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Review Article

A Mini Review of the Main Signaling Pathways and Genetic Predispositions Involved in Breast Carcinogenesis

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ABSTRACT

Breast cancer remains the most deadly cancer in women worldwide. It is a highly heterogeneous disease group, both biologically and molecularly. Mammary carcinogenesis is a multi-stage, complex and progressive process, involving the accumulation of several genetic and epigenetic abnormalities of interest to oncogenes and suppressor genes. Understanding the molecular pathogenesis of breast cancer helps to explain early and aggressive forms of the disease, to understand the mechanisms of therapeutic resistance and to search for new prognostic or theranostic markers. We reviewed 38 synthesis and review articles published between 2008 and 2022, dealing with breast carcinogenesis or focusing on a specific molecular pathway. Among them, we selected 29 articles to summarize the main molecular abnormalities involved in breast carcinogenesis, with particular emphasis on molecules considered in the literature as prognostic or theranostic markers.

Keywords: Breast carcinogenesis; Signaling pathways; Mechanism of action; Genetic predisposition

INTRODUCTION

Determining the origin of breast cancer cells has been elucidated in the light of understanding the normal cellular hierarchy. Comparison of the established molecular characteristics of normal breast epithelial subpopulations with those of different breast cancer subtypes (luminal A, luminal B, HER2-positive, claudin-low and basal-like), has provided an important framework for understanding the cellular origins of this cancer, both sporadic and hereditary. Cancer subtypes appear to aggregate along the hierarchy of normal cellular differentiation, starting with claudin-low undifferentiated tumors, followed by basal-like tumors, HER2 tumors and finally luminal A and B tumor subtypes. Molecularly, MSCs are similar to the low-claudin cancer subtype. The luminal progenitor subset has a molecular profile very similar to that of the tumor cells found in the basal-like subtype. The HER2, luminal A and luminal B subtypes reflect different cell types within the luminal lineage [1].

LITERATURE REVIEW

In the case of familial breast cancer with *BRCA1* mutation, the stem cells of these tumors were for a long time attributed to the degeneration of mammary stem cells residing in the basal layer and carrying the mutation. Today, it is clear that these tumours originate from aberrant luminal progenitor cells, which are more susceptible to malignant transformation than basal cells and produce predominantly basal-like tumours. This is mediated in part by the *BRCA1*-regulated SLUG transcription factor. This epithelial-mesenchymal transition factor is overexpressed in *BRCA1*-mutant tissues, blocking luminal cell differentiation and directing cells towards a basal-like fate.

Cell fate decisions along the mammary epithelial hierarchy may not be strictly unidirectional. Increasing evidence suggests that the dedifferentiation process can occur under non-physiological conditions. Luminal epithelial cells can convert to basal-like cells upon oncogenic stress *in vivo* and induction of a P53 protein mutation in luminal cells produces tumors with basal-like features. These data reflect the inherent plasticity of the mammary luminal compartment during carcinogenesis [2].

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DISCUSSION

Signaling pathways involved in breast cancer development and progression

Cancer is caused by genetic and epigenetic alterations that disrupt cell signaling pathways. In this way, the tumor cell manages to escape the control mechanisms of proliferation, survival and migration. The main alterations in signaling pathways found in breast cancer stem cells are as follows.

Signaling pathways involving estrogen receptors

The estrogen receptor signalling pathway is the most common pathway in breast cancer. It involves the ligand estrogens, which are transcription factors that activate or repress the expression of target genes upon receptor binding. There are two types of estrogen receptor: G protein-coupled membrane receptors and nuclear ERα, Erβ receptors, by far the most involved in carcinogenesis. Normal breast tissue frequently expresses Erβ-type nuclear receptors, which have an antiproliferative role. They are most often active as dimers. Although they share common structural features, homology in the ligand-binding domain does not exceed 55% to 59%, which explains the difference in the affinity of these two receptors for estrogen [3].

Direct genomic pathway: The direct genomic pathway is activated when estrogen (E2) binds to its receptor, resulting in a conformational change. This conformational change in estrogen receptors facilitates the association and dissociation of enzymatic co-regulators. These proteins are either histone acetyltransferases or histone methyltransferases or ATPase complexes such as SWI/SNF, which participate in chromatin remodeling. The receptor is then translocated into the nucleus and binds to specific DNA sequences, the EREs (Estrogen Responsive Elements) and activates the transcription of target genes *via* its domains. A transcriptional machinery containing RNA polymerase II and TBP (TATA binding protein) is recruited to initiate transcription. This step requires the intervention of pioneering factors known as co-activators, including the main ones SRC, GATA3 and the FOXA1 protein. These proteins, especially FOXA1, play an important role in ERα binding to chromatin and activate transcription of genes involved in cell cycle progression, notably CCND1, which encodes cyclin D1, an important activator of Cyclin-Dependent Kinases (CDKs) 4 and 6. In breast tumor lines, it has been shown that ERα binds to chromatin even in the absence of estrogen, but in a FOXA1-dependent manner. The feedback loop between ERα and cyclin D1 could explain the mechanism of resistance to anti-estrogen therapy and justifies the use of kinase 4 and 6 inhibitors in combination with hormone therapy [4].

There are several isoforms with paradoxical effects in the regulation of ERα signaling. ERa36, the isoform most frequently found in metastatic breast cancer not blocked by tamoxifen. On the contrary, once bound to the receptor, ERα 36 promotes disease progression. The ERα 36 isoform accounts for 70% of resistance to hormone therapy.

The indirect genomic pathway: A proportion of estrogen receptors activate the transcription of target genes by binding to other transcription factors already present on chromatin, without binding to ERE (Estrogen Responsive Elements) sites. This pathway is also known as the ERE-independent genomic pathway. In this case, the estrogen receptor acts as a transcriptional cofactor. There are several genes that are activated by Estrogen (E2) *via* the interaction of the nuclear estrogen receptor with transcription factors such as SP-1 (Specificity Protein 1), NF-κB (Nuclear Factor-κB), GATA1, STAT5 (Signal Transducer and Activator of Transcription 5) and AP-1 (Activating Protein 1). Genes activated in this way code for IGF-1 (Insulin Growth Factor 1), cyclin D1, C-Myc protein, Bcl2. Nuclear estrogen receptor activity can be modulated by signals other than estrogen. This is made possible by the ligand-independent transactivation domain. Phosphorylation of estrogen receptors on serine 118 residues enables ERα to interact with several target gene promoters to activate their transcription. This phosphorylation is induced either by type A and C protein kinases (PKA, PKC), cell cycle regulators, neurotransmitters or growth factors such as EGF (EpidermalGrowth Factor), IGF-1 (Insulin-like Growth Factor), TGFβ (Transforming Growth Factor) [5].

HER2 signaling pathways

HER2 is a proto-oncogene corresponding to a transmembrane protein encoded by the *ERBB2* gene, located on the long arm of chromosome 17. HER2 belongs to the epidermal growth factor receptor tyrosine kinase family, which comprises 4 subtypes (EGFR)/HER1, HER2, HER3 and HER4. It controls cell growth, survival, differentiation and migration.

The molecular structure of the EGFR family consists of a large extracellular region, a single-span Transmembrane (TM) domain, an intracellular Juxtamembrane (JM) region, a tyrosine kinase domain and a C-terminal regulatory region. HER3 is the only tyrosine kinase-deficient receptor and assumes no signal transduction. The ligand for HER2 has not yet been identified. HER2 undergoes ligand-independent heterodimerization with the other 3 members of the EGFR family. At high HER2 concentrations, HER2 may undergo homodimerization due to its constitutively active conformation. The formation of homodimers and heterodimers brings the intracellular domains closer together, resulting in asymmetric interaction of the intracellular kinase domain between the amino-terminal lobe of one tyrosine kinase and the carboxy-terminal lobe of the other and promoting autophosphorylation of the tyrosine kinase domains. Several signalling pathways are then activated, including PI3K/Akt, MAPK, PLC γ, ERK1/2, JAK/STAT. MAPK and PI3K/Akt are the two main pathways activated by the EGFR family, in particular the HER2 heterodimer. The activated MAPK pathway promotes transcription of related genes, subsequently enhancing cancer cell proliferation, migration, differentiation, angiogenesis and drug resistance. In the PI3K/Akt pathway, phosphorylated Akt acts on a range of transcription factors including MDM2, mTOR, p27, GSK3β, BAD, NF-κβ FKHR, enhancing proliferation, survival and suppressing apoptosis [6].

Notch signalling pathway

Since the cloning of the notch gene and identification of the structure of this receptor in the 1980's, numerous studies have confirmed the role of this pathway in embryogenesis. It is reactivated during the carcinogenesis of several solid tumors: Bronchial cancer, breast cancer, pancreatic cancer, melanoma and hematological malignancies.

Activation follows engagement of the receptors with their ligands, expressed on a cell adjacent to the one receiving the signal. Ligand-receptor interaction leads to cleavage of the receptor, allowing release of its Intracellular Domain (NICD) and translocation to the nucleus. It then associates with its transcriptional partner $RBPJ_K$, which is linked to the DNA of the promoter of the pathway's target genes (Figure 1). In the absence of NICD, $RBPJ_K$ is associated with transcriptional corepressors. Formation of the NICD-$RBPJ_K$ complex allows exclusion of these corepressors and recruitment of MAML (Master Mind-Like), which appears to serve as a scaffolding protein enabling formation of a transcriptional complex including other coactivators. This leads to chromatin opening and induction of transcription of target genes. Notch signaling activates several direct target genes involved in cell cycle regulation. These include cyclins A, B and D1. It also activates key oncogenic signaling pathways such as c-Myc, Ras and Wnt [7].

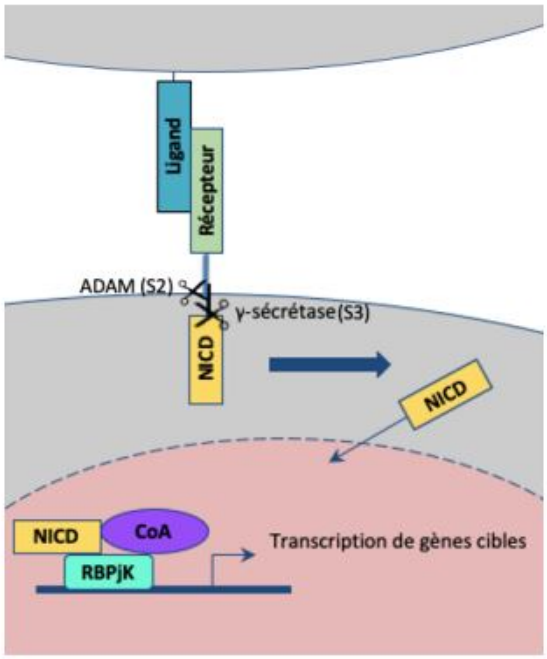

Figure 1: Notch signalling pathway: Ligand-receptor interaction leads to cleavage of the notch receptor, allowing release of its Intracellular Domain (NICD) and translocation to the nucleus. There, it associates with its DNA-bound transcriptional partner $RBPJ_K$ to induce transcription of target genes.

During breast carcinogenesis, the notch pathway inhibits tumor cell apoptosis through various signaling pathways:

- Activates Akt signaling NFB, PI3K and mTOR signaling. Akt is responsible for direct inhibition of p53 or the ASK1/JNK complex.
- Activation of the c-Myc gene, which also has anti-apoptotic activity.
- Upregulates survival by blocking apoptosis direct and indirect inhibition of caspases.
- Up-regulates anti-apoptotic members, notably Bcl-2 and Bcl-XL, while down-regulating pro-apoptotic members such as Bim and Noxa.
- Reduces the sensitivity of triple-negative TNBC breast cancer cells to TRAIL death receptor-induced apoptosis.
- Stimulates synthesis of cyclin-dependent kinase inhibitors p21 and p15, which also contribute to resistance to apoptosis.

In breast cancer tumorigenesis, deregulation of notch signaling is an early event; NICD accumulation is spotted in a wide range of subtypes, including ductal carcinoma *in situ* and epithelial hyperplasia. Notch-mediated metastasis is induced primarily *via* TGFβ activation. It also enables activation of key regulators of the epithelial-mesenchymal transition EMT, notably the transcriptional repressors slug and snail, which mediate loss of cell-cell contacts through inhibition of E-cadherin expression [8]. It is also involved in the upregulation of matrix-degrading enzymes, notably matrix metalloproteinases 2 and 9 and urokinase-type Plasminogen Activator (uPA). The mesenchymal markers ZEB1, β-catenin, N-cadherin and vimentin are upregulated by notch signaling. This pathway is also involved in invasion, upregulating matrix-degrading enzymes including matrix metalloproteinases 2 and 9 and urokinase-type Plasminogen Activator (uPA), as well as β1-integrin. Notch signaling is aberrantly activated in breast cancer. Overexpression of notch receptors and ligands has been correlated with a worse prognosis: Resistance to chemotherapy and early recurrence. The data suggest that deregulation of notch signaling is an early event in breast cancer tumorigenesis, with NICD accumulation in a wide range of subtypes, including ductal carcinoma in situ and epithelial hyperplasia. This implies that aberrant notch signaling plays a causal role in breast tumor initiation [9].

Aberrant notch activation may be secondary to mutations such as:

- Activating mutations in and around the PEST domain serving as a proteasomal degradation signal for the intracytoplasmic domain of the Notch1, 2 and 3 receptor.
- Mutations disrupting the NLR, nuclear signaling motif and heterodimerization domains.
- Notch4 overexpression.

Another cause of aberrant notch signaling frequently found in breast cancer is the loss of the numb protein. The numb protein has long been known for its inhibitory role in the notch signaling pathway. It opposes the notch pathway by inhibiting recycling to the plasma membrane. It induces stabilization of the notch ligand Delta-like 4 (Dll4) for degradation by lysosomes. NumB directly inhibits notch by inducing polyubiquitination and preventing the activated intracytoplasmic domain from reaching the nucleus.

However, a Chinese study published in 2019, which investigated the notch pathway on nerve cells cultured in appropriate media, showed that the numb protein enhances notch signaling in a physiological way. In fact, the intracytoplasmic domain of the type 1 notch receptor, N1ICD, is subject to various post-translational modifications including ubiquitination by the BARD1-BRCA1 complex facilitating degradation of the notch receptor by the proteasome. The team discovered a new protein, BAP1, an enzyme capable of stabilizing N1ICD through its deubiquitination role and its ability to inhibit BRCA1. Numb enhances notch signaling by regulating the ubiquitin activity of the BAP1 protein and facilitating its association with N1ICD (Figure 2) [10].

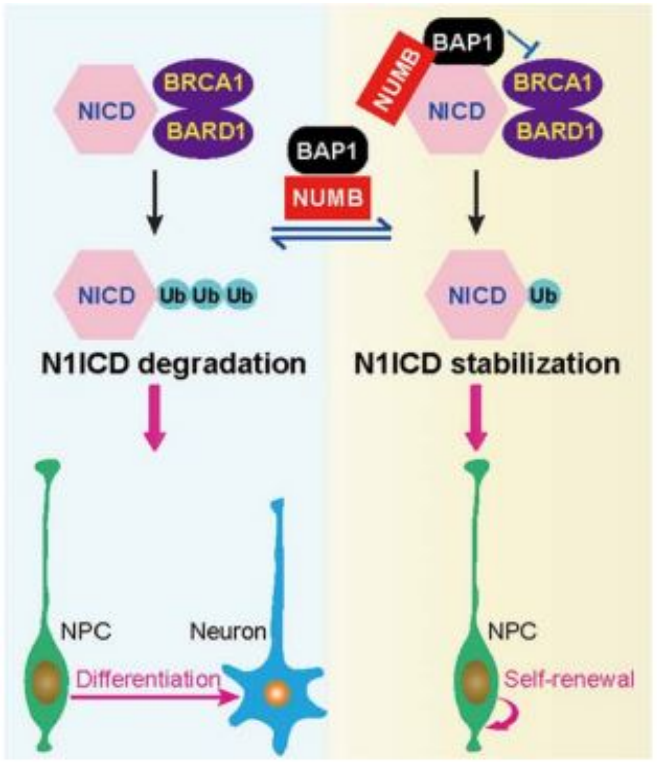

Figure 2: Schematic showing NumB's role in stabilizing N1ICD by associating with BAP1 to repress BRCA1/BARD1 ubiquitination activity in cortical neurons.

According to this experiment, the importance long attributed to the numb protein as a tumor suppressor in breast cancer is called into question. Explaining the relationship between loss of the numb protein and breast cancer will be the subject of further exploration in the future.

The Sonic Hedgehog signaling pathway: SHH

Since its discovery in 1980, numerous studies have established the importance of SHH signaling in human embryogenesis and organogenesis, as well as its involvement in hematopoiesis and carcinogenesis. Sonic Hedgehog (SHH) protein, synthesized by the cell, acts in an autocrine or paracrine manner on target cells. The SHH factor interacts with its receptor: The protein patch homolog, PTCH1, located on the primary cilium. The ligand-receptor interaction triggers internalization of this complex into endosomal vesicles. This internalization lifts the repression on the proteinmoothened SMO receptor, initially located in intracellular vesicles and repressed by PATCH1. SMO will travel to the primary cilium, where it will modulate the complex containing the Suppressor of Fused (SUFU) protein and the inactive form of a protein called Glioma-associated, GLI. Dissociation of the SUFU-GLI complex leads to degradation of the SUFU protein. In turn, the GLI factor undergoes transformations to acquire its active form. Activated GLI is translocated to the nucleus, where it specifically binds to sequences in the promoter regions of target genes, regulating their expression. These target genes include the GLI transcription factor itself, but also PTCH, cyclin D1 and products involved in the proliferation-differentiation balance. In the presence of SHH ligand, PTCH1 receptor repression of SMO protein is lifted. SMO therefore acts on the SUFU/GLI complex. SUFU is degraded, while GLI is activated and translocated to the nucleus. It acts as a transcription factor for several target genes, namely: *PTCH1, GLI1, FOXA2, BCL-2, BCL-Xl, MYC* and *CYCLIN D1* (Figure 3).

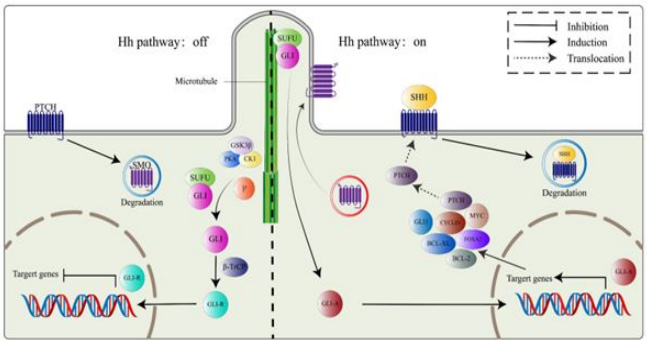

Figure 3: Diagram summarizing the mechanism of action of the Sonic Hedgehog SHH pathway: In the presence of the SHH ligand, the PTCH1 receptor's repression of the SMO protein is lifted. SMO then acts on the SUFU/GLI complex. SUFU is degraded, while GLI is activated and translocated to the nucleus. IL acts as a transcription factor for several target genes: *PTCH1, GLI1, FOXA2, BCL-2, BCL-Xl, MYC* and *CYCLIN D1*.

Activation of the HH signaling pathway in breast cancer has been associated with presentation at a younger age, larger tumor size, presence of lymph node metastasis, negative progesterone receptor status, high proliferation index and poor overall survival.

Mutations in *SHH*, *PTCH1* and *GLI1* are very rare in breast cancer. The pathological involvement of the SHH pathway is explained by several epigenetic mechanisms, the most important of which involves the transcription factor NF-κB. It has been shown that an NF-κB-binding element is normally present in a CpG island of the SHH promoter. This site becomes accessible to NF-κB binding after demethylation. Reduced CpG methylation of the SHH promoter has been linked to increased SHH expression.

The PI3K/AKT/mTOR signalling pathway

Activation of the PI3K/AKT/mTOR signaling pathway is frequently found in breast cancer. The PI3PCA mutation is by far the most frequent mechanism.

Indeed, PI3P is made up of a catalytic subunit p110 and a regulatory subunit p85. There are three isoforms of p110, namely p110a (encoded by PIK3CA), p110b and p110d. PI3K signaling is most often initiated either by the tyrosine kinase of the growth factor-activated receptor or by the RAS protein, following direct interaction with the p85 regulatory subunit, resulting in the recruitment of PI3K to the membrane. PI3P assumes the phosphorylation of Phosphatidylinositol-2-Phosphate (PIP2) to Phosphatidylinositol-3 Phosphate (PIP3). This activating phosphorylation is finely regulated by the phosphatase PTEN (Phosphatase and Tensinhomolog), whose role is to dephosphorylate PIP3 to PIP2. This activates other downstream mediators, AKT and mTOR, leading to increased growth, translation, cell cycle progression and anti-apoptotic action.

The four main somatic mutations in PIK3CA are gain-of-function mutations involving four amino acids: E542K or E545K (glutamic acid at position 542/545 is replaced by lysine) located in exon 9, and H1047R (hestidine at position 1047 is replaced by arginine) or H1047L (hestidine at position 1047 is replaced by leucine) located in exon 20. Mutations in exon 9 allow the p110α catalytic subunit to escape the inhibitory effect of p85. Mutations in exon 20 are located near the activation loop in the kinase domain. The mechanism by which they promote PI3K signaling is not well elucidated.

Since its discovery in 2004, several studies have examined the prognostic and predictive value of PIK3CA gene mutations. One study showed that exon9 mutant patients were associated with a higher recurrence rate than exon20 mutant patients. Experimental and clinical evidence suggests that resistance to hormone therapy is largely due to hyperactivation of the Phosphatidylinositol 3-Kinase (PI3K) pathway. Breast cancers resistant to anti-estrogens often remain sensitive to hormone therapy combined with PI3K inhibitors. In 2018, a analysis of 10329 patients with early-stage breast cancer found a significant association between early recurrence and PIK3CA mutations. In addition, PI3PCA mutations are predictive of poor response to anti-HER2 targeted therapy, with lower pCR (pathological Complete Response) rates than wild-type PI3PCA.

Hereditary predisposition to breast cancer

15%-20% of breast cancers run in families: Patients with breast cancer have one or more first or second-degree relatives with the disease. The high-risk genes that account for around 20% of familial risk are *BRCA1, BRCA2, TP53, STK11, CD1* and *PTEN*. It should be noted that more than 50% of the genetic inheritance of familial breast cancer remains uncertain.

***BRCA1/BRCA2* genes:** In 1994, the *BRCA1* gene was the first to be identified as a susceptibility gene for hereditary breast cancer. It is located on the long arm of chromosome 17 at 17q12-2. *BRCA2* is located on chromosome 13 and was cloned in 1995. Mutations in the *BRCA1/BRCA2* genes are autosomal dominant. In the physiological state, BRCA proteins share a similar, cooperative tumor-suppressing mechanism, repairing DNA damage in double-strand breaks *via* Homology-Directed Repair (HDR). Homologous recombination is based on faithful restoration of the damaged DNA sequence, using the homologous sequence of the undamaged chromosome as a template for repair. When this system is deficient, the relay is taken over by alternative DNA repair pathways that are much less genomically stable and considered mutagenic. This can lead to the activation of oncogenes or the inactivation of tumor suppressor genes. It should be noted that homologous recombination primarily involves the detection of alterations by ATM (Ataxia Telangiectasia Mutated) and ATR (Ataxia Telangiectasia and RAD3-related) proteins and the mediation of signals by CHEK2 Checkpoint Kinase 2) and BRCA1 itself.

PARPs are enzymes involved in DNA repair for single-strand breaks. These repair pathways, *via* BRCA proteins (double-strand breaks) and PARP enzymes (single-strand breaks), are complementary: If one pathway is deficient and the other is blocked, the result is cell death by apoptosis, a phenomenon known as synthetic lethality. Single-strand breaks not repaired by PARP inhibition are converted into double-strand breaks during replication, unrepaired by the homologous repair system in the case of *BRCA1* or *BRCA2* mutations, leading to cell cycle arrest and apoptosis: This is known as double blockade. PARP inhibitors were first proposed and developed in ovarian cancer, then in breast cancer, in cases of somatic or constitutional BRCA mutation and more recently more widely, with significant positive results.

The *PALB2* gene: The *PALB2* gene was discovered in 2009. This gene is responsible for Fonconi anemia in the case of a biallelic mutation. Located on the short bottom of chromosome 16 (16p12.2), it codes for a protein enabling interaction between BRCA1, BRCA2 and other proteins involved in the repair of double-strand breaks. Recently, several studies have shown that patients with mutations in the *PALB2* gene have as high a risk of developing breast cancer as patients with mutations in the *BRCA1* and *BRA2* genes. These patients develop breast cancer of predominantly triple-negative phenotype, with a significantly shorter life expectancy than BRCA1-mutated patients 25.

The *BRIP1* gene: The BRIP1 (BRCA1-interacting protein C-terminal helicase 1) gene, located on chromosome 17, 17q23, codes for a protein belonging to the helicase family. It interacts with numerous other proteins involved in regulating responses to double-strand DNA damage, notably BRCA1, as well as checkpoint signaling during DNA replication. In 2006, truncated heterozygous germline mutations were identified in hereditary breast cancer without *BRCA1* or *BRCA2* gene abnormalities. This type of mutation results in overexpression of a short protein unable to interact with the BRCA1 protein. Deletion of BRIP1 mRNA leads to cell-cycle arrest at G1/S phase and reduced expression of the cMYC, Ras GTPase and Rb genes.

CONCLUSION

However, high levels of BRIP1 mRNA expression are associated with decreased expression of metalloproteases, down-regulation of the *MGAT5* gene, involved in cell growth and motility and the chemokine CXCL12, the only ligand for CXCR4, involved in the formation of the pre-metastatic niche. This provides further evidence of the dual behaviour of the *BRIP1* gene and calls for further study to clarify its role in mammary carcinogenesis. Other genetic susceptibility genes for hereditary breast cancer include: *CDH1 STK11 P53, NF1, NBN, CHEK2, RAD51C, RAD51D*.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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None.

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