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Review Article

The role of genes in cancer: A review

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ABSTRACT

One of the most deadly illnesses is cancer, where genes contribute to metabolic and molecular alterations in cells that eventually alter the cell's structure or ability to divide. Their function in regulating the cell life cycle, division, DNA repair, aging, apoptosis, angiogenesis, invasion, and other metabolic activities makes these genes dangerous. Tumor suppressor genes and oncogenes are the two primary gene types implicated in cancer. Genes that typically control cell growth can become oncogenes when they are mutated or amplified. These include EGFR, which causes some forms of lung cancer, and HER2, which causes breast cancer. Cancer may result from unchecked cell division brought on by certain oncogenes. It is not entirely clear how mutations in normal genes turn them into oncogenes. Normally, tumor suppressor genes prevent cancer by encoding proteins that either block aberrant cell development or repair damaged DNA. When DNA damage disrupts the function of tumor suppressor genes, enabling impacted cells to divide and expand uncontrollably, cancer is more likely to develop. A certain number of malignancies, including breast cancer, may be caused by mutations in tumor suppressor genes inherited from a parent; these mutations typically arise early in life and impact multiple family members. Oncogenes, tumor suppressor genes, or both are genetically altered in the majority of malignancies. Tumor suppressor genes contribute to oncogenesis by losing their function, while oncogenes cause aberrant growth by gaining function. Together, the two mutation kinds generate cancer; the alterations are not constant but rather multiply as the tumor progresses from benign to increasingly malignant. The accumulation of the genetic alterations leads to cancer. Tumor suppressor genes and oncogenes offer crucial information on how cell growth is controlled. The role of genes in the spread of tumors and the impact of certain environmental factors on raising the risk of cancer are the main topics of this review.

Keywords: DNA, cancer, genes, review

INTRODUCTION

Our knowledge of the genetic causes of human disease has advanced significantly during the last ten years. The field of cancer genetics has arguably been most significantly impacted, as the proliferation of molecular profiling and genomic sequence data has demonstrated the intricacy of cancers of human. Hundreds or thousands of genes may be differentially expressed in a tumor cell, and dozens of genes may show structural or copy number abnormalities. While several family cancer genes with high-penetrance alterations have been identified, the contribution of low-penetrance genetic different form or polymorphisms to the risk of sporadic cancer development remains to be defined. The germline mutations that confer an increased susceptibility may be much easier to find with the aid of studies on the intricate somatic genetic events occurring in the developing cancer cell. Although new treatment approaches have been made possible by insights into the molecular pathogenesis of cancer, a deeper comprehension of

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the disease will necessitate the development of computational and new statistical methods for analyzing the genetic and signaling of networks that coordinate tumor behavior and individual cancer susceptibility [1].

METHODOLOGY

ONCOGENE

Since the cells in our bodies are individuals capable of growth, reproduction, and death, natural selection can take place inside them and result in a variety of alterations, including cancer. Cancer can develop as a result of pure chance or the impact of outside variables. A proto-oncogene may become active if it has a lot of copies or mutations. In this instance, it turns into a tumor gene and causes the cells to grow out of control when it shouldn't [2]. These gene mutations or physical alterations can be divided into two categories: modifications to the protein's structure and modifications to the way protein expression is regulated. The encoded protein typically acquires a novel function or has an excessively normal function. These mutations are also called "gain of Function" mutations for this very reason. Chromosome translocation mutations and point mutations of RAS proto-oncogenes that result in hybrid genes are examples of protein structural mutations. When these genes are expressed more frequently, tumor amplification increases [3]. Upon mutation, the other set of genes that control apoptosis results in apoptosis suppression, which increases cell survival. When subjected to mutation4, the final set of genes that use cell division to fix a random DNA flaw may stop functioning normally [4]. These differences may be inherited from the germ line or acquired by recognized (e.g., viral infections and environmental influences) or unknown reasons. The most prevalent type of cancer is acquired type [5]. Cancer genes affect the coding of a family of proteins called oncoproteins, which affects several of the cell's vital and reproductive processes, as we have already covered. Growth factors attach to growth receptors on the cell of surface during normal physiologic cell cycle proliferation, in the cytoplasm activating many intracellular signaling pathways that in turn activate the regulatory proteins in the nucleus. The nuclear factors that started transcription of DNA were activated by that process [4-6]. There are a number of kinds of growth factors, surface receptors, intra-nuclear proteins, and proteins involved in cytoplasmic metabolism. The cell divides more than usual and uncontrollably as a result of this process. Cyclins, cyclin-dependent kinases, and inhibitors control cell cycles. Because these processes also rely on several protein subtypes, the resulting malignant proteins may likewise have multiple subtypes, which can increase the incidence of cancer [4].

RESULTS AND DISCUSSION

TUMOUR SUPPRESSOR GENE

One class of genes that is crucial to the genesis of cancer development is tumor suppressor genes (TSGs). Following transcription and translation, these genes produce proteins that control apoptosis, govern the cell life cycle, and fix any mutations in DNA. Tumor suppressor gene mutations cause cells to become uncontrollable, which promotes the proliferation of cancerous cells. The brake pedal on an automobile can be compared to a tumor suppressor gene. Similar to how a brake keeps a car from moving too fast, the tumor suppressor gene stops the cell from dividing too quickly [7]. TSGs cause apoptosis, or cell death, in cells that have DNA damage. Stopping this process might hinder apoptosis, causing injured cells to divide abnormally and aiding in the growth of the tumor [8, 9]. Metastasis inhibition: Certain TSGs are linked to reducing cancer cell invasion or metastasis. For instance, there is a strong correlation between a lower expression of the CDH1 gene and a higher risk of tumor development, indicating that the gene may have a preventive function against the development of cancer [10]. The majority of human carcinogenic mutations include polysomies and trisomies of chromosomes 1, 5, 7, 11, 12, and 20 as well as partial or monosomy of chromosomes 1, 3, 4,

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6, 9, 14, 15, 18, 19, and 22. Numerous oncogenes and tumor-suppressor genes are most likely involved in the development of malignant tumors, according to this collection of nonrandom chromosome deletions found in human mesotheliomas [11].

BRCA 1 and *BRACA 2* GENE:

Some individuals with a positive family history have been identified as having heritable cancer factors. One of the most harmful genetic variables to date identified is breast cancer [12], early type (BRCA1), which affects the protein that codes for a nuclear phosphoprotein that is essential for maintaining genomic integrity. According to recent estimations, pregnant women with BRCA1 genetic mutations are more likely to develop breast and ovarian malignancies during their lifetime. The human chromosome 17q21 is connected to the BRCA1 gene maps [13]. The 22-exon BRCA1 gene produces a nuclear protein of 1863 amino acids and a molecular weight of 220 kDa. Its amino terminus region contains a zinc binding ring domain, while its carboxyl terminus is acidic. The BRCA1 gene is expressed in a number of tissues, including breast and ovarian tissue. The first changes discovered in the BRCA1 gene were a missense substitution, a stop codon, a 1-base pair insertion, so that an 11-base pair deletion [14]. A second gene, BRCA2, was discovered to be linked to hereditary breast cancer 20 in 1995. It encodes a 3 418 amino acid protein and spans roughly 70 kb of genomic sequence at 13q12. There are 27 exons in the BRCA2 coding region, including the non-translating exon [15] (Fig. 1).

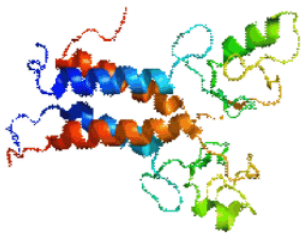
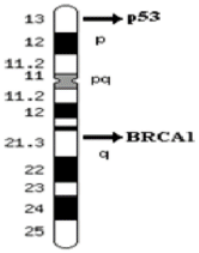
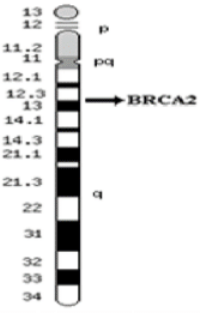
Gene and 3D protein structure	Chromosome location	Function	Primary tumor	Syndrome
BRCA1 	17q21 	Interacts with Rad 51 protein; Repair of double-strand breaks; involved also in transcriptional transactivation apoptosis and cell cycle control	Breast cancer	Familial breast cancer
BRCA2 	13q12 	Interacts with Rad 51 protein; repair of double-strand breaks; Also has a role in transcriptional regulation.	Breast cancer	Familial Breast cancer 2

Fig 1. Genes, Structure, Location, and Function of BRCA1 and BRCA2 (sours: Suman K R and Yamini M. BRCA 1 and BRCA 2: Role in Breast Cancer. IJSRR 2019, 8(1), 2219-2229)

The genes *BRCA1* and *BRCA2* are essential for several biological functions that are necessary for maintaining cellular homeostasis and genomic stability. The exact method by which the *BRCA1* protein raises the risk of breast cancer is yet unknown, though. In response to genotoxic stressors, the *BRCA1* protein participates in a cellular DNA damage response (DDR) network that recognizes, signals, and fixes DNA/chromatin damage (Fig 2). Additionally, it drives cells to undergo apoptosis or synchronizes the repair process with cellular metabolism and cell cycle progression. Ionizing radiation, oxidative stress, and mistakes in DNA replication can all lead to DSBs [16]. Nevertheless, they could also be brought on by designed DSBs that occur at particular genomic regions during meiosis, V (D) J, and heavy chain of immunoglobulin class switch recombination (CSR)

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[17]. The majority mutations in *BRCA1* gene result in either an excessively short *BRCA1* protein or the inability to produce any protein from a single copy of the gene. Because of this, there is less of this protein available to help mend mutations in other genes or repair damaged DNA. A tumor may develop as a result of the accumulation of these flaws, which can cause cells to proliferate and divide uncontrolled [18].

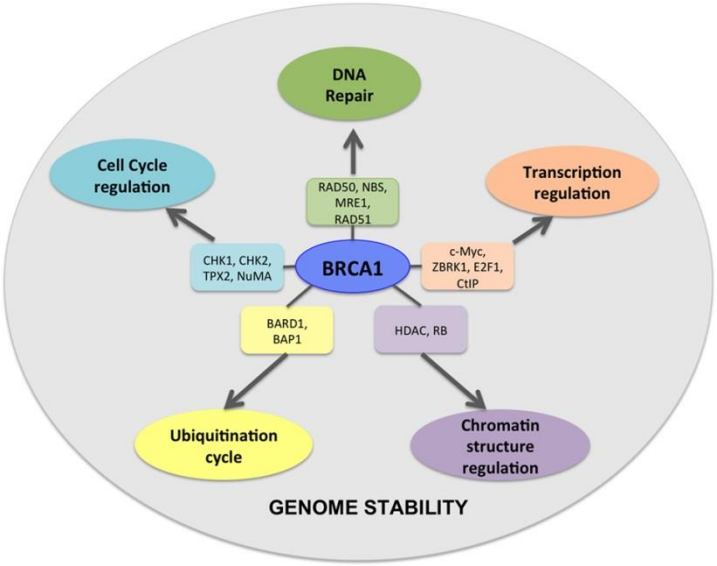

Fig 2. Cellular pathways of *BRACA 1 gene* in cells

Twelve Central and South American countries, including Argentina, Ecuador, Bolivia, Paraguay, Brazil, Chile, Colombia, Mexico, Costa Rica, Peru, Uruguay, and Venezuela, have pathogenic point mutations for BRCA1 and BRCA2, said one study. Eight publications on BRCA mutations in these nations were published between January 2002 and February 2017 indicates that nine countries—Argentina, Brazil, Colombia, Chile, Costa Rica, Uruguay, Mexico, Peru, and Venezuela—were the sites of the investigations. In Bolivia, Ecuador, and Paraguay, no BRCA mutations were reported. Together, the 28 investigations found 190 distinct harmful mutations after screening 5956 people [19]. One study has reported that women with a deleterious genetic alteration in either *BRCA1* or *BRCA2* who have been diagnosed with breast cancer are at increased risk of developing cancer in the opposite (contralateral) breast over time compared with women without such a change [20]. By 20 years after their initial breast cancer diagnosis, approximately 30–40% of breast cancer survivors with inherited BRCA1 mutations and 25% of those with inherited BRCA2 mutations will have developed contralateral breast cancer, compared with about 8% of the general population [21].

DIFFERENCES BETWEEN *BRCA1* and *BRCA2*

They are two completely different genes, even though mutations on both are associated with a higher risk of breast cancer. Along with a few additional variations shown in Figure 3, *BRCA1*, discovered in the year 1990, is located on Chromosome 17, while *BRCA2*, discovered after four years from the discovery of the *BRCA1* gene, is located on the Chromosome 13.

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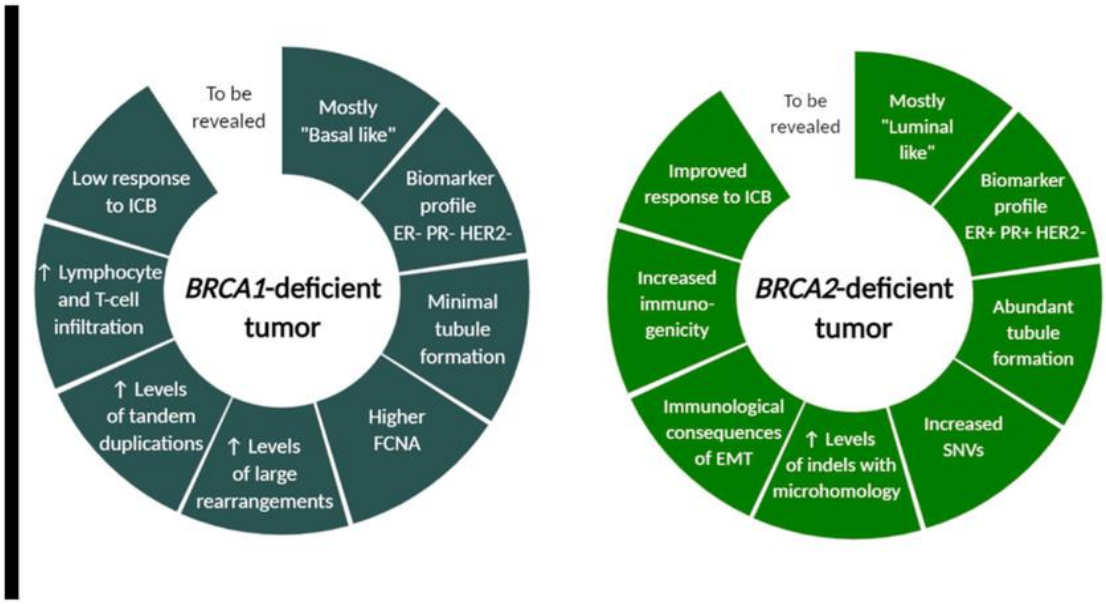

Fig. 3. Different morphological, molecular, and immunological properties of tumors with and without *BRCA1*

Despite the identification of countless tumor cell-intrinsic differences between BRCA1- and BRCA2-associated cancer, this field still requires more investigation in order to design clinical trials effectively. EMT, epithelial-to-mesenchymal transition; SNVs, single-nucleotide variations; ICB, immune checkpoint blockade; FCNA, fraction copy-number alterations; indels, insertions and deletions. Created with BioRender.com. Source: The Role of BRCA1/2-Mutated Tumor Microenvironment in Breast Cancer, Lenka T, Jana P, and Martin B. Cancers, 2021(3):575.

PTEN GENE

PTEN (phosphatase and tensin homologue deleted on chromosome 10) is one of the suppressor genes that is most often changed in malignant tumors. By inhibiting several kinases that promote cell growth, the PTEN protein reverses the carcinogenesis process [22]. An antagonist of the phosphoinositol-3-kinase/AKT signaling pathway, the PTEN tumor suppressor is a phosphatase that inhibits both cell survival and proliferation. After p53, PTEN is the gene with the second-highest frequency of mutations in cancer of human . Cancer susceptibility syndromes have been linked to gremlin mutations of PTEN [23, 24]. The 1997 cloning of PTEN/MMAC1 was made possible by its connection with the human cancer susceptibility locus at 10q2324.

The primary enzymatic activity of PTEN, a dual-specificity protein phosphatase with 403 amino acids spread over five functional domains, is on phosphatidylinositol (3,4,5)-triphosphate (PIP3) [25] (Figure 4).

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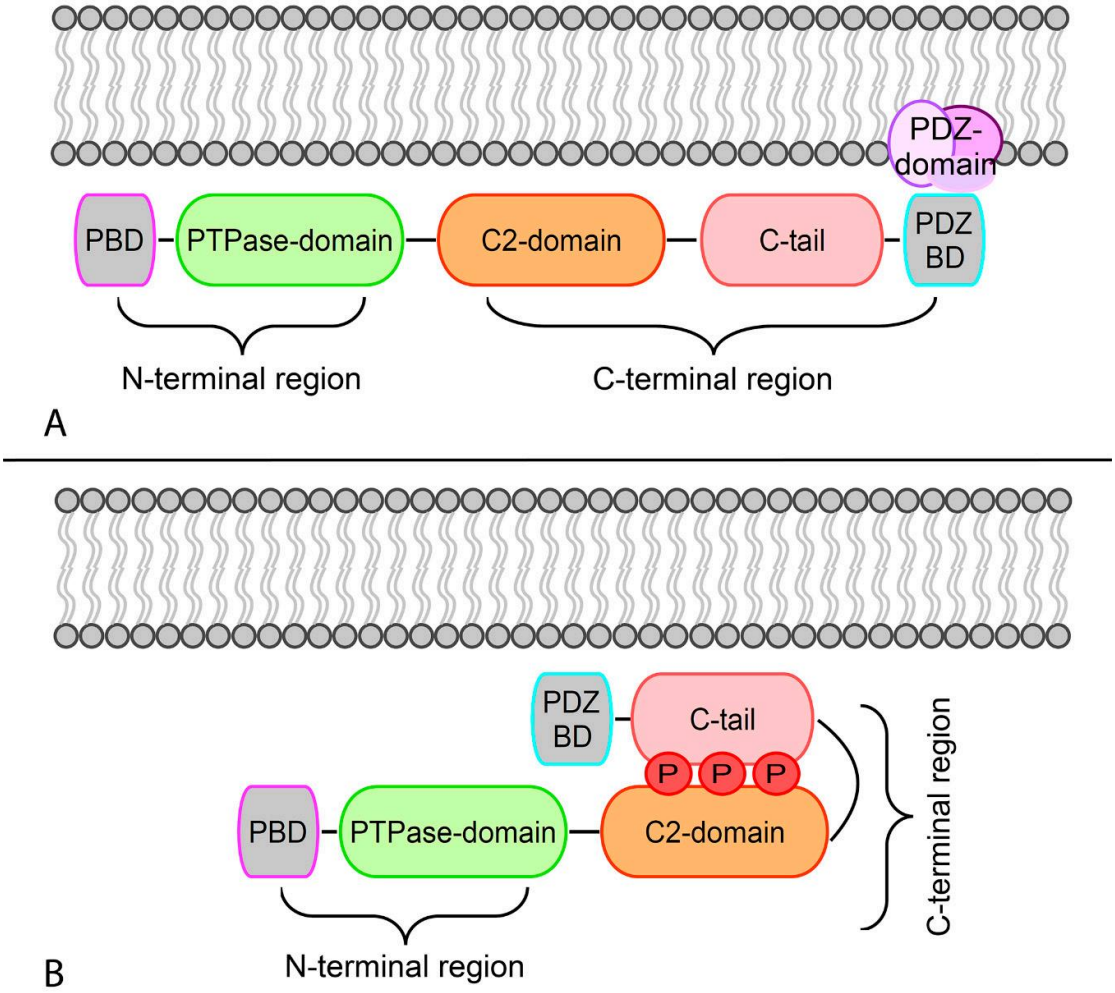

Fig. 4. Simplified view of the closed and open conformations of phosphatase and tensin homolog (PTEN) based on its phosphorylation state

A. Dephosphorylation induces an open conformation of PTEN that allows it to interact with the membrane. The electrostatic interactions enable PTEN to dock to the negatively charged membrane.

B. The C-tail domain of phosphatase is activated and adopts a conformational change upon the binding of the C2 domain to phosphatidylserine (Source: Genes 2020, 11, 719; doi: 10.3390/genes11070719) PTEN Alterations and Their Role in Cancer Management: Are We Making Progress on Precision Medicine? Advanced glial tumors, endometrial, prostate, thyroid, ovarian and bladder carcinomas and malignant melanoma are some of the malignant tumors in which somatic mutations in PTEN have been described.1, 5 loss of heterozygosity (LOH) of PTEN occurs in about 10–40% of sporadic breast tumors; intragenic mutations are present less than 1% of the time. It was later one of the PTEN gene-silencing mechanisms proposed that PTEN promoter hypermethylation [26–27]. There is an association between liver cancer [28] and PTEN gene alterations. It remains controversial, however, whether PTEN also regulates insulin-activated mitogenic pathways in vivo or in vitro [29]. Although nothing is known about the role of PTEN in the regulation of insulin signaling in cultured hepatocytes, two studies in which PTEN was specifically deleted from the livers of mice demonstrated that the loss of PTEN function enhances insulin sensitivity and glucose tolerance in general [30]. Likewise, PTEN antisense oligonucleotides normalized plasma glucose in the db/db mice and corrected hyperglycemia in the ob/ob animals by reducing PTEN expression in the liver and adipose tissue.11. Finally, PTEN-/+ heterozygous mice demonstrated enhanced glucose tolerance and whole-body insulin sensitivity.

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CONCLUSION

Cancer is one of the most complex and difficult diseases to understand and treat because of its complex relationship with genetic alterations. The review puts genes in a central position in the development, progression, and treatment outcomes of cancer. Genetic mutations, whether inherited or acquired, disrupt normal cellular mechanisms such as growth regulation, apoptosis, and DNA repair, thereby fostering tumorigenesis. Thus, the most important oncogenes and tumor suppressor genes, such as TP53, BRCA1, and MYC, are considered to be major determinants of cancer behavior. Epigenetic modifications and non-coding RNAs have become increasingly recognized as fundamental regulators of gene expression and, thus, new targets for therapeutic modulation.

Next-generation sequencing and precision medicine have revolutionized our understanding of cancer genomics. Technological development has, therefore, enabled the possibility of identifying tumor-driving specific genetic mutations and pathways hence opening unprecedented opportunities for targeted therapies and personalized treatment strategies in selected cases. The outcomes of targeted pathway drugs, including HER2, EGFR, and BRAF, have largely improved in subtypes of cancers, clearly stating the importance of genetic profiling within clinical practice.

However, challenges still remain in the form of tumor heterogeneity, resistance to targeted therapies, and ethical considerations surrounding genetic testing. Much more research is needed to understand the complexities of genetic interactions in cancer and to develop new diagnostic and therapeutic strategies.

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