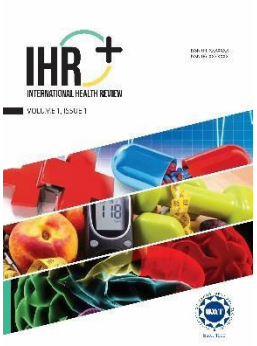

International Health Review (IHR)
Volume 1 Issue 1, Spring 2021
Homepage: https://journals.umt.edu.pk/index.php/ihr

Article: **Progression of Benign Breast Tumors: A Review of Differential Expression of BRCA1**

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Citation: Fatima W, Yasin U. Progression of benign breast tumors: A review of differential expression of BRCA1 *Int Health Rev*. 2021;1(1):00−00.

Journal QR

Article QR

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A publication of the
School of Health Sciences,
University of Management and Technology, Lahore, Pakistan

Progression of Benign Breast Tumors: A Review of Differential Expression of BRCA1

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Abstract

Benign breast tumors, a group of heterogeneous disorders, have a high incidence in females which is the effect of multiple environmental and genetic factors. Some notable genetic factors include the involvement of the highly penetrant BRCA1 gene and its major interactions with other genetic activators. BRCA1's interaction with certain proteins, such as 53BP-1 and ATM kinases, is initiated through the phosphorylation of their respective domains to create varied complexes with different functions. Consequently, BRCA1/BACH complex formation, in particular, helps in DNA repair processes. When this formation mutates, it can produce severe benign breast tumors. On the other hand, TP53 gene mutation also causes high damage to breast epithelia, irrespective of its interaction with BRCA1 function. BARD1 protein is also known to assist BRCA1 in maintaining its phenotype during the entire process of repair. These complex formations reveal the dual functioning of BRCA1 in relation to different proteinaceous entities as a tumor suppressor gene and a breast disease causing gene. Thus, this study focuses on BRCA1 mutation, its interaction with other genes, and its role in the DNA repair processes.

Keywords: benign tumor, BRCA1, carcinoma, genomic stability, polymorphism

Introduction

Benign breast tumors and their related consequences are often a major health concern for women, especially young women. These tumors are extremely diverse in their origin, etiology, and treatment [1, 2]. Benign breast tumors referred to as benign breast diseases (BBD) are a combination of several patterns of physiological changes in the breast of an individual.

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Furthermore, these changes are often linked with an increased probability of the patient developing breast cancer [3].

Genetically, these problematic events may arise because of a marked variation in the expression of DNA repair genes such as *BRCA1*, *BRCA2*, *RAD50*, and *MRE11* [4]. Most benign breast tumors occur due to some sort of alteration that transpire during the differentiation processes of epithelial cells lining the membrane of the female breast [5, 6].

It is important to note that benign tumors and their related clinical problems are associated with different macroscopic factors including female patient's family history, age, marital status, menstrual status, number of births, number of abortions, and the presence of tumors (both benign and cancerous) [7]. For this reason, when going through the disease history of any female patient, it is necessary to highlight some of the family and personal details since they provide a better understanding of the circumstances that lead to a diseased state.

Prevalence

Breast disorders are usually more prevalent in females as compared to males. Although men also exhibit their symptoms but not as much as women. Wholly benign breast tumors along with their lesion, scars, and wounds are collectively termed as non-malignant breast disorders and are referred to as benign breast diseases (BBD) [8]. A major sign of BBD is the thickening of the lining or membrane of the breast [9] which has varied manifestations and each manifestation has a varied prevalence in different populations. One can also predict the possible outcomes of a tumor by visualizing the clinical pattern of a breast lump, either through mammography or computerized scanning.

In most cases of breast tumors, analogous complications are observed. Breast lesions contribute up to 90% in the development of benign tumors, which is why it is predominantly perceived that benign tumors are much more dangerous than the malignant ones [10]. In the case of mild tumors, breast pain is the first indication, while the second indication is lump formation in the breast. On the other hand, female breasts remain under the influence of different hormones, which may cause a shift in hormonal symmetry that can initiate a tumor or breast illness [11, 12].

Clinical Manifestation

Some complications of breast illness comprise breast pain, lump formation, nipple discharge, swelling of the breast, and change in the skin texture of the affected area. These complications act as contributing factors in the formation of benign breast tumors. Usually, benign tumors display a less proliferative rate of cell division; however, a few of them show clinical symptoms related to later proliferative stages which can sprain to cancer [13]. Although, most carcinomas usually develop from pre-existing breast lesions existing as benign tumors, only a small fraction of these lesions develop into cancer, which can be clearly discerned through their histological, molecular, and biological features [14].

Genetic Variation and Consequences of Benign Breast Tumors

Advances in the field of genomics, as well as biological and molecular researches, have prepared the ground to study and investigate various genetic and phenotypic factors that contribute to the development of benign tumors or breast lumps [15]. Benign breast tumors can be detected by recurrent medical problems or phenotypic changes in the affected areas of the female breast.

It has been stated often that tumorous appearances are usually the result of the successive mutation of tumor suppressor genes and oncogenes [16]. Any variation or shift in the expression of these genes makes them susceptible to mutation, which can lead to the development of benign tumor. In the case of BRCA1 and BRCA2, if the DNA repairs these genes and they undergo any mutation (e.g. BRCA1 mutation), then they may cause breast tumors. Furthermore, the prognosis or proliferating rate of these mutated genes define whether they develop into cancer or not. Tumors continue to mutate, which is why their diagnostic assessment needs careful reconsideration [17].

Significance of Benign Breast Diseases

Breast diseases are among those clinical problems that are usually faced by most women during their reproductive cycle [18, 19]. The incidence of breast disease cases in males is very low; however, some exceptional cases are observed, although with an intensity that is less severe than females [20]. Among these cases, some are benign while others are malignant.

Adaptation of female breast may take various forms such as adenomas (tumors), inflammatory changes at various sites, neoplasm in breast tissue, epithelial uncontrolled proliferation, and fibrocystic. However, fibrocysts are more observed in malignant tumors [21]. At present, the frequency of benign tumors is gradually increasing [22].

Fibroadenoma are the most common benign tumors found in the affected female population. An initial symptom of this benign tumor is lump formation in the breast. Lumps are produced because of the lesions caused by the inflammatory epithelial cells. The rate of the occurrence of these lumps is usually much higher in young women (age 20-30). Along with these issues, other major clinical problems can also arise which may also vary in their etiology. According to a number of clinical researchers, medical geneticists and oncologists, benign tumors are a cause of concern because they are susceptible to complications and can develop into breast cancer [23].

BRCA1 Gene

BRCA1 is among the major tumor suppressor genes (TSG) in human beings that is involved in various biochemical and metabolic activities. BRCA1 protein product interacts with other genes and their products to produce expressional changes in the body, either at phenotypic or genotypic level (Fig 1). BRCA1 gene is a large polypeptide having different domains attributed with different functions. Domains that interact with genes regulating various tasks are present in multiple isoforms, particularly in BRCA1, the second isoform (isoform 2) is prevalent in the structures of other regulatory proteins [24] (Fig 2).

Another important BRCA1 gene feature is the C terminal domain that is referred to as BRCT domain. It is usually observed in the structure of disparate proteins that are mostly involved in DNA repair processes and are found at regulatory check point pathways. BRCT domain, globular in appearance, helps to form hetero/homo dimers with other proteins aimed to control various pathways. These BRCT and non-BRCT interactions mediate the repair of double stranded DNA breaks [25].

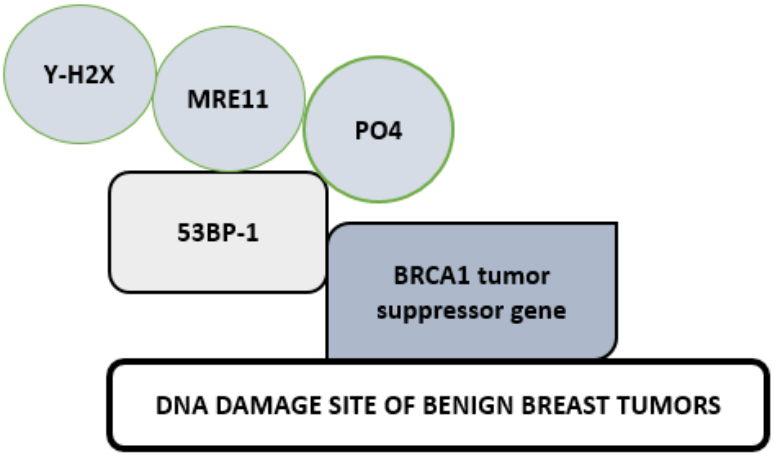

Figure 1. Interaction between breast cancer susceptibility gene and binding protein mediated through phosphorylation. After getting phosphorylated, it also binds to other genes involved in DNA damage signaling pathways

Figure 2. Structure of BRCA1 gene isoform rs80356932 involved in benign breast tumor and DNA repair

BRCA1 has separate nuclear dots or foci during the various phases of the cell cycle. These foci are frequently found in the S phase. A loss or mutation in the foci of BRCA1 results in its inability to phosphorylate BRCA1 gene, which is necessary to repair DNA damage. Nuclear foci secreted by BRCA1 are an integral part of the gene; therefore, BRCA1 is known to needed for the maintenance of genomic integrity [26, 27].

BRCA1 Functions

Cell cycle regulates the life of a cell and major check points in a cycle ensure the proper expression of every phase. Variation in the duration of phases and changes in the completion of the function of each phase affect the mitotic stages of the cell. All such incidences consequently affect genome stability. Even if the various stages of cell cycle are correctly practiced by

each cell, certain complications in replication affect the cell, causing DS breaks (double stranded) or SS breaks (single stranded). Breaks usually arise due to the exogenous and endogenous imbalance. In particular, damage inflicted to the DNA disturbs the control over the cell cycle.

It is difficult to repair double stranded breaks as there is no complementary sequence that may act as a template for it [28]. BRCA1 was found to be involved in repairing the damage by interacting with BARD1 [29]. Cells that are BRCA1-deficient are much more susceptible to mutation by exo- and endogenic sources including ionizing radiation and exhibit structural and chromosomal abnormalities, they are also a clear indication of a damaged cell without repair. It was witnessed that the entire process of repair is regulated through the combination of genes and their interaction with other proteins such as BARD1 product [30]. Genomic stability is one of the highly discussed properties of BRCA1 due to its association with multiple cognate proteins, especially with proteins related to the DNA repair processes (Fig 3).

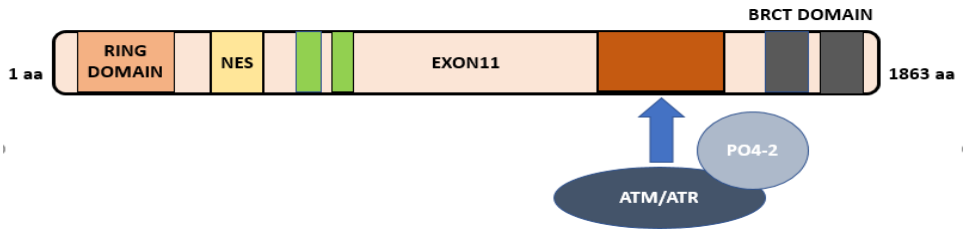

Figure 3. Necessary role of kinases in the activation of essential DNA repair genes and associated activators. ATM/ATR kinase acts on the serine residues at different sites and activates the region involved in signaling the damaged site

BRCA1 Role in Genomic Stability

In most mammalian cells, a number of biological activities are governed by their specialized targeting proteins. Genes and their respective proteinaceous products are the driving key of an individual organism. Any sort of variation in the normal working, structure, and processes of genes can lead to major visible changes in an organism's health and lifestyle. These variations may disturb the entire working balance of the body,

leading to the instability of genome. Thus, stability is the utmost requirement to achieve a better performance of the body (Fig 4).

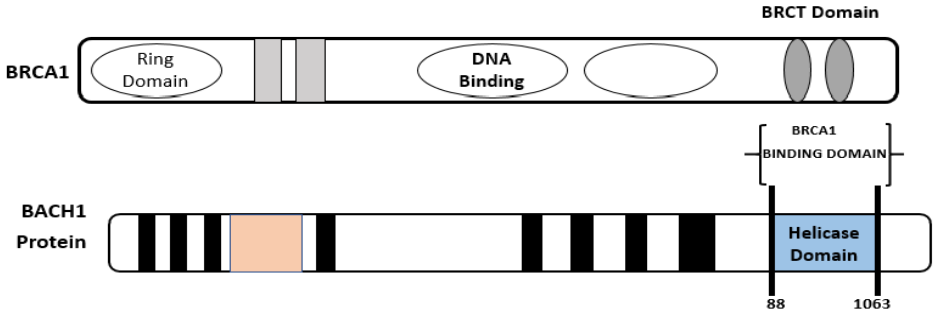

Figure 4. BRCA1 gene-BACH1 Protein Interactions. BRCA1 gene binds to the helicase domain of BACH1 protein rendering DNA repair functions, indicating the importance of their association with BRCA1. If disturbed, it might contribute in the development of benign breast tumors

BRCA1 and 53BP1 Protein

The interaction of BRCA1 with other genetic domains assists in the repair processes of genes. A major association of BRCA1 likely to occur in response to DNA damage is with 53 BP-1 proteins. When any damage appears in the DNA, 53 binding protein-1 (53BP-1) gets phosphorylated and is involved in its repair. It also interacts with BRCA1 at the site of DNA damage and acts as a major checkpoint [31]. Protein is brought to the repair site through localization with MRE11 gene and a histone variant y-H2X. This binding of DNA repair genes at the affected site may reduce the chance of tumor generation.

Certain 53BP-1 defective cells lack a functioning BRCA1 gene. It is an indication of an unrepaired and damaged DNA which disturbs the balance of the body, resulting in genetic variability and leading to tumor formation in the breast. Thus, 53BP-1 appears to be an essential element in the repair mechanism and is involved in maintaining genomic stability [32]. It is also required for p53 accumulation as it binds to it in the case of damaged DNA. When phosphorylated, 53BP-1 becomes a part of the arrangement of BRCA1 pathway of repairing DNA damage in which the signaling of protein is done at the presumptive sites of the variations [33] (Fig 5).

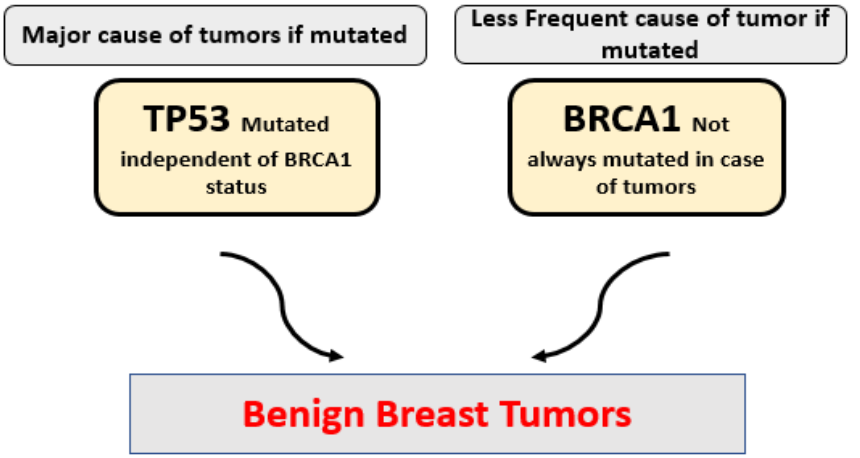

Figure 5. Variable Frequency of TP53 and BRCA1 Mutations in the Generation of Benign Breast Tumors. Independent nature of TP53 mutations cause it to be involved in tumor formation, while BRCA1 mutations are less prominent causative agents of breast tumors

BRCA1 Functions as DNA Repair Gene

A complete balance in genome is necessary for the appropriate survival of an individual organism. As genetic information is being transmitted among the cells at all times, so maintaining a balanced environment for gene transfer is needed to control the genomic stability. For the provision of variability, cells activate a DNA damage signaling complex which sorts out and responds at the site where the damage has transpired.

Any instability may increase the chance of tumor formation. Repairing damaged DNA contributes to maintaining the balance in the genome. Mutation in BRCA1 gene, if improperly dealt, can lead to various disorders and can increase the chance of tumor development and enlargement. However, the exact process which produces tumor during mutation is not yet clearly understood. Up till now, the only function that has been studied is the role of BRCA1 gene in maintaining the genetic stability of the genome by repairing damage such as double stranded breaks [34-36] and damage inflicted during the replication or recombination processes. The response to such mutations by organisms differs behaviorally and genetically [37].

Phosphorylation and DNA Damage Repair

BRCA1 gene consists of 2 BRCT domain motifs involved in binding with regulatory and targeting proteins. Motifs play a key role in repairing breaks in DNA strands and in recombination [38]. Homologous and non-homologous recombination comprise the processes carried out in an individual's body for the repair of double stranded breaks in DNA by BRCA1 gene and other repair factors. BRCA1 is recognized to have a repairing property only if it is phosphorylated. Once phosphorylated, it can be responsive towards the damage in DNA. Thus, phosphorylation is a notable factor in DNA damage repair, initiated by ATM and ATR protein kinase.

Furthermore, kinase resides inside the structure of BRCA1 domains, where it phosphorylates certain serine-glutamine residues such as p Ser-XXX-XXX [39]. When amino acid gets phosphorylated, it activates nearby regulatory regions or genes. If any site is not phosphorylated, then that particular region is not activated. It acts as a checkpoint for DNA damage repair; indeed, lack of phosphorylation pauses or inhibits the process of DNA repair. Therefore, double-stranded breaks can only be treated if BRCA1 domains are phosphorylated by ATM and other kinases [40].

Interaction of BRCA1 and BACH1 Protein

Some other interactions of BRCA1 gene further enhance its working as a DNA repair gene. For example, BRCA1 gene interacts with a protein called BACH1, which mediates certain steps in transcription. This novel protein is a member of a group of zinc transcription factors. When BACH 1 protein interacts with BRCA1, it forms BACH1/BRCA1 complex. This complex renders its services to DNA repair processes. BRCA1 binds to a specific portion of BACH1 888-1603 residues at the C terminus with the helicase domain of its structure.

If BACH 1 or BRCA1 domain binding gets mutated, it affects the interaction between them. For instance, a missense mutation in BACH1 is often observed when there is an improper placement of amino acid. Similarly, if any further variation occurs in conjunction with the first variation, it further aggravates the entire procedure [41] (Fig 6).

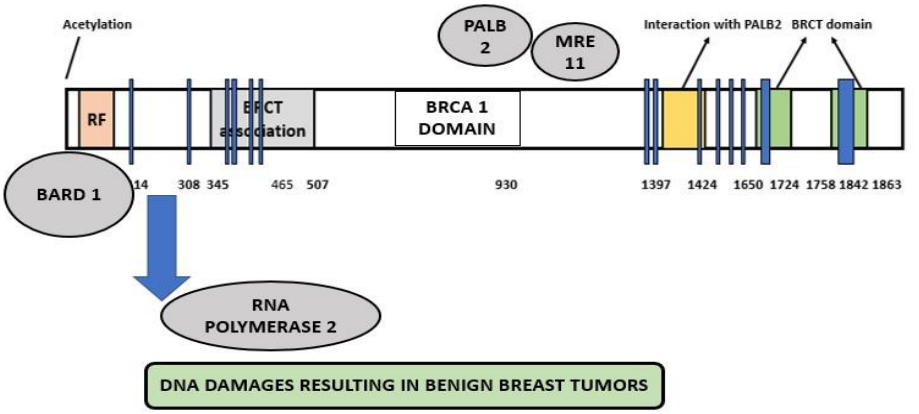

Figure 6. Stability of BRCA1 Structure and Function is provided by BARD1 protein. This interaction helps RNA polymerase to recognize the damaged part of the DNA in breast due to abortive translation

TP53 Mutation and BRCA1 Gene in Benign Breast Tumors

Benign breast tumors are formed due to germ line mutation in BRCA1 gene. However, there may also be an association between TP53 mutations and BRCA1 gene. Various manifestations of breast tumors occur due to mutation in another tumor suppressor gene called TP53 gene. This gene has a prominent role in transcription and cell cycle control. It was also observed that TP53 gene remains mutated without being dependent on BRCA1 status.

After experimentation and research, it has become evident that luminal breast tumor shows few incidences of BRCA1 mutation, while the incidences of tumor generation are high in the case of TP53 mutation. These luminal tumors were found to be independent of the mutated status of BRCA1 gene and remain strongly associated with the hereditary mutation of TP53. Furthermore, if substitution in TP53 gene (such as insertion, deletion) occurs to a large extent, then it may enhance the chances of BRCA1 mutation [42].

Role of BRCA1 and the Related BARD1 Protein in DNA Repair

In response to DNA damage in the breast, a complex is formed between BRCA1 and BARD1. This protein is similar to the BARD1 structure and it appears as a heterodimer. Interaction between these two proteins is mediated by domains which are homologous in their structures such as the

ring domain and the C terminal domains [43]. Together, they exhibit U3 ubiquitin ligase activity, which is lost if any mutation occurs in the domains of BRCA1 gene. Variations in the normal working of the genes affect the repair of the damaged DNA, which causes breast tumors. Analyzing the interaction of BRCA1 gene with multiple proteins helps to sketch the tumor and cancer causing mechanisms at genetic level [44].

BARD1 binds to BRCA1 tumor suppressor gene to maintain its phenotype. It also mediates the repair mechanism of double stranded breaks through a homologous recombination. However, BRCA1-BARD1 complex is also a point of concern as it functions to ubiquitinate RNA polymerase 2 function in response to DNA damage, which usually occurs in the shape of premature inhibition of transcription and translation [45, 46]. This feature may result in tumor formation in the breast. This complex, under the stress of tumor generation, eliminates any presence of truncated RNA transcript after being processed and may form immature proteins with inappropriate functions [47].

Conclusion

DNA repair genes function to repair defects carried in DNA, whose severity can lead to the complications of benign breast tumors. If any defect that could result in tumor generation is spotted, then BRCA1 activates by forming complexes with proteinaceous entities and inhibits lump formation in the breast. Complex formation not only repairs the damage but also enhances the function of BRCA1 gene. Also, there are other tumor suppressor genes which maintain hetero-dimeric complexes with BRCA1. However, if these complexes are mutated even once, they may have a greater chance to develop into a benign tumor independently of BRCA1. However, certain deletions in the genes (BACH1, BARD1, TP53) may complicate the BRCA1 gene function.

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