How latent viruses cause breast cancer: An explanation based on the microcompetition model

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ABSTRACT

Most breast cancer cases show a decrease in the concentration of the breast cancer type 1 susceptibility protein (BRCA1). However, only a small portion of these cases have a mutated *BRCA1* gene. Although many attempts have been made to identify the reason for the decrease in BRCA1 concentration in sporadic, non-heritable breast cancer cases, the cause is still unknown. In this review, we use the Microcompetition Model to explain how certain latent viruses, which are frequently detected in breast cancer tumors, can decrease the expression of the *BRCA1* gene and cause the development of breast tumors.

KEY WORDS: Breast cancer; microcompetition; GABP; p300/CBP; HPV; EBV; latent viruses; BRCA1; BRCA1 mutation

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INTRODUCTION

Most breast cancer cases show low concentrations of the breast cancer type 1 susceptibility protein (BRCA1) [1,2]. Surprisingly, only a small number of these patients have a mutated *BRCA1* gene [3]. Studies estimated that *BRCA1* and *BRCA2* mutations account for less than 5% of all breast cancer cases and less than 25% of familial breast cancer patients [4,5]. These low numbers are consistent across the globe. For instance, an American study showed that only 3.3% of the women diagnosed with breast cancer had a mutation in their *BRCA1* gene [6]. A British study showed that only 3% of the studied breast cancer patients had mutated *BRCA1/2* genes [7]. A genetic study, done on 204 North Indian breast cancer patients, showed that only 6 patients (2.9%) had a *BRCA1/2* mutation [8]. Similarly, low numbers have been shown in a Chinese study that identified a mutation in the *BRCA1/2* genes in only 7 out of 645 (1.1%) of the women with breast cancer [9].

Although the observed decrease in *BRCA1* gene expression in the majority of the non-heritable or sporadic breast cancer cases is of great interest to the scientific and medical community, the cause is still unknown [3]. In this paper, we use the Microcompetition Model to show how certain latent viruses, which are frequently detected in breast cancer, can decrease the expression of the *BRCA1* gene and cause the development of breast tumors.

BRCA1 PROTEIN FUNCTION

BRCA1 functions as a tumor suppressor protein through various mechanisms. One of the methods of BRCA1 to suppress tumor is by repairing double-stranded DNA breaks [1]. Another method is by regulating cell cycle checkpoints and centrosome duplication during the cell's replication. Also, BRCA1 has been known to interact with RNA polymerase II to modulate the transcription of several genes, including genes that are responsible for nucleotide excision repair [1]. These repair mechanisms show the importance of the BRCA1 protein in preventing genome instability.

BRCA1 AND BREAST CANCER

Breast cancer is the most common cancer among women, affecting one in ten women during their lifetime [1]. Many risk factors exist for breast cancer, with the most important one being a family history of the disease. Although this is the strongest risk factor, only a small proportion of breast cancer, 5–10%, has a hereditary cause. Even within this 5–10%, only 4–5% of breast cancer cases are due to the heritability of mutations of the high penetrance genes, such as *BRCA1* or *BRCA2* [1].

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Non-heritable or sporadic breast cancer accounts for 90–95% of breast cancer cases. In sporadic breast cancer, there is no mutation in the *BRCA1* gene. Yet, most cases show absent or reduced BRCA1 protein expression [1]. Thus, the question arises of what could be causing the decrease in BRCA1 protein levels in these breast cancer cases.

One possible cause of decreased *BRCA1* expression in breast cancer is hypermethylation of the *BRCA1* promoter. Methylation has been shown to play an important role in tumorigenesis, particularly in the promoter regions of tumor suppressor and DNA repair genes [10]. Although methylation is important in tumor formation, in a study on 193 primary breast carcinoma tissue samples only 13% were shown to have hypermethylation in the *BRCA1* promoter region [11]. The results of that study indicate that hypermethylation of the *BRCA1* promoter decreases the expression of the *BRCA1* gene in only a minority of cases [11].

BRCA1 GENE AND GA-BINDING PROTEIN (GABP) TRANSCRIPTION FACTOR

GABP is a transcription factor composed of two subunits, GABPα and GABPβ [12]. GABP binds the cis-regulatory element called the N-box. GABP is responsible for the regulation of a variety of cellular genes related to growth, respiration, and cell differentiation [12].

Several studies showed that GABP transactivates the *BRCA1* gene. A study published in 2000 by Atlas et al. [13] identified a 22 base-pair-long conserved region on the *BRCA1* promoter, called the EcoRI Bandshift (RIBS) element. The study showed that the GABPα/β transcription complex binds this element and transactivates the *BRCA1* gene [13]. Another study, published in 2007 by MacDonald et al. [14], discovered that an additional element, called the UP element, also binds the GABPα/β complex. They showed that "in isolation both the RIBS and UP elements act as GABPα/β dependent activator elements" [14].

Then, a study by Antonova and Mueller [15], published in 2008, showed that the stress hormone hydrocortisone (cortisol) decreased the expression of *BRCA1* gene in the nonmalignant mouse mammary cell line EPH4. Then, Antonova and Mueller showed that the effect of hydrocortisone is mediated through a decrease in the binding of GABP to the RIBS and UP regulatory elements.

In 2011, Thompson et al. [16] showed that a decrease in the activity of GABP caused a decrease in the expression of *BRCA1* in the SK-BR-3 cell line. First, they used western blot analysis to confirm that SK-BR-3 cells have low levels of BRCA1 protein. Next, they investigated the cause of the low BRCA1 protein levels by looking at the level of the *BRCA1* proximal promoter expression in SK-BR-3 cells compared to MCF-7 cells. Using ChIP (chromatin immunoprecipitation), Thompson et al. [16] showed that the *BRCA1* promoter is not occupied by RNA polymerase II in the SK-BR-3 cells, indicating a lack of transcription in this cell line. Then, they used a short hairpin RNA (shRNA) directed against the alpha subunit of GABP and observed a great reduction in the promoter activity in MCF-7 cells. Finally, they cotransfected vectors expressing GABP in SK-BR-3 cells and observed a large increase in the transcription of the promoter. These results indicate that there is a link between the low levels of GABP in the SK-BR-3 cell line, relative to MCF-7 and T-47D cell lines, and the low levels of *BRCA1* expression in this cell line [16].

In 2012, Ritter et al. showed that in breast cells, in the absence of hydrocortisone, the glucocorticoid receptor (GR) interacts with GABPβ at the RIBS element of the *BRCA1* promoter and activates the transcription of the *BRCA1* gene [12].

To summarize, these studies showed that GABP binds to the *BRCA1* promoter and transactivates the gene.

ONCOVIRUSES AND BREAST CANCER

Many studies observed a link between certain viruses and breast cancer in humans. One of these viruses is the mouse mammary tumor virus (MMTV), a beta retrovirus and a known cause of mammary tumors in mice [17]. MMTV-like retroviral particles were found in breast cancer biopsies, and MMTV proteins were detected in breast tumors using anti-MMTV antisera and MMTV reactive antibodies [17]. One study screened DNA samples of 80 Pakistani breast cancer patients for MMTV gene sequences and found that up to 26% of the samples were positive for the presence of the MMTV envelope and long terminal repeat (LTR) sequences [17]. These results indicate a possible association between breast cancer and MMTV.

Other studies found human papillomaviruses (HPV) and the Epstein-Barr virus (EBV) in breast tumors [18-21].

A systematic review and meta-analysis of 29 studies that included 2211 breast tissue samples from across the globe found that 23% of breast cancer patients had HPV DNA compared to 12.9% controls [20]. Also, the researchers pooled the data of nine case-control studies and calculated an odds ratio (OR) of 5.9, indicating that HPV positive women are 5.9 times more likely to have breast cancer [20]. Furthermore, a case-control study in Northern Iran, including 130 individuals, used polymerase chain reaction (PCR) analysis and detected HPV DNA in 25.9% of breast cancer tumors compared to 2.4% in non-cancer breast tissue, where 53% and 0% were the "high risk" HPV subtypes, such as HPV-16 and 18, in breast cancer tumors and non-cancer breast tissue, respectively [21].

The high prevalence of HPV-positive DNA in breast cancer patients suggests a possible link between HPV and breast cancer. In addition, it has been shown that the E6 and E7 oncoproteins of HPV-16 and 18 directly interact with and inactivate *BRCA1* in breast cancer cells [22].

Studies also found EBV in breast cancer patients. One European study, which included 196 breast cancer specimens, found EBV DNA in 33.2% of the cases using real-time quantitative PCR (real-time PCR). Interestingly, the EBV-positive breast cancers tended to be tumors with a more aggressive phenotype. These EBV-positive tumors were also more frequently estrogen receptor negative and had a higher histological grade [23]. A large meta-analysis of 24 studies, which included 1535 cases from all over the world, found an EBV infection in 29.3% of the patients with breast cancer. Also, patients with a positive EBV status showed a significant increase in breast malignancy risk (OR = 6.3) [24]. These studies provide evidence that EBV is statistically associated with an increased risk of breast cancer, especially of some specific types of breast cancer, such as lobular breast carcinoma [24].

Viruses have not only been implicated in breast cancer but they have also been linked to several other types of cancers. Most notably, HPV is known to be a necessary factor for the development of cervical cancers [25]. Increasing evidence linking EBV and colorectal cancer (CRC) has emerged. In a study of 90 CRC specimens, EBV proteins were detected in nearly a third of the tissues, compared to a detection rate of only 4% in adjacent non-cancerous control specimens [26]. Another study used PCR and tissue microarray (TMA) analysis to show that EBV was present in 36% of 102 CRC tissue samples, and EBV was also associated with a more aggressive type of CRC [27]. Recent research suggests that a coinfection of EBV and HPV may play an important role in the progression of cervical cancer [28]. The study found that EBV and high-risk HPV were copresent in 34% of the 44 cervical cancer tissues sampled, and the cancers with both infections were likely to be more aggressive [28].

VIRUSES REDUCE AVAILABLE GABP VIA MICROCOMPETITION

Many common viruses, which establish a latent infection, have a strong N-box in their promoters/enhancers. These viruses include EBV, cytomegalovirus (CMV), herpes simplex virus 1 (HSV-1), human immunodeficiency virus (HIV) and human T-cell lymphotropic virus (HTLV). The ICP4 promoter of HSV-1 contains an N-box sequence of CGGAAR as a tandem repeat. Hagmann et al. analyzed GABPα/β expression in mammalian cell lines and neural tissues. They observed a ternary complex consisting of a single GABPα/β heterodimer on a single CGGAAR site in the ICP4 promoter [29]. The CMV genome includes the major immediate early promoter (MIEP), which controls the immediate early 1 and 2 (IE1 and IE2) proteins [30]. This MIEP promoter contains an N-box [31]. Chan et al. reported that the human CMV major IE region contains an SEE (SRF/ETS element) at -538 to -523 which includes the presence of an ETS class GABP binding site [32].

After establishing a latent infection, the viral N-boxes bind and sequester the cellular GABP•p300/CBP transcription complex. Since the p300/CBP coactivator is limiting [33-37], the GABP•p300/CBP transcription complex is limiting. As a result, the sequestering of the complex by the viral promoter/enhancer decreases the binding of GABP•p300/CBP to cellular genes, specifically, to the *BRCA1* gene. Since the complex transactivates the *BRCA1* gene, the decrease in binding of the complex decreases the expression of the gene. The decrease in BRCA1 protein levels increases the infected cell proliferation, which leads to the development of breast cancer (Figure 1) [2]. This explanation is based on the Microcompetition Model, first described in the book "Microcompetition with Foreign DNA and the Origin of Chronic Disease", and subsequent papers [38,39].

Many of the viruses mentioned above are highly prevalent. For example, approximately 67% of the global population, or 3.7 billion people worldwide, are estimated to have HSV-1 [40]. The question is, why only a fraction of the people infected with these latent viruses develop breast cancer. The answer is, although the prevalence of these viruses is high, only a small portion of the infected individuals have a high enough copy number of the latent viruses. What increases the copy number? Many events can increase the copy number of the virus during the latent phase. For instance, aging [41], certain medications [42,43], surgery [44-46], chemotherapy [47], radiation [48], and stress [49] can decrease the efficiency of the immune system and increase the copy number of the latent virus. Zuo et al. discussed the connection between the copy number of latent EBV and its effect on oncogenicity [50]. According to Zuo et al. [50], "It has been noticed that EBV load in tumor tissues or blood is associated with the clinical progression and prognosis in both lymphoma and [nasopharyngeal carcinoma] NPC. Our result verifies this association. We also emphasize the importance to measure the level of gene expression or copy number in the virus study instead of only concerning 'with and without'."

CONCLUSION

The Microcompetition Model shows how an increase in the copy number of the latent virus that infects breast cancer tissues increases the sequestering of the limiting GABP•CBP p300 transcription complex. This disrupts the allocation of the transcription complex to cellular genes,

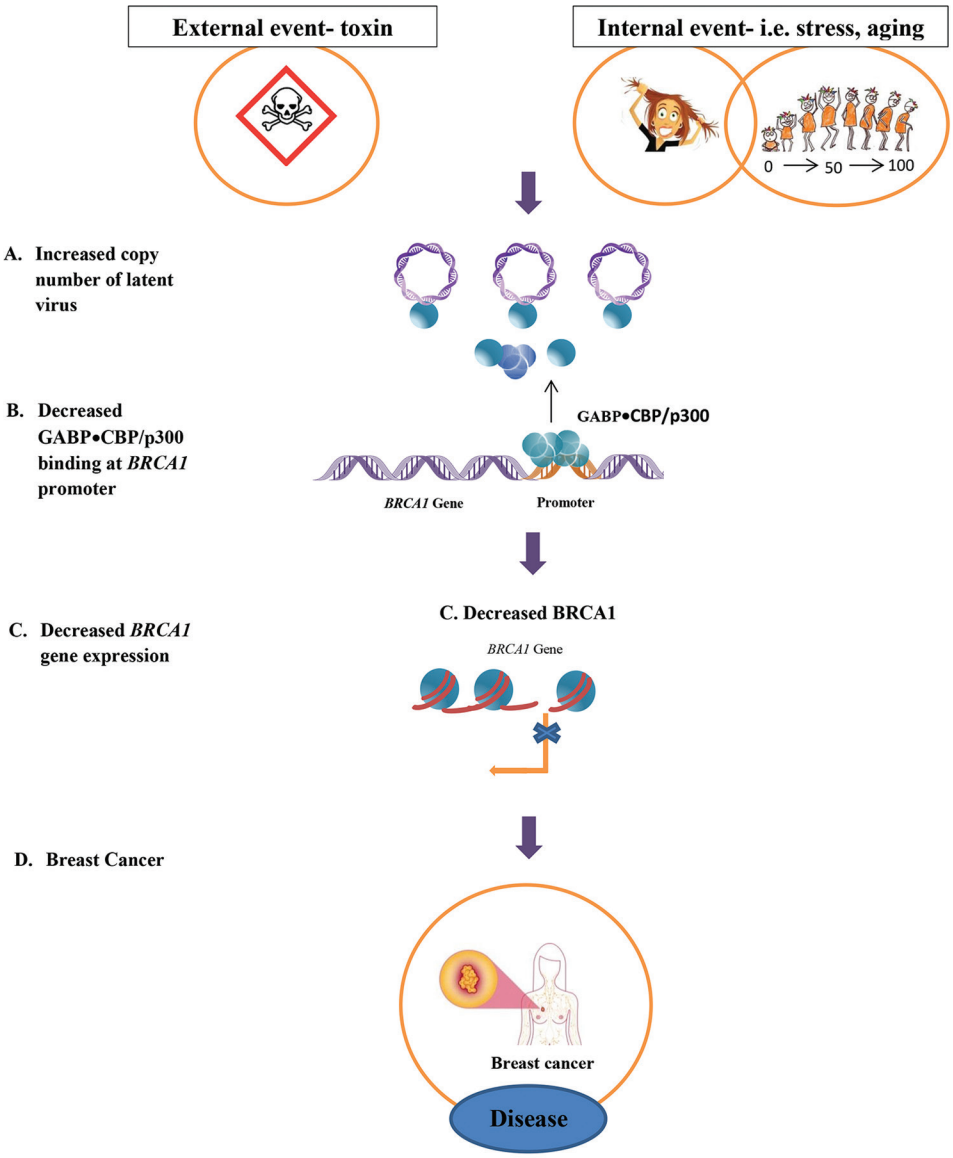

FIGURE 1. The process by which external and internal events lead to breast cancer by way of GABP dysregulation at the *BRCA1* promoter. External/internal events cause A) increased latent virus copy number; B) decreased GABP•CBP/p300 binding at *BRCA1* promoter; C) decreased *BRCA1* gene expression and *BRCA1* protein; D) development of breast cancer. GABP: GA-binding protein; *BRCA1*: Breast cancer type 1 susceptibility protein.

specifically the tumor suppressor *BRCA1*, which decreases the levels of the BRCA1 protein and causes the development of breast cancer.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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