How do Different Factors Play a Role in the Development of Cancer?

A Review of the Literature

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Abstract

The paper reviews cancer, and the different factors or causes that may contribute to cancer in humans cells. Cancer is affecting people worldwide and the fact that there is no cure for it and that researchers still do not know everything about it makes it even more lethal and important to research. The different factors that may contribute to the formation of cancer include the activation and deactivation of tumor suppressor genes and proto-oncogenes, other important types of genes, the function of the mitochondria, gene amplification, and oxidative stress.

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What is Cancer and What are Some of the Factors that Influence the Formation of Cancer?

Cancer is defined as the uncontrolled growth of cells. Mutations in genes can cause cancer by accelerating cell division rates or by inhibiting normal controls on the system. As more and more cancerous cells clump together, they form a mass called a tumor. Since cancerous cells grow unchecked, they surpass all the cell cycle checkpoints and some cancer cells don't respond to the external growth regulators, while some fail to produce the internal regulators to ensure orderly growth. Some of the most influential factors in the development of cancer include tumor suppressor genes and proto-oncogenes, other important types of genes, the function of the mitochondria, gene amplification, and oxidative stress.

Tumor Suppressor Genes and Proto-Oncogenes

Both tumor suppressor genes and proto-oncogenes, two of the main types of genes, participate in the regulation of cancer and cancerous cells. These non-mutated forms of genes both normally help cells grow and without these, cells can grow out of control and unchecked, leading to the formation of cancer. Tumor suppressor genes and proto-oncogenes encode for many different proteins that help control cell cycle growth and proliferation. The mutated forms of tumor suppressor genes and proto-oncogenes affect the original genes and its normal functions, running the risk of it becoming cancerous.

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mutations, or tell cells when to perform apoptosis, or controlled cell death. According to Molecular Cell Biology, 4th Edition by Lodish, *et al*

> **"**Tumor suppressor genes encode proteins that slow or inhibit progression through specific stage of the cell cycle, checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal, receptors for secreted hormones that function to inhibit cell proliferation, proteins that promote apoptosis, and DNA repair enzymes."

When tumor suppressor cells do not work properly, normal cells can grow out of control and run the risk of becoming cancerous. Proto-oncogenes produce proteins that normally enhance cell division or inhibit normal cell death. Apart from this, some proto-oncogenes may produce signals that lead to cell division or that lead cells to perform apoptosis

Mutated Tumor Suppressor Genes and Proto-Oncogenes

An oncogene, or a mutated proto-oncogene, is any gene that encodes a protein that can transform cells or has the ability to induce cancer in organisms. All but a few oncogenes are derived from normal cellular genes. Stated by Lodish, *et al*

> "At least three mechanisms can produce oncogenes from the corresponding proto-oncogenes. Point mutations in a proto-oncogene that result in a constitutively acting protein product, local reduplication (gene amplification) of a DNA segment that includes a proto-oncogene, leading to the overexpression of the encoded protein, and chromosomal translocation that brings a

> growth-regulatory gene under the control of a different promoter and that causes inappropriate expression of the gene."

Chromosomal translocations bring a growth-regulatory gene under the control of a different promoter, which causes inappropriate expression of the gene. Stated by Lodish, *et al*, "An oncogene formed by the first mechanism encodes an oncoprotein that differs slightly from the normal protein encoded by the corresponding proto-oncogene. In contrast, the latter two mechanisms generate oncogenes whose protein products are identical with the normal proteins; their oncogenic effect is due to their being expressed at higher-than-normal levels or in cells where they normally are not expressed…" so they could be called silent mutations as the mutation has no effect on the resulting polypeptide.

Two common oncogenes, or mutated proto-oncogenes, include the HER2, a specialized protein found in some cancer cells, including breast and ovarian cells, that keeps cancer growth and spread in check and the RAS family of genes, which make proteins involved with the cell communication pathway, cell growth, and cell death.

Examples of tumor suppressor genes and effects of when they are mutated include the von Hippel-Lindau gene, which is a tumor suppressor gene. Mutations in this gene prevent production of the vHL protein, which restricts cells from uncontrolled growth, can lead to the production of abnormal forms of the protein, and eventually to the Hippel Lindau syndrome, a rare genetic disease that can cause either cancerous or benign tumors to develop in places like the CNS (brain and spinal cord), the kidneys, pancreas, retina, and the genital tract in men. Loss of activation of both alleles in the vHL gene has been shown to directly cause sporadic cell renal carcinomas, or the regular appearance of cancer arising in the epithelial tissue; loss of

heterozygosity leads to premalignant lesions of the kidney, or a lesion involving abnormal cells that are associated with an increased chance of forming cancer, and because of this, the inactivation of the vHL protein seems to be a major factor in the development of kidney cancer. vHL resides in, but is not restricted to, the cytoplasm and binds to elongin B and C, which have functions in the proteasomal degradation of proteins including the vHL protein, and thus by binding to elongin B and C, it contributes to tumor suppression by vHL. The simplest interpretations of the segregation of mutant vHL alleles based on their tendency to cause pheochromocytomas, or the development of tumors in your adrenal gland, shows that, "...biochemical functions unrelated to binding to elongin B/C and Hs-Cul2 contribute to tumor suppression by pVHL, and that the relative contribution of these activities to tumor suppression by pVHL differs in different tissues" (2 Ohh, *et al*).

Additionally, other tumor suppressor genes, specifically the p53 gene, have, "...come to the forefront of cancer research because it is commonly mutated in human cancer and the spectrum of p53 mutations in these cancers is providing clues to the etiology and molecular pathogenesis in neoplasia" (1 Greenblatt *et al*). The protein acts as a growth regulator to make sure cells aren't dividing too fast and binds directly to DNA. As stated by Greenblatt *et al*, "The potential for a missense mutation to cause loss of tumor suppressor function add gain oncogenic activity, i.e., to transform cells by two mechanisms, is one explanation for the commonality of p53 mutations in human cancer" (1). The most commonly mutated protein that directly influences the formation of cancer is the p53 gene; over 50% of all cancers involve a mutated p53 gene. Although most p53 gene mutations are acquired, germline p53 mutations can occur despite the fact that they are rare and patients with germline p53 mutations are at a higher risk of

developing cancer. Recent studies show that the p53 gene is involved in gene transcription, DNA synthesis and repair, genomic plasticity, and programmed cell death, or apoptosis. According to Greenblatt *et al*, "These complex biochemical processes are performed by multicomponent protein machines; therefore it is not surprising that the p53 protein forms complexes with other cellular proteins and that some viral oncoproteins alter the functions of these machines by binding to p53 and perturbing its interaction with other cellular protein components" (1). If the p53 protein mutates, abnormalities in the processes it controls can result in the mutated phenotype as well, progressively increasing the chance of both neoplastic transformation and the generation of malignant subclones during tumor progression.

Other examples of tumor suppressor genes include the BRCA1 and BRCA2. Germline mutations in these genes can increase a woman's chance of developing hereditary breast or ovarian cancers and a man's chance of developing hereditary prostate or breast cancers. In both men and women, germline mutations in the BRCA1 and BRCA2 can lead to pancreatic cancer and melanoma.

The Influence of Other Types of Genes on Cancer

Genes like the BRCA1, BRCA2, p53, and multiple other tumor suppressor genes are also considered to be DNA repair genes, as they fix mistakes when DNA is replicated or transcribed. If the DNA repair genes do not fix and error, the mistakes remain unchanged and are known as mutations, and a buildup of these mutations can lead to the potential risk of developing cancer. Mutations in DNA repair genes may be either inherited or acquired through an individual's life, and examples of syndromes that occur when mutations in DNA repair genes are inherited include

the Lynch syndrome, or the hereditary nonpolyposis colorectal cancer (HNPCC), which is an autosomal dominant conditions that leads to a high risk of colon, endometrial, ovary, stomach, small intestine, upper urinary tract, skin, brain, and hepatobiliary tract cancer.

Mitochondria in Cancerous Cells

Discovered by Dr. Otto Warburg, low oxygen is a characteristic of cancer cells because of a change in cellular respiration from using aerobic respiration to fermentation. According to him, the prime cause of cancer is the "replacement of the respiration of oxygen in normal cells by a fermentation of sugar." Although he believed that a lack of oxygen was the prime cause of cancer, he was proved wrong when he tried to cure cancer with oxygen and it failed, because the prime cause of cancer is actually toxins. Stated by Tony Isaacs, "Cancer cells are low in oxygen primarily because they have changed from taking in and utilizing oxygen for respiration to a more primitive form of respiration which utilizes sugar instead of oxygen. It is the cancer process itself which causes most of the lack of oxygen, not the lack of oxygen which causes the cancer process." Overtime, because of the stress and inflammation from exposure to toxins, a dysfunction in mitochondria occurs, and results in a "cellular defense mechanism in which cells revert to a more primitive form of respiration (sugar fermentation), refuse to die, multiply, and form a protective barrier." Since cancer cannot exist in alkaline rich environment, the body begins to turn more and more acidic as the stages of cancer progress. Although cancer causes a lack of oxygen, just providing oxygen to the cells around the tumor or into the bloodstream, isn't enough because no matter how much oxygen is present, cancerous cells stop taking in oxygen. Oxygen does play an important role in apoptosis because of the oxidative damage caused by

ROS, or reactive oxygen species, which are chemically active molecules containing oxygen that are formed as a waste product of the metabolism of oxygen.

Since mitochondria have their own DNA, as proved by the endosymbiont theory, "mutations in mitochondrial genes are common and have been shown to be involved in human diseases, such as mitochondrial myopathy. The resurgence of interest in metabolism in cancer cells has started to focus attention back on the mitochondria and there is increasing evidence that mutations in mitochondrial DNA encoded genes can contribute to the development of cancer. It is possible that such mutations provide metabolic adaptivity to the cancer cell."

Mitochondria are important for almost every cancerous cell not only because of their ability to produce ATP, but also because of "their ability to provide building blocks for anabolism via anaplerosis [the process of replenishing depleted metabolic cycle intermediates, most often referring to TCA, or the tricarboxylic acid cycle, also referred to as the citric acid cycle or the Krebs Cycle], their capacity to produce ROS, and their central position in RCD signaling" as stated by Poporato, *et al* (267).

Gene Amplification

Recently, researchers have come up with the idea that gene amplification may induce the appearance and reappearance of prostate cancer in men. The primary way to treat prostate cancer is androgen deprivation, or an anti-hormone therapy with the purpose to reduce the levels of male hormones, or androgens, in the body to stop them from affecting prostate cancerous cells. Androgens, including testosterone, androstenedione, estradiol, and estriol, produce the secondary sex characteristics in males, such as voice deepening, facial and body hair, and the development

of muscle mass. Almost 95% of all androgens are secreted from the testes and the other 5% are secreted from the adrenal gland, or an endocrine gland that functions in the secretion of hormones into the bloodstream to target cells.

However, results from recent experiments show that "tumor cells often exhibited multiple copies of the gene encoding the androgen receptor (AR), which binds the hormone to the cell. Tumors taken from the same patients before treatment contained only the usual single copy of the gene," according to the National Human Genome Research Center, NIH. Researchers hypothesize that the AR gene is amplified during androgen deprivation therapy and they continue to grow despite the fact that the AR gene concentration is low. Gene amplification has been seen before during *in vitro* experiments, but this was the first time that the mechanism has been seen in patients undergoing the treatment at the time. Based on these results, Tapio Visakorpi tells us that, "some recurrent prostate cancers are highly dependent on low levels on androgen." The fact that the AR gene is amplified over and over again in prostate cancer cells is supported by 7 of 23 different tumor samples and shows us that gene amplification can lead to the reactivation of prostate cancer in males.

Oxidative Stress

Oxidative stress can be seen when the production of oxygen, a highly reactive gas, is greater than the body's ability to detoxify the reactive intermediates and is directly related to oxidative damage in proteins, molecules, and genes in the body, and can permanently damage our tissues, DNA, and plasma membranes. The process is caused by free radicals, or unstable molecules that oxidize cells by oxidative stress, which are byproducts of energy produced by

anaerobic respiration. Although there isn't enough evidence supporting the fact that cancer cells are oxidatively stressed, the stress is usually not pronounced enough to cause cell death. However, there is persistent oxidative stress in cancer cells which may activate transcription factors, or proteins that can control the rate of transcription of DNA or RNA, in the case of retroviruses, by binding to a specific DNA sequence called the promoter or by binding directly to the RNA polymerase. Secondly, oxidative stress causes damage to DNA sequences that can lead to added mutations and genomic instability, and lastly, it can activate certain antioxidant systems that make cancerous cells resistant to chemotherapy. Because of the effects of oxidative stress on normal cells in the body, researchers believe that oxidative stress can explain some of the characteristics of cancer and even be involved in the formation of cancerous cells.

According to Martinez-Outschoorn, *et al*, "Loss of stromal fibroblast caveolin-1 is a powerful single independent predictor of poor prognosis in human breast cancer patients, and is associated with early tumor recurrence, lymph node metastasis, and tamoxifen-resistance." Cancerous cells can induce oxidative stress in cancer related fibroblasts and they act as metabolic and mutagenic motors that drive the tumor-stroma co-evolution, DNA damage, and aneuploidy in cancer cells. "Also we propose that that defective mitochondria are removed from cancer-associated fibroblasts by autophagy/mitophagy that is induced by oxidative stress," states Martinez-Outschoorn, *et al*.

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