viral oncogenes.

What genes can mutate when normal cells become cancerous?

Recombinant DNA technology was also used to investigate the genes involved in tumors caused by mutagens. For example, cancer cells from tumors in mice that were induced by a chemical carcinogen have been studied. DNA from the cancer cells can "**transform**" normal cells into cancer cells, either in living mice or in tissue culture cells that grow in a layer across the surface of a petri plate. When the DNA from transformed cells was fragmented and cloned into virus vectors, it was eventually possible to pinpoint the specific genes that caused the tumors to form (transformation). These genes are also oncogenes, which in this case were referred to as cellular or *c-onc* genes. Once they were sequenced, it was immediately clear that *c-onc* and *v-onc* genes were actually the same genes! The normal allele of the *c-onc* gene was referred to as a "proto-oncogene" to indicate that it was a gene that could act as an oncogene as a result of a mutation.

Normal cells placed in tissue culture will generally grow in a monolayer until the surface of the growth medium is covered. They will only divide for a certain number of times and then stop dividing, even if transferred to fresh medium. The NIH3T3 mouse tissue culture cells often used to test potential carcinogens are abnormal in that they keep on dividing, transfer after transfer. They still show contact inhibition so that cells do not pile up on one-another unless they are transformed. Thus, even these cells may have already had at least one change that is required for tumor formation; they are "immortal". It also means that cancer researchers around the world can study cells that have the same genetic origin.

Although it is not surprising based on what we know today, it was also a shock when copies of virtually the same oncogenes were found in the DNA of chickens, mice *Drosophila* and even man. Now we know that oncogenes such as *ras*, *myc* and *abl* -at least in their normal functional versions- are typically genes involved in **turning on cell division**. Thus when a copy of the gene is present on an RNA virus it may be over-expressed, causing cells to divide when they should not.