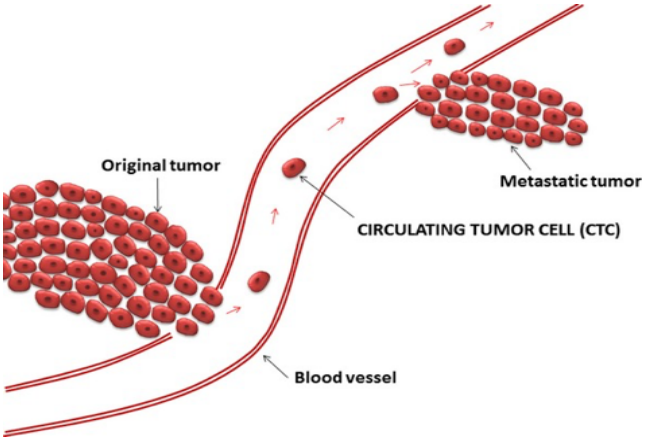
Cancer genetics

What is cancer?
Cancer is a collective name for a group of acquired genetic diseases where genetically abnormal cells begin to grow and divide, disrupting normal organ function and thereby causing disease. All cancers begin in cells. Our bodies are made up of more than a hundred million million (100,000,000,000,000) cells. Cancer starts with changes in one cell or a small group of those cells. All cancer diseases have in common that the abnormal cells begin to accumulate, forming a lump, and no longer stay in their place but begin spreading from the lump throughout the body. The reason is that certain molecular checks on their behavior have been inactivated, freeing them to grow and spread selfishly throughout the body. This is the root cause of cancer: The cancer cells accumulate by growing and dividing and no longer selfdestructing normally when they have become spent or damaged. The cancer cells spread by crawling into surrounding tissue and into the blood vessels. The blood vessels become inadvertant conduits for the abnormal cells to reach distant parts of the body, such as the bone marrow, the lungs or the liver, where they may settle and form metastases.

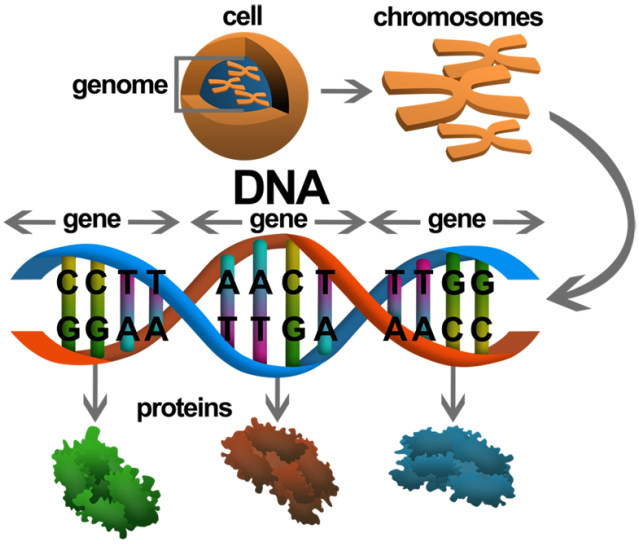


How does cancer develop?
A cancer cell develops from a normal cell because a number of degenerative changes have become fixed in the cell's genetic inheritance, it's DNA. Cells are continuously exposed to genetic damage, but have mechanisms in place to repair such damage. This is known as DNA repair. If the cell damage cannot be repaired for any reason, there are built in mechanisms to self destruct, as an additional layer of protection. The degenerative genetic defects only become fixed when those mechanisms fail. Such fixed degenerative genetic changes are called mutations. Mutations accumulate normally over time as we age, gradually increasing the risk of cancer. That is why cancer is more common among the elderly. At least 2 mutations in espescially sensitive genes are required for a cancer cell to transform a normal cell, but there may be as many as 10 or more mutations required for many other cancers. The mutations have to occur collectively inside a single cell to cause cancer, not be spread out over many cells. To acquire several mutations specifically in sensitive genes inside a single cell is fortunately a very rare event indeed. That explains the relative rarety of cancer. It can take many years for a damaged cell to divide and grow and form a tumor big enough to cause symptoms or show up on a scan. Low level mutation is a part of normal ageing and is something we can live with.

The genes that are critically sensitive to cancer are those that form part of the controls for the balance between cell growth and division on the one hand and the built-in cellular "self destruction" mechanism on the other. Scientists now estimate there may exist a total of about 700 genes that control these kinds of sensitive events, of which we already know most. Once they have been mutated they take on properties that either stimulate the development of cancer, and are called oncogenes, or are genes that normally supress tumor formation, but fail in their mission because of mutation, and are called tumor suppressor genes.

What are genes?
Genes are pieces of DNA (deoxyribonucleic acid) inside each cell that tell the cell what to do and when to grow and divide. Each gene is made up of a specific DNA sequence that contains the code (the instructions) to make a certain protein, each of which has a specific job or function in the body. Each human cell has about 20,000 genes.

Most genes are contained in chromosomes. A chromosome is a long strand of DNA wrapped around spools of special proteins called histones. Most chromosomes contain many different genes.



Inherited cancer syndromes
There are 2 major types of gene mutations, inherited and acquired. An acquired mutation is not present in the zygote, but is acquired some time later in life. Most cancers are caused by acquired mutations. This type of mutation is also called sporadic, or somatic. A few cancer syndromes are caused by inherited mutations of proto-oncogenes that cause the oncogene to be turned on (activated). But most cancer-causing mutations involving oncogenes are acquired, not inherited.

Genes and cancer treatment
Drugs have been developed that target some of the gene changes in certain cancers. Actually these drugs often target the protein made by the abnormal gene (and not the gene itself).

For example, HER2/neu is a proto-oncogene in normal cells that helps them grow. It becomes an oncogene when a cell has too many copies of this gene. When this happens, the cells make too much HER2/neu protein and the cancer is said to be HER2-positive. Patients with breast cancer with cells that are HER2-positive do not respond as well to certain chemotherapy drugs. But newer drugs such as trastuzumab (Herceptin®), lapatinib (Tykerb®), and several others, have been designed to specifically attack cells that are HER2-positive. These drugs can slow cancer cell growth and improve outcomes in patients with HER2 positive cancers. Breast cancers are now routinely tested to see if they are HER2-positive to identify which patients will benefit from these drugs. Other cancers can also be HER2-positive. Anti-HER2 therapy has also helped people with stomach cancer that is HER2-positive.

DNA methylation is one way to turn-off genes. Drugs called hypomethylating agents can reverse methylation. This can be helpful in treating some cancers in which some genes are abnormally methylated. For example, in myelodysplastic syndrome, certain genes that are often methylated in the cancer cells when they aren't supposed to be. The hypomethylating agents decitabine (Dacogen®) and azacytidine (Vidaza®) can decrease this abnormal methylation, which can be useful in treating this disease. Other drugs that help fight cancer by activating genes are

the histone deacetylase inhibitors, such as vorinostat (Zolinza®) and romidepsin (Istodax®).

Gene testing to help predict if a drug will work
Some drugs don't help patients if the cancer cells have certain gene mutations. For example, cetuximab (Erbitux®) and panitumumab (Vectibix®) are drugs used to treat advanced colorectal cancers. However, these drugs don't help patients with cancers that have mutations in the KRAS gene, so doctors check the cancer cells for these mutations before they give either of these drugs.

Some drugs work better in people with certain mutations. For example, the drug erlotinib (Tarceva®), which can be used to treat non-small cell lung cancer, works better in patients whose cancer cells have a certain mutation in the EGFR gene.

Future directions
The future of cancer treatments is based on the specific gene changes found in cancer cells, and this is a very active area of research. There are many clinical trials under way today that could lead to better treatments for many types of cancer.

Glossary
Cell = the smallest building block of our body. Each cell contains a copy of our genetic inheritance encoded in the DNA that is in the cell's nucleus. The root cause of cancer is mutations in the DNA of either a single cell, or a small number of very similar cells.
Mutation = a degenerative change in the cellular genetic inheritance, encoded in the DNA
Driver mutation = a mutation that gives a selective advantage to a clone of cells, through either increasing its growth or its survival. Driver mutations thereby cause clonal expansions. At least some driver mutations provide targets for new therapies that aim to home in on the root cause, the driver mutations, of the cancer.
Passenger mutation = a mutation that has no effect on the fitness of a clone but may be associated with a clonal expansion because it occurs in the same genome as a driver mutation. This is known as a hitchhiker in evolutionary biology. Passenger mutations may provide targets for the immune system to home in on, potentially providing a cure, even though they themselves do not drive the progression of the disease.
Clone = a set of cells that all descend from a common ancestor cell. A clone is usually distinguished through inheritance of a distinctive genetic change (mutation) that occurred in the ancestor cell.
Metastasis = spread of cancer cells to distant organs where they first settle and then grow. Metastases are associated with therapy resistance and a worse prognosis.
Zygote = a fertilized egg, or an individual developing from such an egg.