

Oncogenes and Tumor Suppressor Genes: An Essential Building Block of Cancer

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Abstract: Cancer is a hyperplastic cellular malignancy that affects approximately 1.5 million Americans annually. Oncogenesis is associated with both genetic predisposition and environmental onslaught, with a mixture of the two being required for the malignancy to progress. An understanding of the underlying genetic injuries is useful in the research of cancer and its prevention and treatment. This paper will present a short literature review of the role of oncogenes and tumor suppressor genes and their role in the initiation of malignancy.

Key Words: Oncogenes, Tumor Suppressor Genes, Cancer, Malignant, Benign.

INTRODUCTION

The disease state known as cancer is aggressive, degenerative and affects many people worldwide. In 2014, it was estimated there would be 587,720 cancer deaths in the United States alone, and 1,665,540 new diagnoses [1]. In 2012, there were 14,100,000 cases diagnosed worldwide in that single year [2]. Birindelli et al. [3] described cancer as “the result of circumvention of the apoptotic machinery, promotion of cell division and cell proliferation, loss of cell differentiation pathways, and disruption of cell-cell communication and interaction”. All of these stages can be traced back to the activity of oncogenes.

The beginning of cancer, known as the process of carcinogenesis, is composed of many steps involving specific genes prone to producing such a state and signals provided and controlled by the products thereof [3]. The resulting disease state produces malignant tissue that invades and destroys nearby tissue and can metastasize to other areas of the body [4]. There is a large genetic component to cancer since it arises from alterations in cellular DNA or in the transcriptional or translational processes that produce abnormalities in gene expression [5]. Although all cancer is not hereditary, over 200 hereditary cancer syndromes have been described, and an individual's risk for cancer is increased if multiple family members are afflicted [6].

RATIONALE

Basic knowledge of the genes involved in carcinogenesis is a valuable tool in the investigation of cancer and the potential for a resultant therapeutic solution. Oncogenes and tumor suppressor genes are the primary entities involved in carcinogenesis and thus it becomes necessary to understand them to understand cancer on a molecular level. All cancers have a genetic component, whether somatic or inherited [5]. This statement alone indicates the importance of studying the genes implicated in carcinogenesis, as they may provide some method of predicting its occurrence. The alterations of the genes therein may also allow for more accurate diagnosis of cancer by providing molecular markers of its appearance [3]. The targets of action of the revised gene products are primarily the commitment to DNA synthesis in the G1 phase of the cell cycle and the commitment to mitosis in the G2 phase [7]. This functional alteration contributes greatly to the neoplastic phenotype by allowing a cell to both proliferate freely and escape regulation by apoptosis. Such alterations of proto-oncogenes (genes that code for protein products that regulate cell proliferation) and tumor suppressor genes are caused by many insults such as chemicals, ionizing radiation, and viruses.

DISCUSSION

Oncogenes arise from proto-oncogenes that regulate the cells' signaling pathways. When a mutation occurs in a proto-oncogene that activates it to oncogene status, production of the protein produced by the transcription thereof is either increased or the protein itself is altered in structure or function [6]. Proto-oncogenes normally encode proteins that act to promote cellular proliferation by participating in signaling pathways that relay growth stimulating signals through cells and are essential to many normal cell functions [5]. This communication proceeds by way of a cascade of intracellular biochemical signals and the result is activation or repression of various genes. The function of proto-oncogenes is critical to the control of normal cell growth and differentiation [7]. Growth factors and growth factor receptors are two types of pro-oncogene products that get altered by an oncogene [5]. Proto-oncogenes are often located near chromosomal breakpoints, making them targets for potential mutation and increasing the likelihood of carcinogenesis [7].

Normal cells, in which isolated occurrences of these mutations occur, have several methods of combating their destructive effects. One method of regulation is the traditional cellular technique of altering the controlling enzymatic activity. Transcription factors also regulate cell behavior by affecting growth factor genes, among others. If the pathway to apoptosis remains intact, the cell may activate this "self-destruct" function to eliminate the offending gene or gene product. The complexity of the regulatory processes controlling the expression of proto-oncogenes has two implications for neoplastic (cancerous) cells: 1) the large number of components involved provides a large number of potential mutation targets, and 2) multiple regulatory pathways ensure that mutation/carcinogenesis must occur in multiple proto-oncogenes to be effective [5].

Activating mutations, that is, mutations resulting in the beginning stages of carcinogenesis, are usually somatic events [5]. A somatic event refers to one occurring as the result of some outer stimuli and not from genetic inheritance. Loescher and Whitesell [5] predict that inherited mutations would likely be lethal during embryonic development. Mutations affect normal cellular processes such as apoptosis, signal transduction, and DNA replication [7]. Oncogenes can also be initiated by viruses to start the carcinogenic process. Viruses such as the Hepatitis C virus (HCV), Epstein-Barr Virus (EBV), and Human T-Cell Leukemia Virus-1 (HTLV-1) mimic

components of the cellular signaling pathways like ligands and receptors to affect production of oncogenic proteins [8].

Oncogenes are classified into six different categories. One category consists of growth factors involved in cellular communication such as proliferation, growth, differentiation and survival. Their overproduction is associated with cancer and has proven to be a key to the process of angiogenesis. Examples include vascular endothelial factor in breast and colorectal cancers and fibroblast growth factor in hemangiomas. A second category is growth factor receptors. They relay the signals conducted by growth factors to the target cell. Their overproduction is also associated with cancer as they continue to release proliferative signals in the absence of growth factors. Their overexpression is especially found in non-small-cell lung cancer, breast, ovarian, and colorectal cancers. Category three consists of nonreceptor tyrosine kinases that initiate tyrosine kinase activity (phosphorylation of tyrosine residues) in the absence of receptors as their name suggests. They are also found to be increased in cancers such as neuroblastoma and small-cell lung cancer [5].

A fourth category is membrane-associated G proteins, or guanine nucleotide-binding proteins. These proteins act as on-off switches (signal transducers) for growth factor receptors on the cell surface. Their increase is implicated in cancer by altering the cell membrane in malignant transformation as well as transmitting stimulatory signals without prompt. These oncogenes are implicated in two-thirds of malignant tumors, a fraction containing virtually all types of human cancer. The fifth category is serine threonine kinases, which are components of intracellular signal transduction. They begin a cascade leading to cell division and are over-stimulated in cancer states. Transcription factors are the sixth and final category of oncogenes. They bind to DNA and initiate changes in gene expression, either regulatory or transformational. These factors can cause chromosomal translocation resulting in a malignant phenotype and are associated with Ewing's sarcoma, clear-cell sarcoma, alveolar rhabdomyosarcoma, and several kinds of leukemia [5].

One proto-oncogene whose mutation often produces cancerous effects is named c-myc. If c-myc is up-regulated, a transcription factor is produced in excess which results in transformed cells and rapid cell proliferation. The concomitant mutation of bcl-2 with c-myc mutation results in the cells' additional ability to escape apoptosis, producing both an immortalized and a transformed phenotype [9]. Both c-myc and bcl-2 have diagnostic and

prognostic value in suspected cancer patients [3]. Bcl-2 acts as a potent inhibitor of apoptosis and becomes overexpressed by chromosomal rearrangement, especially in lymphoid malignancy. The study of bcl-2 became the origin of the study of apoptosis and cancer. [9].

Yet another example of oncogene mutation is found in the effects of the oncogenic virus, human papilloma virus (HPV). HPV encodes a protein known as E7, which inactivates the RB (retinoblastoma) gene whose function is cell regulation. The result of this inactivation is stimulated cell cycle progression. Viral-induced mutation alone is not enough to induce total transformation, because it usually leads to apoptosis [9]. Since apoptosis ends with the death of the cell, the inhibition of apoptosis is the process that is key to carcinogenesis.

Tumor suppressor genes are those whose protein products negatively regulate cell growth by blocking the action of growth promoting proteins [5]. Some have been seen to directly antagonize the action of proto-oncogenes in growth regulation [10]. Some of these genes are normally active transcription factors within the cell nucleus. Abnormal repression of tumor suppressor genes results in deregulation of the cell cycle (excess cellular proliferation by prolonging proliferation signals) or cellular disorganization [5].

Tumor suppressor genes (TSGs) function in the cell cycle by inducing checkpoints, pauses, or arrests in certain stages of the cycle. These checkpoints allow for DNA repair and act to ensure the integrity of the cell's genome [9]. TSGs mutations differ from other potential carcinogenic mutations because the alteration of TSGs produces a modification in the protein products that directly contributes to the transformed phenotype, as opposed to the other classes (proto-oncogenes, DNA repair genes) which produce indirect effects. More than 12 such genes have been localized and identified, though some of these may be mislabeled due to their change in expression in cancer cells [10].

The majority of hereditary cancers are caused by mutation of tumor suppressor genes in germline cells. TSGs require a germline mutation and a somatic mutation or two somatic mutations to initiate carcinogenesis. This theory is referred to as Knudson's Two-Hit Hypothesis and is based on Knudson's study of the autosomal dominant inheritance witnessed in epidemiological studies of retinoblastoma [6]. The first damaged allele may be transmitted in the germline cells of offspring with the second mutation of somatic origin, or both mutations may be somatic. The first mutation (germ line) is small and confined to one gene, otherwise it would be lethal and the

process would end. The second mutation results in complete loss of all or part of a chromosome [5].

Methods for identification have been circuitous at best but studies, have yielded several useful facts. To begin with, inheritance of TSGs seems to be dominant in contrast to other cancer-related genes, but they behave recessively on the cellular level [6]. Additionally, fully functional TSGs may suppress tumorigenicity even in the presence of activated oncogenes, indicating the importance of these genes in normal cell functionality and regulation [10]. Suppression of TSGs is crucial to the progress of carcinogenesis as is evidenced by the observation of Park [7] that oncogene expression precedes tumor formation by several months, with the conclusion that other events must be necessary.

TP53 (the p53 gene) is a tumor suppressor gene which codes for the protein called p53. It is the most commonly mutated gene in human malignancy. Even heterozygous mutation of p53 is associated with high rates of carcinogenesis in many tissues [9]. This gene is normally present, but in very low levels with a short half-life and acts as a transcription factor, activating or repressing the expression of various genes [8]. Assault in the form of DNA damage or viral infection may produce up-regulation of p53 to protect the cell. Loss of p53 as effected by many methods of carcinogenesis correlates with a loss of or resistance to apoptosis. The method of this action is unknown. Mutation resulting in p53 inactivation is unique in that it both eliminates a negative regulatory control on proliferation and increases the cell's resistance to apoptosis. This double utility may indicate an explanation for the frequency of the mutation [9]. Mutations of p53 and its corresponding gene TP53 are also used as prognostic tools indicating poor prognosis, increased risk of relapse, and cancer-related death [3].

Another gene, known as the retinoblastoma gene (RB), is also inactivated in many tumors and represents the first isolation of a tumor suppressor gene [5]. So called because it was first studied in the inheritance of retinoblastoma, RB gene functions as a cell cycle regulator. It interacts with a family of transcription factors to inhibit their activity and prevent entrance into the synthesis (S) phase of the cell cycle [9]. Phosphorylation of RB is required for entrance to this phase [11]. Like p53, mutation of even one RB allele increases the possibility of carcinogenesis in many tissues [9]. Retinoblastoma occurs via Knudson's Two-Hit Hypothesis where a loss of heterozygosity (loss or damage of a functioning allele) increases the likelihood of tumor formation and a second "hit" causes the malignancy [10].

In some cases, and possibly more often in the future, these genetic alterations of proto-oncogenes and tumor suppressor genes may be used as tumor markers for diagnosis of different types of cancer. They may also have some prognostic value to categorize patients based on predicting their likelihood of relapse and response to treatment [12]. For example, bcl-2 is found in prostate and breast cancer (both tumors responsive to hormones) and has prognostic value in the measurement of the level of its expression. The oncogene myc is found to be amplified in breast cancer, neuroblastoma, and retinoblastoma, can be a progression marker in advanced stage cancer, and is also related to poor prognosis in solid tumors [3].

CONCLUSION

In conclusion, evidence abounds for the crucial relationships of oncogenes and tumor suppressor genes with the process of carcinogenesis. Activation of multiple oncogenes and inactivation of several growth suppression genes is required for the acquisition of a completely neoplastic phenotype [7]. This is the result of the incorporation of oncogenes and tumor suppressor genes in signaling pathways and cellular regulation [13]. Oncogenes and tumor suppressor genes can be said to cause cells to ignore warning signals at their built-in checkpoints concerning the cell cycle, such as DNA damage, replication defects, or chromosome attachment to the spindle [7]. The gene alterations thereof can be used not only to better understand the disease state and underlying mechanisms, but also as both diagnostic and prognostic indicators of the disease process in the human body.

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