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Research Progress of PALB2 as a Susceptibility Gene for Breast Cancer

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Abstract:

Breast cancer is a complex disease that endangers women's health worldwide. The research on breast cancer susceptibility genes is increasing, especially the newly discovered PALB2, which has aroused the enthusiasm of many researchers. At present, the correlation between PALB2 and breast cancer and the susceptibility of PABLB2 mutation to breast cancer has been a large number of clinical studies and clinical statistics around the world. PALB2 plays an important role in DNA homologous recombination repair (HRR) together with BRCA1 and BRCA2 in normal cells, and the mechanism of PALB2 mutation causing breast cancer is also related. The BRCA pathway inhibitor PARPi has also been well studied, but there is still room to study the specific resistance mechanism. In addition, PALB2 has been implicated in ovarian cancer, pancreatic cancer, and lung cell carcinoma. This provides a reference for the study of PALB2 in cancers other than breast cancer, and the role and mechanism of PALB2 can also be explored in more different cancers.

Keywords: PALB2; Breast cancer; BRCA2.

1. Introduction

BC (breast cancer) has attracted global attention due to its high incidence around the world, and it is also an important cause of cancer death among women worldwide. The complicated nature of BC results from the interplay of multiple genetic and environmental factors. Different cancer predisposition genes have germline pathogenic mutations that account for 5–10% of all BC cases. The BC genes BRCA1 and BRCA2, which are linked to hereditary ovarian and breast cancer, are the most prevalent pathogenic factor of all hereditary BC cases. BARD1(BRCA1-associated RING domain protein 1), CHEK2(Checkpoint kinase), PALB2(Partner and Localizer of BRCA2), et al. have been identified as genes that predispose people to cancer and have a high to moderate risk of BC. For these cancer predisposition genes, there can be further new research, such as the development of new treatments, research on new therapeutic targets, and the discovery of new markers for BC, which are all very important for the treatment of BC and research progress [1]. Based on the analysis of recent research on new targets in BC, this article found that PALB2 is a very interesting and promising BC-related gene and has great developmental promise. However, the current application and research of PALB2 still need to be further explored.

BRCA2-interacting protein PALB2 interacts with BRCA1 and is necessary for BRCA2 genome maintenance activities [2]. A woman with a PALB2 mutation is nearly as likely to develop BC as a woman carrying a BRCA mutation, with a 40% to 60% higher risk. The PLCA2 gene encodes proteins that interact with BRCA2 proteins and participate in the DNA repair process. Maintaining genomic integrity, preventing the spread of cancer, and reacting to DNA double-strand breaks (DSB) in cells all depend on the BRCA1-PALB2-BRCA2 axis [3]. BRCA1 is drawn to double-strand breaks in response to DNA damage. Here, it aids in end resection and draws in PALB2 and BRCA2 in order to load the central recombination enzyme RAD51 and start HRR. Heterozygous carriers of the loss-of-function variant of the PALB2 germline have a substantially increased risk of developing BC during their lifetime. Although it is established that shorter PALB2 mutations raise the risk of cancer, missense variations of unclear significance are still mostly misinterpreted.

The purpose of this paper is to synthesize the currently available research and assess the developmental prospects and research value of PALB2. The authors will evaluate the application value of PALB2 through the clinical application of PALB2 and the current application of this gene in treatment. Based on existing research and experiments, this article aims to find optimization directions for animal models for in-depth research on PALB2.

2. PALB2 and BC

2.1 Functional Analysis of PALB2

About one decade ago, PALB2 germline pathogenic variants (PVs) were initially linked to a higher risk of BC. Multiple research that resulted in a sizable multinational study conducted by the PALB2 Interest Group (PALB2-IG) verified this, and the findings support PALB2 as a significant gene associated with breast cancer risk. Based on data from 154 families, they calculated the absolute risk of BC to be 14% by the age of 50 and 44% by the age of 80 [4]. This finding can indirectly confirm that the disease of BC is related to PALB2 and age, but its underlying mechanism needs further explanation and elucidation.

Germline loss-of-function (LOF) mutations in the BRCA1 and BRCA2 genes have been shown to raise the lifetime risk of breast cancer by around ten times. Like these genes, bi-allelic LOF variations result in Fanconi anemia (FA). In contrast, mono-allelic LOF mutations in PAB2, the gene that codes for BRCA2‘s partner and localizer, also increase the risk of breast cancer [5]. Understanding how VUS affects PALB2 protein activity is a crucial aspect of deciphering VUS in PALB2. In addition to BRCA1 and BRCA2, PALB2 may also form oligomers with the recombinase RAD51. This is related to the interaction between PALB2 and BRCA1 through its N-terminal coiled-coil (CC) domain and BRCA2 through its C-terminal WD40 domain. A crucial mechanism for the repair of highly-deleterious DSB is HR, which is facilitated by the PALB2-BRCA1/2-RAD51 complex. The ends of a DSB are resected when they are detected, producing lengths of 3‘ single-stranded DNA (ssDNA), to which the ssDNA-binding protein RPA binds. In order to promote the assembly of BRCA2 and RAD51 onto damaged DNA ends, PALB2 is recruited to these resected DSB ends in a way that is reliant on BRCA1. In turn, RAD51 catalyzes DNA transfer and strand invasion, often from a sister chromatid that is present in the S/G2 phase, which eventually results in error-free DSB repair [5].

2.2 Control of BRCA2 Cellular Functions by the PALB2

According to research on the genes linked to breast cancer susceptibility and their functional characteristics, about 50% of BRCA2 is linked to PALB2, and more than 50% of PALB2 is complexed with BRCA2. According to the study‘s results, PALB2 is firmly thought to facilitate BRCA2‘s stable intranuclear localization and accumulation, which in turn helps both BRCA2 and PALB2 activate an effective intra-S phase DNA damage checkpoint response. PALB2 appears to enhance BRCA2 function as well as the stability of the BRCA2 subpopulation that is linked to these nuclear structures by facilitating stable BRCA2 interaction with them, such as P100. This subpopulation of BRCA2 has to be prevented, at least in part, from becoming stranded in the nuclear soluble fraction, where proteasome-mediated degradation renders it intrinsically less stable.

The fact that the five genes—BRCA1, BRCA2, CHK2, TP53, and ATM—that are known to cause familial breast cancer all support the DNA damage response raises the possibility that the illness results, at least partially, from a disruption of the regulation of genome stability. Therefore, it has been suggested that BRCA2‘s capacity to maintain genomic integrity plays an essential role in its tumor suppression method. Findings showing PALB2 ensures proper BRCA2 nuclear presence and that PALB2-depleted cells phenocopy BRCA2-deficient cells demonstrate the necessity of PALB2 for important BRCA2 nuclear caretaker duties. The findings above also suggest that PALB2 plays a crucial tumor-suppressing role in genomic stability management, much like BRCA2. Three distinct mutations linked to cancer-associated BRCA2 that impair its ability to bind PALB2 have been found, providing evidence in favor of this theory [6].

2.3 PALB2 and BC Susceptibility

A five-fold relative risk has been related to PALB2 truncations; however, estimates from several research conducted in various groups have been shown to disagree. When comparing female PALB2 mutation carriers to the general population, their risk of breast cancer was eight to nine times higher in the under-40 age group, six to eight times higher in the 40–60 age group, and five times higher in the over-60 age group. Based on these findings, it is concluded that there is a correlation between PALB2 and BC susceptibility, and more attention should be paid to the function of PALB2 in breast cancer [7].

2.4 PALB2 and PARPi

Poly (ADP-ribose) polymerases, or PARPs, are essential for many biological functions, including DNA repair, chromatin remodeling, recombination, and replication. Cancer researchers have targeted the PARP pathway in an effort to generate drugs that preferentially target cancer cells and boost their susceptibility to other anticancer medicines while sparing healthy cells. This is done in an attempt to highlight PARP‘s involvement in enabling DNA repair. Certain malignancies (BRCA1/2 mutants) rely on PARP-mediated base excision repair to survive because they lack functional homologous recombination repair mechanisms. Therefore, blocking PARP is a viable method for killing cancer cells only by deactivating complementary DNA repair processes.

The most researched PARPs for their function in repairing

DNA damage are PARP-1 and PARP-2. PARP1 recognizes the break in DNA caused by lesions in DNA and catalyzes the attachment of poly (ADP-ribose) (PAR) chains to target proteins. PARP-catalyzed PARylation is a post-translational alteration that facilitates the recruitment of extra DNA repair components, such as BRCA1 and BRCA2, to the DNA lesion [8].

A distinctive profile of genomic instability linked to HR deficit is produced by germline nonsense and frameshift mutations in BRCA1, BRCA2, and PALB2. It has been shown that targeting this HR deficiency is beneficial for treating cancer with PARP inhibitors (PARPi), as the resulting double-strand breaks (DSBs) may be repaired by HR in healthy cells but not in cancer cells with HR deficiencies. The treatment of HR-deficient malignancies may benefit greatly from PARPi-based therapy, but a significant challenge is that clinical testing of these tumors frequently finds multiple VUS in BRCA1, BRCA2, and PALB2, for which further research is needed to determine the impact on HR and the responsiveness to PARPi-based therapy. The mechanism of PARPi resistance in breast cancer might be the focus of future studies [5].

3. Evaluate Value and Development Prospects, Application and Treatment

3.1 BRCA1-PALB2-BRCA2 Axis

The BRCA1-PALB2-BRCA2 axis is essential for preserving genomic integrity, blocking the development of cancer, and figuring out how cells respond to DNA DSB. Following DNA damage, HR repair is started when BRCA1 is drawn to the DSB, which encourages terminal resection. It also draws in PALB2 and its corresponding BRCA2 to load the central recombinase RAD51. Numerous PALB2 recruitment methods that are not dependent on BRCA1 have also been documented in recent years. When considered collectively, the existing findings show that independent of BRCA1 status, a variety of stratified, context-sensitive, and cooperative mechanisms recruited by PALB2 are essential to HR and treatment response. This research examines the significance of these BRCA1-dependent and independent pathways in DSB repair, cancer formation, and therapy. The BRCA1-independent PALB2 recruitment mechanism may offer a novel approach to treating BRCA1-mutated cancers as BRCA1-mutated cancer cells recover HR function, which PALB2 normally requires, and grow resistant to targeted treatments like PARP inhibitors.

Backup mechanisms may recruit PALB2 to sustain residual HR when BRCA1 is absent or when BRCA1 or PALB2 mutations interfere with their interactions. These secondary processes often involve the lack of 53BP1 at the break site and rely on its interaction with RNF168 and NCP acidic plaques. They may also depend on their MRG15 and DNA binding. Because these mechanisms can partially restore HR in BRCA1-mutated cancer cells and drive therapeutic resistance, they represent viable targets for therapeutic intervention that could further sensitize cancers with the previously mentioned parpi inefficient BRCA1 or PALB2 mutations or re-sensitize recurring BRCA1-mutated cancers. Platinum salts and similar DNA damage treatments. Furthermore, some HR-skilled or semi-skilled cancers may become responsive to the aforementioned medicines without experiencing undue toxicity due to the measured reduction of PALB2 recruitment [9].

3.2 PALB2 Variants and Cancer Susceptibility

It is now obvious that women who possess the pathogenic version of BRCA2 or PALB2 are at a comparable risk of developing breast cancer. Therefore, PALB2 has a place in breast cancer susceptibility genomic testing and is widely incorporated into breast cancer clinical genetics practice. The PALB2 protein product plays a key role in maintaining genome integrity. Here, the first functional assessment to be discussed is a missense variant of uncertain significance (VUS) of PALB2.

The role of PALB2 in OC (ovarian cancer), PC (pancreatic cancer), and BC, the prevalence of pathogenic variants in cancer cases, and its interaction with BRCA1 and BRCA2 suggest that PALB2 is also a major cancer susceptibility gene. While the significance of missense variations to cancer risk is yet unknown, the relevance of truncated variants that abolish PALB 2 function in cancer risk is well recognized. This ambiguity significantly hampers the clinical care of patients with these variations. In this literature, recent functional evaluations of missense variants in a large population with potential clinical implications are discussed. The function and carcinogenic potential of PALB2 depend on its last four amino acid residues, suggesting that the WD 40 domain plays a crucial role in the tumor suppressor function of PALB2. As a result, truncating variations over the whole PALB2 coding sequence impairs HR repair and raises the risk of cancer [10].

3.3 PD1/PD-L1 Checkpoint

On the surface of T cells, PD1 is a ubiquitous immunosuppressive component that is essential for reducing immune system activity and enhancing self-tolerance. Its ligand PD-L1 binds to PD1, inhibits the development of PD1-positive cells, promotes tumor immune escape, and is overexpressed on the surface of malignant tumor cells, which is the cause of treatment failure. In recent years, the PD1/PDL1 pathway has emerged as an important immune checkpoint and a useful target for cancer therapy.

Thus, knowing how PD1/PD-L1 functions is crucial for

both the prognosis of patients and combination treatment. In several malignancies, PD1/PD-L1 inhibitors have demonstrated therapeutic benefit. For instance, inhibiting PD1 or PD-L1 with certain antibodies boosts T-cell responses and mediates anticancer activity. Unfortunately, certain individuals are more likely to acquire medication resistance, which stems from their insensitivity to targeted inhibitors and leads to poor treatment outcomes [11].

3.4 Consequences of Disrupted BRCA1-PALB2 Interaction

The contact between BRCA1 and PALB2 facilitates HR and DNA DSB repair; interruption of this relationship contributes to the development of tumors. Its exact role in hepatocellular carcinoma (HCC) is still unclear. It has been demonstrated that animals with abnormal BRCA1-PALB2 interaction are more prone than wild-type mice to develop HCC. These mice‘s HCC tumors had significant T-lymphocyte infiltration and responded more favorably to therapy with an antibody targeting PD-1 cells. Mechanistically, DNA damage in HCC cells persists at high levels due to the breakdown of the BRCA1-PALB2 connection. Consequently, this triggers the cGAS-STING signal in the tumor microenvironment‘s malignant hepatocytes and M1 macrophages.

Through the STING-IRF3-STAT1 pathway, the activated cGAS-STING pathway stimulates PD-L1 expression, suppressing the immune system and encouraging the growth and metastasis of tumors. T lymphocyte infiltration in the tumor can result from M1 macrophages stimulated by the cGAS-STING pathway recruiting T cells via the STING-IRF3 pathway. When PD-1 antibody therapy restores the immune system to normal, invading T lymphocytes assault tumor cells with speed and efficiency. According to the previously mentioned results, T-cell infiltration and tumor immunosuppression in HCC are induced by persistent DNA damage caused by defects in the BRCA pathway through the cGAS-STING pathway. These findings offer new insights into the remodeling of the tumor immune microenvironment and may enhance the HCC response to PD-1 antibody therapy [12].

4. Conclusion

The purpose of this review is to synthesize existing studies and evaluate the development prospects and research value of PALB2. This review mainly summarizes the research progress of PALB2, including the mechanism of PALB2 in tumor cells, the therapeutic drugs targeting this mechanism, the susceptibility of breast cancer, and the treatment of PALB2 mutation. Based on the existing research, we can evaluate the development prospect and research value of PALB2, explore the unknown areas of PALB2 research, and provide cutting-edge references for future research. However, some studies on Breast cancer are not mentioned in this paper, such as breast cancer risk in families with mutations in PALB2. For future researchers, the therapeutic drug PARPi developed for PALB2, a DNA repair pathway, and its resistance mechanism of breast cancer remains to be explored in detail.

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