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This Article will Directly Affect 1 in 4 of you: a Primer on Cancer

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What is Cancer?

Over 100 different diseases – each of which is characterized by uncontrolled growth of abnormal cells – are collectively called c*ancer*. Abnormal cell proliferation is necessary, although often insufficient alone, for tumor formation. It is the increase in tumor cell number, and thus the *tumor burden*, that ultimately accounts for the adverse effects on the host. Cancer cells are characterized by two heritable properties: they and their progeny (a) reproduce in defiance of the normal restraints, and (b) invade and colonize other tissues. Both of these features make cancers peculiarly dangerous. Isolated abnormal cells that do not grow and divide more than their normal neighbors pose no significant threat no matter what other disagreeable properties they may have. But if the proliferation is out of control, it will eventually give rise to a tumor or *neoplasm* – a relentlessly growing mass of abnormal cells. As long as the tumor cells remain confined to a location as a single mass of cells, the tumor is said to be *benign*, and it can safely be removed surgically. A tumor is counted as cancer only if it is *malignant*, that is, its cells have the ability to invade surrounding tissue. Invasiveness usually implies that cancer cells have acquired the ability to break loose from the tumor mass, enter the blood stream, and form secondary tumors at other sites in the body. The more widely a cancer invades, or *metastasizes*, the harder it becomes to eradicate.

Cancers are classified according to the tissue and cell type from which they arise. Cancers arising from *epithelial* cells (cells that form the covering of all body surfaces, and line body cavities and hollow organs) are termed *carcinomas*; approximately 85% of all malignant neoplasms are carcinomas, perhaps because epithelial tissues are most frequently exposed to the various forms of physical and chemical damage that favor the development of cancer. Those arising from connective tissue or muscle cells are termed *sarcomas*. Cancers that do not fit in either of these two broad categories include the various *leukemias*, derived from blood cells, and cancers derived from cells of the nervous system. In parallel with the set of names for malignant tumors, there is a related set of names for benign tumors: an *adenoma,* for example, is a benign epithelial tumor with a glandular organization, the corresponding type of malignant tumor being an *adenocarcinoma;* a *chondroma* and a *chondrosarcoma* are, respectively, benign and malignant tumors of cartilage. See http://www.cancer.ca for categories and latest Canadian statistics of various cancers. In your lifetime, it has been suggested that there is a 1 in 4 likelihood of you contracting this feared disease.

Cancer is of clonal origin

Even the origin of a malignant cancer can usually be traced to a single primary tumor, arising in an identified organ and presumed to be derived from a single cell. One type of demonstration to confirm clonal origin comes from analysis of the cell's DNA. In almost all patients with *chronic myelogenous leukemia (CML),* for example, the leukemic white blood cells are distinguished from the normal cells by a specific chromosomal abnormality (the so-called Philadelphia chromosome, created by a translocation between chromosomes 9 and 22). When the sequence of DNA at the site of translocation is determined, it is found that the site of breakage and rejoining of the translocated fragments is identical in all the leukemic cells in any given patient but differs slightly (by a few hundred or thousand base pairs) from one patient to another, as expected if each case of the leukemia arises from a unique accident occurring in a single cell.

How does cancer develop?

Genetic changes are involved in most forms of cancer as we discussed above for CML. Further evidence that genetic change can be a *cause* of cancer comes from a study of agents known to give rise to the disease. The fact that c*arcinogenesis* (the generation of cancer) and *mutagenesis* (the production of a change in the DNA sequence) are correlated is clear for three classes of agents: chemical carcinogens (which typically cause simple local changes in the nucleotide sequence), ionizing radiation such as x-rays (which typically cause chromosome breaks and translocations), and viruses (which introduce foreign DNA into the cell).

Most chemical carcinogens never gain entry into our cells because of alert defense mechanisms that destroy invaders. Enzymes from our cells' lysosomes and peroxisomes usually inactivate those that do enter the cells. Even with these protective mechanisms, some of the carcinogens may still enter the nucleus and bind with DNA. Cancer is still unlikely, however, because the body has a built-in DNA repair system. This system detects the altered DNA, removes it in a type of molecular surgery, and prompts the synthesis of a new normal DNA segment. If the repair is faulty or if cell division occurs before the DNA is repaired, the altered DNA segment is copied abnormally and the daughter cells receive a mutated gene. In most cases the mutated gene destroys only a single cell and cancer still cannot develop. With radiation and viruses, the sequence of events before interaction with DNA is slightly different, but the effect is the same – altered DNA. Cancer development therefore depends on the body's ability to "detoxify" the cancer-causing agents and repair the DNA damage. Perhaps with age, the body's immune system as well as our cells' ability to repair DNA damage weakens. The risk of developing cancer therefore increases rapidly with age.

Recent research has made it clear that, in general, a given cancer cannot be blamed entirely on a single event or a single cause. Tumors arise as a rule from the chance occurrence in one cell of several independent accidents with cumulative effects that drive the progressive transformation of normal human cells into highly malignant derivatives. Most human cancers require four to seven random mutations to develop.

That a single mutation is not sufficient to turn a normal cell into a cancerous one, can also be seen by considering that something on the order of 10^{16} cell divisions take place in a human body in the course of a lifetime. Even in an environment that is free of mutagens, mutations will occur spontaneously at an estimated rate of about 10^{-6} mutations per gene per cell division - a value set by fundamental limitations on the accuracy of DNA replication and repair. Thus, in a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being. Among the resulting mutant cells one might expect that there would be many that have disturbances in genes involved in the regulation of cell division and that consequently disobey the normal restrictions on cell proliferation. From this point of view, the problem of cancer seems to be not why it occurs but why it occurs so infrequently.

The hallmarks of cancer – molecular insights

We have so far emphasized that cancer cells defy the normal controls on cell division; this is their central property. But there are other requirements to allow a tumor is to grow without limit. The overall picture that has emerged due to extensive research over the past two or three decades suggests that cancer is a manifestation of six essential alternations in cell physiology that collectively dictate malignant growth (*Hanahan and Weinberg,* ***cell*** *100, 57-70, 2000*):

1. Self-sufficiency in growth signals

Normal cells require signals from their environment to commit cell division. These signals are transmitted into the cells through protein molecules embedded in cell membrane, known as *receptors*, that bind distinctive classes of signaling molecules: soluble *growth factors* or *hormones*, proteins that comprise the *extracellular matrix* (the stuff that 'glues' cells together) and cell-cell interaction molecules. No type of normal cell can proliferate in the absence of such stimulatory signals. Tumor cells, on the other hand, generate many of their own growth signals, thereby reducing their dependence on stimulation from their normal tissue microenvironment.

2. Non-responsiveness to anti-growth signals

Multiple anti-proliferative signals operate to maintain cells in a quiescent state in order to maintain a constant tissue microenvironment. These antigrowth signals, like their positively acting counterparts, are received by transmembrane cell surface receptors coupled to intracellular signaling circuits. Antigrowth signals can block proliferation by forcing cells out of the active proliferative cycle into a quiescent non-proliferative state from which they may reemerge on some future occasion when extracellular signals permit.

Cancer cells evade these antiproliferative signals in order to prosper. To accomplish this, they disrupt a key pathway – retinoblastoma protein (pRb) and two of its related proteins – that block proliferation by sequestering and altering the function of a family of *transcription factors*, E2Fs, that control the expres-

sion of a set of genes essential for DNA synthesis and hence proliferation.

3. Avoiding death

A balance between the rates of cell proliferation and death determines the increase in tumor cell number. The evidence is mounting that acquired resistance towards *apoptosis* (programmed cell death) is a hallmark of most and perhaps all types of cancer.

The apoptotic machinery of a cell can broadly be classified into two components – the sensors and effectors. The sensors are responsible for monitoring the extracellular and intracellular environment for conditions of normality or abnormality that in turns determine whether a cell should live or die. The sensors also regulate the effectors of apoptosis. Intracellular sensors monitor the cell's well-being and activate the death pathway in response to detecting abnormalities including DNA damage, signaling imbalance created by overexpression of an *oncogene* (abnormal form of a gene whose expression can promote cancer development) or *hypoxia* (too low an oxygen levels). Further, the life of most cells is in part maintained by cell-extracellular matrix and cell-cell adherence based survival signals whose abrogation also elicits apoptosis. The ultimate effectors of apoptosis include an array of enzymes called caspases.

Cancer cells through a variety of strategies can acquire resistance to apoptosis. The most common one being the loss of a pro-apoptotic p53 tumor suppressor gene through mutations that renders its product, the p53 protein, functionally inactive. More than 50% of human cancers have mutations in p53 gene that results in the removal of a key component of the DNA damage sensor machinery as well as an inducer of the apoptotic effector cascade.

4. Unlimited replicative potential

The three capabilities of cancer cells discussed above lead to uncoupling of a cell's proliferation from its environment. They are, however, still insufficient to enable generation of a vast cell population that constitute tumors. Mammalian cells also have a cell autonomous program that limits their multiplication potential. Cancer cells must also disrupt this program in order for clones of the mutated cell to expand to a size that constitutes a life-threatening tumor. In vitro culture studies of tumor cells have shown that they appear to be immortalized, confirming that limitless replicative potential is a characteristic that was acquired in vivo during tumor progression and was essential for the development of their malignant growth state.

Telomeres, the ends of chromosomes, are composed of several thousand repeats of a six base pair sequence and appear to act as a counting device for cell doublings. There is a 50-100 base pair loss of telomeric DNA during every cell doubling due to the inability of DNA ploymerases to completely replicate the ends of chromosomes while copying DNA. This gradual loss of telomeric DNA after every replicative cycle eventually reaches to a critical threshold after which cells stops dividing.

Telomere maintenance is evident in virtually all types of cancer cells. The majority of cancer cells succeed in maintaining telomeric DNA by upregulating (that is, increasing) the expression of a telomerase enzyme that adds the nucleotides to the ends of chromosomes.

5. Continuous blood supply

Proliferating cells require both oxygen and nutrients for their survival and growth. For this reason, most of the cells in a normal tissue reside within 100 mm of a capillary blood vessel. Because of this dependence on nearby capillaries, it would seem plausible that proliferating cells within a tissue would have an intrinsic ability to encourage blood vessel growth. But the evidence is otherwise. The cells within a tumor initially lack the ability to induce blood vessel formation, a process known as *angiogenesis*, curtailing their capability for expansion. Tumors therefore acquire this ability in a discrete step (or steps) during tumor development before they start to invade surrounding tissue. Tumors appear to activate the angiogenic switch by changing the balance of angiogenesis inducers and countervailing inhibitors. The overall mechanism is quite complex and incompletely understood, but appears to involve altered gene expression.

6. Tissue invasion and metastasis

Most human cancers eventually develop the ability to move out and invade adjacent tissues and travel to distant sites where they may succeed in developing new colonies. This metastasis is the cause of 90% of human cancer deaths. Invasion and metastasis are exceedingly complex processes and are incompletely understood at molecular level. Expression of many of the cell surface proteins that promote adhesion between cell-cell and cell-extracellular matrix components appear to be modified by tumor cells during invasion and metastasis.

Stem Cells, differentiation and cancer development

It may be appreciated by now that cancer development is quite a complex process and multiple factors are at work. Increase in the frequency of cell division will not by itself produce a steadily growing tumor in many tissues. The example of the uterine cervix illustrates this point. Like the skin, the epithelium of the

uterine cervix normally renews itself continually by shedding terminally *differentiated* cells from its outer surface and generating replacements from *stem cells* in the basal layer. On average, each normal stem cell division generates one daughter stem cell and one cell that is fated to terminal differentiation and a cessation of cell division. If the stem cell simply divides more rapidly, terminally differentiated cells will be produced and shed more rapidly, and a balance of genesis and destruction will still be maintained. Thus if a transformed stem cell is to generate a steadily growing tumor of cloned progeny, the basic rules must be upset: either more than 50% of the daughter cells must remain as stem cells or the process of differentiation must be deranged so that daughter cells embarked on this route retain an ability to carry on dividing indefinitely and avoid apoptosis or being discarded at the end of the production line.

Similar considerations apply to the development of cancer in other tissues that rely on stem cells, such as the skin, the lining of the gut, and the blood. Several forms of leukemia, for example, seem to arise from a disruption of the normal program of differentiation, such that a committed progenitor of a particular type of blood cell continues to divide indefinitely, instead of differentiating terminally in the normal way and dying after a strictly limited number of division cycles. In general, changes that block the normal maturation of cells toward a nondividing, terminally differentiated state or prevent normal programmed cell death must play an essential part in many cancers. In the treatment of cancer, therefore, there is some prospect that drugs that promote cell differentiation may turn out to be a useful alternative to drugs that simply kill dividing cells.

Cancer treatments

A key feature of human cancer is inter-individual heterogeneity in biologic characteristics and response to treatment. Clearly, cancer of the breast, colon, or any tissue represents a family of diseases. As laboratory methodology improves, we will be able to sub-classify cancers according to molecular, biochemical, genetic, and biologic characteristics.

A. Cancer screening and early detection

Cancer screening and early detection have major importance in the survival of patients with many cancers. A feature common to most of the common cancers (that is, cancers of the skin, breast, cervix, ovary, testis, colon and rectum, prostate, and lung) is that prognosis generally is better and treatment more successful if the disease is detected when still localized.

B. Nutrition and cancer

Scientific data published so far has made it clear that nutritional status has a major influence on the risk of cancer development. Nutrients are classified into six main categories: protein, carbohydrate, fat, vitamins, minerals, and water with protein, carbohydrates, and fat are the only components that provide energy. Vitamins and minerals function as structural components or cofactors in numerous vital metabolic processes and do not provide any energy. Dietary fiber has not been considered an essential nutrient category, although considerable efforts have been devoted to understanding its complexities and role in human health and disease. Alcohol also has been a component of the human diet throughout recorded history and has numerous metabolic and physiologic effects. The potential complex interactions among the dozens of established nutrients and the genetic as well as environmental factors participating in human carcinogenesis have precluded precise quantification of the risks and benefits associated with any single nutrient.

C. Radiation treatment

Radiation oncology is a field devoted to the treatment of benign and malignant diseases with ionizing radiation such as x-rays. The usage of radiation in the treatments of human malignancies dates back to early twentieth century. It was also soon recognized, however, that radiation produced adverse effects on normal tissues. In fact, due to the significant toxicity associated with the available low-energy machines, radiation therapy had limited applicability until the introduction of high-energy (megavoltage) therapy in the 1950s. Only then was it possible to treat deep-seated tumors without excessive toxicity.

Over the past two decades, tremendous advances have been made in imaging and treatment delivery, allowing for improved targeting and increased sparing of normal tissues. Increased understanding of radiobiology has also provided a means of further reducing the risk of side effects while increasing the efficacy of treatment. Radiation therapy is currently being used in the management of benign and malignant diseases throughout the body in both children and adults and offers an effective means of palliation when cure is not possible.

D. Surgical treatment

Surgery is the oldest component of cancer therapy and still forms the mainstay of treatment in solid tumors. It remains a paradigm that more patients are cured by surgery when used as a single treatment, as compared with any other type of cancer therapy. Even in the contemporary multi-modality cancer therapy milieu, it is the rare patient with a solid tumor whose care does not include a surgical component.

When surgery is carried out, 100% of the excised tumor cells are killed. In contrast, chemotherapy and radiation therapy result in only a fraction of tumor cells being killed by each treatment. However, surgery and chemo- or radiotherapies are complementary. Surgical resection reduces the tumor burden, which hopefully increases the efficacy of non-surgical adjuvant therapies intended to eliminate microscopic residual disease, thereby decreasing the risk of recurrence.

E. Chemotherapy

Chemotherapy refers to application of drugs that are toxic to cells to eradicate cancer cells. Most of the chemotherapeutic agents are non-specific in the sense that they target the dividing cells. Consequently, both malignant and normal cells are affected alike. This results in many of the side effects of chemotherapy such as hair loss, vomiting, nausea etc. The identification of novel, clinically active agents has been central to progress in cancer chemotherapy. The optimal use of such agents, of which more than 40 have been identified over the past 50 years, has been crucial.

Chemotherapeutic agents fall under various categories. Methotrexate, for example, inhibits dihydrofolate reductase (DHFR), an enzyme involved in folic acid metabolism. 5-flurouracil, on the other hand, belongs to the class of purines and pyrimidines antimetabolities that target the DNA synthesis pathways. Alkylating agents such as Cyclophosphamide exert their toxic effect due to inhibition of DNA replication and cell division produced by their reactions with DNA.

Why is cancer so difficult to eradicate?

When viewed under the microscope, cancer cells often display an abnormal variability in the size and shape of their nuclei. There is often variation in the number and structure of their chromosomes as well. When cancer cells are grown in vitro, they are often found to have an extraordinarily unstable genome: genes become amplified or deleted and often chromosomes become lost, duplicated, or translocated. This happens at a far higher frequency compared to normal cells in culture. Such chromosomal variability suggests that the cancer cells have some heritable fault in the machinery or control of chromosome replication, repair, recombination, or segregation. Such faults usually result from mutations and are liable to increase the likelihood of subsequent mutations in other classes of genes and hence to provide a short cut to the accumulation of the multiple mutations required for cancerous behavior.

This abnormally high mutability of cancer cells provides malignant cells the capability of evolving at an alarming rate when subjected to new selection pressures. This greatly aggravates the difficulties of cancer therapy. Repeated treatments with drugs that are selectively toxic to dividing cells can be used to kill the majority of cancer cells but it is rarely possible to kill them all. Usually a small population of cancer cells develops drug-resistance, and the treatment essentially favors the spread and evolution of cells with this trait.

To make matters worse, cancer cells that are exposed to one drug often develop a resistance not only to that drug, but also to other drugs to which they have never been exposed. This phenomenon of multidrug resistance frequently results due to a massive increase in the copies of a gene known as *multidrug resistance (mdr1)* gene which codes a transport protein located in cell membrane. This protein is actually an enzyme called dihydrofolate reductase (DHFR) which essentially acts as a "pump" driving the drugs out as soon as they enter the cell. The gene for the enzyme DHFR often becomes amplified in response to treatment with methotrexate. The amplification of other types of genes can also give the cancer cell a selective advantage. For example, *myc* proto-oncogenes whose products stimulate cell proliferation, are similarly amplified in some cancers.

Useful cancer related web sites

Glossary of Cancer-related Terminology: http://info.cancer.ca/e/glossary/glossary.html Canadian Cancer Society website has this useful glossary of technical terms commonly used in cancer diagnosis, treatment, and research.