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Review

DNA repair and damage pathways in breast cancer development and therapy

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ABSTRACT

DNA damage/repair constitutes several key pathways working in concert to eliminate DNA lesions and maintain genome stability and integrity. Defective components in DNA damage and repair machinery are an underlying cause for the development and progression of different types of cancers, and breast cancer is no exception. In this paper, we will briefly explain the importance of DNA damage and repair, introduce the current classification schemes for breast cancer, and review the known defects in the repair machinery that have been associated with the risk of breast cancer. Finally, we discuss how the understanding of these pathways can help to design therapeutics for specific targeting of breast cancer tumors.

1. Introduction

Cells are continuously exposed to internal and external stressors such as reactive oxygen species (ROS) and ionizing radiations, which have the potential to induce repairable and unrepairable DNA damage [1]. The most common forms of DNA damage include base adducts, insertion/deletion, DNA mismatch, O6 alkyguanine formation, inter-strand DNA crosslinking, single-strand breaks (SSB) and double-strand breaks (DSBs) [2]. In response to such DNA damage, cells activate checkpoints to prevent progression through the cell cycle and decide to either activate the repair machinery for complete elimination of damages or proceed toward apoptosis, when the DNA lesions are too severe. Therefore, this response enables the cells to preserve the overall genome stability and integrity and continue replication and transcription [3]. This intricate signaling network is commonly referred to as the DNA damage response (DDR) and is responsible for monitoring genome health [4]. The importance of a timely and correct repair of various DNA damages is emphasized by the energy investment in cells clearance. It has been estimated that more than 10^4 ATP molecules must be hydrolyzed for repairing a single DSB [5]. The importance of the DDR and repair for genome maintenance and cancer prevention is further demonstrated by the investigation of genes encoding essential components of the DDR and particularly of DNA repair pathways, which are among the most frequently mutated genes in cancer [6,7]. In this review, we will discuss the importance of defects in DNA repair machinery and DDR in the development and progression of breast cancer. The classification schemes of breast cancers will be introduced in the beginning and then, the involvement of various DNA repair machinery pathways in breast cancer will be discussed.

2. Breast cancer classification

Breast cancer, as the second leading cause of cancer-related mortality, is a disease with varying histopathology, biology and response to systemic treatment [8]. Malignant transformations in the breast tissue starts from a heterozygous population of diseases of the breast, which subsequently turn into breast tumors [9]. These tumors can progress to become invasive and deadly, if left untreated [10]. Similar to a number of other cancer, breast cancer has been classified (and subclassified) to facilitate the treatment by type-specific therapeutic regimens. Recent genetic and clinical investigational efforts have classified breast cancer into several sub-types based on hormone and growth factor receptor status, the levels of biomarkers such as HER2-overexpression or Claudin downregulation, and more important genomic descriptions of cancer cell sub-types (Luminal A, Luminal B, Basal-like, HER2+) which have been the basis of modified models of breast cancer development [9].

Breast cancer can be simply classified into hereditary (familial) or sporadic categories. Inherited susceptibility to breast cancer gets back to a number of germline heterozygous mutations in genes such as BRCA1, BRCA2, CHEK 2, TP53 or PTEN or other tumor suppressor genes with a high penetrance susceptibility [11,12]. The other important characteristic of this subtype of breast cancer is the early occurrence in pre-menopausal years which is due to increased risk of

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loss of heterozygosity, and subsequently loss of gene expression of a DDR or cell cycle control effectors [11,13]. In contrast with the inherited breast cancer, which only accounts for 5–10% of cancer cases, the majority of breast cancers belong to sporadic subtype [12,14,15]. This subtype is developed by an increasing accumulation of unrepaired acquired mutations in somatic genes, with no germline mutations. Development of sporadic breast tumors is usually initiated by mutational activation of oncogenes, along with non-mutational inactivation of tumor suppressor genes. This is followed by four or five independent mutations in other genes, and the order of these mutations is not very important in development of tumor [11,16].

A second classification of breast cancer is based on hormone receptor positivity. The receptors underlying this system of classification include estrogen and progesterone receptors and epidermal growth factor receptor (EGFR). As such, breast tumors can be classified into three different categories: hormone receptor positive; hormone receptor negative with HER2 over-expression, and "triple negative" or TNBCs, in which none of these receptors are overexpressed [14,17]. Typically, hormone receptor positive cancers are responsive to selective estrogen receptor modulators (SERMs) including e.g. Raloxifene and Tamoxifen or selective estrogen receptor down-regulators (SERDs) such as Fulvestrant, which is employed to decrease cancer cell growth rate [18,19]. Unfortunately hormone receptive positive breast cancers can evolve hormone insensitivity and subsequently develop resistance to SERMs and SERDs, upon recurrence [20]. In hormone receptor negative breast cancers with HER-2 over-expression, treatment courses normally consist of Trastuzumab or other HER-2 antagonists. TNBCs, as the breast cancer subtype with the poorest survival, are both hormone receptor insensitive and HER-2 negative. Although TNBCs usually respond to traditional chemotherapeutic agents, they often relapse and metastasize more aggressively [14,21].

A third classification system for pre-malignant and malignant breast lesions and tumors, which has been suggested by Allred et al. [22], is based upon microarray analysis and associated cell-type of origin. In this type of classification, cancers are grouped as Luminal A, Luminal B, Basal or ErbB2-over-expressing. Since the mammary epithelium is composed of multiple cell-types, the purpose of this classification scheme is the prediction of the therapy outcome by predicting the behavior of the cancer cell-type of origin in association with breast cancer development. Some important characteristics of the four subgroup of this classification are summarized in Table 1. Accumulating epidemiological studies have yet to be performed to determine the efficacy of these breast cancer stratifications in creating predictive models in treatment strategies and outcomes.

3. DNA repair machinery in breast cancer

3.1. Homologous recombination (HR) pathway

Homologous recombination (HR) is the major and a high fidelity repair mechanism for reparation of DSB lesions, which are the most dangerous and threatening genotoxic damages with high potential in producing chromosomal rearrangement and cell death [23]. HR eliminates DSB lesions by using the sister chromatid as an undamaged homologous template, and repairing damage in an error-free way [24]. At the damaged location, initially, the damaged DNA ends are recognized, followed by the nucleolytic processing of the damaged DNA to create a single-stranded 3′ overhang at each broken end. Then, the homologous template is searched and a "homologous joint molecule" is formed between the template and the 3′ overhang on the broken ends. At the end, both 3′ ends are extended by the synthesis of strands complementary to the homologous templates, and the recombination intermediate is dissociated. Some key proteins involved in HR process include RAD51 – which recognizes the single-stranded DNA produced early in the process, Rad52, Rad54, replication protein A (RPA), several Rad51-related proteins (Rad51B, Rad51C, Rad51D, X-ray repair cross complementing proteins-2 [XRCC2], and -3 [XRCC3]), as well as the breast cancer susceptibility genes (BRCA1, and BRCA2), which function as accessory proteins for Rad51 at several steps [25]. Several studies have shown that various proteins involved in HR are deregulated in breast cancer. For example, Rad51 and its related proteins Rad51C and Rad51L1, have been found to be overexpressed and deregulated in bilateral breast cancer, invasive ductal breast cancer, invasive breast cancer, and TNBC [26–30]. Mutations in Rad51 result in the reduced mitotic and meiotic recombination, defect in the repair of DSB lesions, and hypersensitivity to ionizing radiation. Therefore, it has been postulated that the dysfunction of this pathway may be a common event in the majority of hereditary breast cancers. In other word, alternations in the Rad21 gene is possibly involved in the development of hereditary breast cancer [30]. As a result, it might be appropriate to consider Rad51 as the third breast cancer susceptibility gene, similar to BRCA1, which is associated with an increase in the risk of early-onset breast cancer and BRCA2, which is related to increased risk of breast cancer in both men and women [31]. The exact role of BRCA1 in HR includes 5′ to 3′ resection of DSBs to form 3′ ssDNA overhangs and loading RAD51 onto the ssDNA. In this regard, the main role of BRCA2 would be to load Rad51 onto ssDNA [32]. A high incidence of heterozygosity(LOH) loss in the chromosomal region of Rad51, Rad52, Rad54, BRCA1 and BRCA2 has been documented in sporadic breast cancer [33]. Identification of chromosomal regions with

Table 1
The major characteristics of molecular subtype of breast cancer.

Subtypes of breast cancer	Gene expression profile	Clinical features	Response to chemotherapy	Targeted therapies	Grade	Outcome	Prevalence
Luminal A	[ER + |PR +] HER2 − KI67 −	Luminal B tend to be higher histological grade than luminal A	Lower	Hormone therapies	1/2	Good	23.7%
Luminal B	[ER + |PR +] HER2 − KI67 +	Some overexpress HER2 (luminal B)	Intermediate	Hormone therapies	2/3	Intermediate Poor	38.8% 14%
Basal type	[ER − PR −] HER2 − , basal marker +	Most ER/PR/HER2 negative ('triple negative') BRCA1 dysfunction (germline, sporadic) Particularly common in African-American women	Higher	Currently investigational	3	Poor	12.3%
ErbB2-overexpressing	[ER − PR −] HER2 +	More likely to be high grade and node positive	Higher	HER-2-targeted therapies	2/3	Poor	11.2%

allelic loss is a useful strategy for screening genes contributing to the pathogenesis of human malignancies, and offers the opportunity to evaluate novel parameters with potential high specificity and sensitivity for use as prognostic factors. It has been suggested that the genes of such regions may have significant impacts on the specific pathological phenotypes of breast cancers, because they might have common or synergistic functions in the regulation and progression of breast tumor cells, participating in these processes through the HR repair system and normal chromosomal recombination mechanisms [33].

PALB2 (partner and localizer of BRCA2) encodes a recently discovered protein that interacts with BRCA2, and as the name suggests, is implicated in the nuclear localization and stability of BRCA2. PALB2 assists BRCA2 in HR and DSB repair. It has been shown that PALB2 binds DNA, particularly D-loop structures, and directly interacts with RAD51 recombinase to trigger strand invasion, as a key step in HR process [34]. Studies have identified monoallelic truncating PALB2 mutations in familial breast cancer, which increase the risk of breast cancer by a factor of 2.3 fold. The results implicate PALB2 as a breast cancer susceptibility gene and highlight the relationship of DNA repair pathways with predisposition to breast cancer [35]. The dysregulation of a number of other proteins has also been shown to be associated with the pathogenesis of breast cancer. For example, survivin, which is frequently overexpressed in breast cancers, is as a constitutive actor of HR. Survivin silencing has been shown to result in DNA DSBs in breast cancer cells and reduction in HR. Survivin depletion decreases the transcription of a group of genes implicated in HR, and reduces RAD51 protein expression [36]. Polycomb group protein EZH2, is yet another example, which is a transcriptional repressor involved in regulating cellular memory and has been associated with aggressive and metastatic breast cancer. EZH2 has been shown to downregulate five RAD51 paralog proteins RAD51B/RAD51L1, RAD51C/RAD51L2, RAD51D/RAD51L3, XRCC2, and XRCC3, which involved in HR repair of DNA DSBs. EZH2 overexpression was also shown to compromise the formation of RAD51 repair foci at the sites of DNA damage. Therefore, it has been suggested that EZH2 may be involved in breast tumorigenesis by specifically down-regulating RAD51-like proteins and thus impairing HR repair [37]. Another study found that HORMAD1 drives the allelic imbalance phenotype in TNBC by inhibition of RAD51-dependent HR. HORMAD1 is a cancer testis antigen which promotes nonconservative recombination in meiosis. In other words, HORMAD1 overexpression suppresses RAD51-dependent HR and engages other DNA repair pathways [38].

Multiple genetic polymorphisms, especially single nucleotide polymorphisms (SNPs), have been recognized in genes involved in HR pathway (e.g., XRCC1, XRCC2, XRCC3, NBS1 and RAD51) that may confer genetic predisposition to disease and also affect the repair capacity of breast cancer patients to different extents [39–45].

3.2. Non-homologous end joining (NHEJ) pathway

Non-homologous end joining (NHEJ) repair machinery is another important pathway for eliminating DSBs [46]. In contrast to HR, NHEJ does not require a homologous chromatid template to couple to the ssDNA ends formed in DSBs [47]. Under normal circumstances, NHEJ plays a key role in the repairing of the DSBs generated during V(D)J immunoglobulin recombination in immune cells, as well as T-cell receptor gene rearrangements. Since there is no need for a homologous strand, NHEJ repairs DSBs by involvement of fewer proteins. NHEJ pathway is induced by the recognition of the DSB and subsequent high affinity binding of the Ku heterodimer (Ku70 and Ku86) to DNA ends. Ku heterodimer then provides a scaffold to recruit NHEJ factors including DNA-dependent protein kinase (DNA-PKcs), XRCC4, XRC-C4-like factor (XLF), DNA Ligase IV, and Aprataxin-and-PNK-like factor (APLF) to the damage site. As NHEJ components simply bind to the damaged DNA ends together and no homology is required, it is more error prone and may result in chromosomal damage [48]. Several studies have previously shown that DSB repair mechanisms are significantly involved in breast tumorigenesis. For example in the study by Bau et al. [49], individual differences in DNA end-joining (EJ) capacity for repairing DSB has been implicated a risk factor predisposing women to breast cancer. This was manifested by the evidence that peripheral blood mononuclear cells (PBMCs) from patients with breast cancer possessed reduced levels of in vivo and in vitro EJ capacities in comparison with those from healthy women. The EJ capacity assay used in the above study produced an estimation of the global NHEJ capacity and was not focused on a particular enzymatic step. The findings of the study support the notion that NHEJ might play a key role in the susceptibility to breast cancer.

Various studies have focused on the genotypic polymorphisms of the genes participating in NHEJ, including Ku70, Ku80, DNA-PKcs, XRCC4 and Ligase IV, as well as their association with increased breast cancer risk [50–53]. All the studies found that key genes involved in NHEJ have implications in tumor cancer development. In other word, they precisely investigated individual susceptibility genes and provided a better insight into breast tumorigenesis triggered by estrogen exposure and how this is altered by DNA repair capacity. The association of enhanced breast cancer risk with the cooperative impact of SNPs in NHEJ genes, provides evidence for the tumorigenic role of NHEJ pathway. However, to prove the existence of a link between NHEJ and breast cancer, the link between malfunctioning NHEJ genes and hereditary breast cancer must be identified. Recently, it was shown that BRCA1-deficiency in mouse embryonic fibroblasts can significantly decrease NHEJ activity. Bau et al. [54] reported that EJ capacity was significantly reduced in MCF-7 cells upon BRCA1 knockdown by small interfering RNA. These results indicate that BRCA1, a well-known breast cancer susceptibility gene, has a role in NHEJ. Furthermore, they also support the fact that NHEJ is involved in breast cancer development.

3.3. Base excision repair (BER) pathway

Base excision repair (BER) is a repair machinery responsible for repairing oxidized, alkylated, and deaminated bases, which do not significantly destroy the helical structure of DNA [55]. BER is generally initiated by a set of damage-specific DNA glycosylases that remove the damaged base by cleaving the N-glycosidic bond, producing an AP or a basic site [56]. AP sites are generally repaired by apurinc/apyrmidinic endonuclease 1 (APE1), the second enzyme in the BER machinery and the missing nucleotide is inserted by DNA polymerase-β. Sealing of the nick is performed by DNA ligase. Other proteins involved in BER include XRCC1 – which is a scaffold for the enzymatic reactions, polynucleotide kinase 3′-phosphatase (PNKP); tyrosyl-DNA phosphodiesterase 1 (Tdp1) and aprataxin (APTX) – which are end-processing enzymes-, and DNA polymerase β [56]. Epidemiologic studies have reported the involvement of various SNPs in both BER core protein and DNA glycosylase genes in susceptibility to multiple malignancies including breast cancer. Efficiency of BER is believed to be a key determinant of breast cancer risk, as BER functions in the repair of oxidative DNA damages induced by free radicals generated during cellular estrogen metabolism or by exogenous exposure to ionizing radiation and chemicals. Several studies have associated polymorphisms in BER genes including XRCC1, OGG1, and APEX1, with breast carcinogenesis [56–60]. However, in the case of XRCC1, the results are very controversial. Some researchers have showed a link between the XRCC1 R194W allele and breast cancer [43,61–63], while others have reported no such association [13,64–67], and one group found a decreased breast cancer risk associated with this allele [68]. Similarly, XRCC1 R280H has been associated with breast cancer in one report [13], but not in others [63,13]. Generally, XRCC1 R399Q has not been associated with breast cancer risk, though one group reported a positive association [63], and another group found a correlation in African-American women, but not in Caucasian women [64].

Gene/ protein	Function in DDR	Alternation in breast cancer	Prognosis	Other comments	Ref
ATM	Is activated by autophosphorylation on serine residues upon DNA damage and phosphorylates several target proteins	Higher levels in ER negative breast cancers	High ATM protein is associated with Recurrence in breast cancer	ERa downregulates miR-18a andmiR-106a to downregulate ATM protein expression, and miR-18a directly binds to the ATM-30-UTR	[91–93]
ATR	Is involved in sensing DNA damage and activating the DNA damage checkpoint, leading to cell cycle arrest.	N/A	N/A	ATR is functionally downregulated by Era transactivated AKT signaling, which suppresses the DNA damage induced association between ATR:TOPBP1	[94,95]
DNA-Pcs	Is induced upon detection of DSBs, phosphorylates itself and other substrates	N/A	N/A	The DNA-PK: ERa protein complex increases Era phosphorylation and reduces ERa turnover. The DNA-PK: Era complex binds to ERa responsive gene promoters, an effect that is not dependent on DNA damage	[96]
γ-H2AX	Histone H2A variant, Following DNA damage, extensively phosphorylated by ATM and ATR	Higher levels in triple-negative breast cancer	N/A	There is a significant association between elevated levels of γ-H2AX in patients with BMI $<$ 25	[97]
BRCA1	Is part of a complex that repairs DSBs in DNA and interacts with the DNA mismatch repair protein MSH2	Low BRCA1/ BRCA1(because of mutation, methylation, or low mRNA) is associated with ER negative breast cancers	Oophorectomy (resulting in decreased estrogen levels) is protective against breast cancer in BRCA1 familial breast cancers	TheBRCA1: Oct1complexdirectlybindsthe ESR1 promoter to drive Era transcription. BRCA1suppressesERa-mediated transcription through direct binding and co-activators ERa promotesBRCA1 transcription via an ERa/ p300transcriptional complex	[98–104]
BRCA2	Binds to the single strand DNA and directly interacts with the recombinase RAD51	Higher levels in ER negative breast cancers	High BRCA2 predicts poor disease-free survival	BRCA2 is upregulated by estrogen treatment, possibly as an indirect target rather than via Era	[104]
CHK1	Is required for checkpoint-mediated cell cycle arrest and activation of DNA repair	High expression levels of CHK1 in ER negative and triple negative breast cancer	CHK1 not prognostic for outcome metastasis in breast cancer	CHK1 is phosphorylated via Era transactivated AKT signaling, which suppresses theDNAdamageinducedCLASPIN:CHK1interaction	[94,97,105]
CHEK2	Regulates cell division	Breast cancers with CHEK2 mutation tend to be ERα positive	In ER positive breast cancers, CHEK2 mutation is associated with increased risk of death and second breast cancers, but not in ER negative cancers	N/A	[106,107]
Cyclin E	Binds to G1 phase Cdk2, which is required for the transition from G1 to S phase of the cell cycle that determines initiation of DNA duplication	High expression levels in inflammatory breast cancer	Cytoplasmic cyclin E was highly correlated with poor prognosis	CDK2-targeted combinations may be viable strategies in inflammatory breast cancer	[108]
c-ABL	Following damage detection, interacts with DNA-PKcs, Rad51 and Rad52, and BRCA1	There is no correlation between expression of c-ABL and ERa	Co-expression of c-ABL and Era is associated with advanced tumor stage and lymph node	c-ABL enhances estrogen receptor Era transcriptional activity through its Era stabilization by phosphorylation	[109,110]

			involvement		
FANCD2	Is monoubiquitinated in response to DNA damage, resulting in its localization to nuclear foci with BRCA1 and BRCA2	Higher levels in ER negative breast cancers	N/A	N/A	[111]
MDM2	Is an important negative regulator of p53	High MDM2 proteinis correlated with ER positive breast cancers	Low MDM2 protein is correlated with high nuclear grade and lymph node involvement	MDM2 interacts with ERa in aternary complex with p53. MDM2 positively regulates ERa transcriptional activity, but downregulates overall activity through Era monoubiquitination	[112–115]
P53	The guardian of the genome, because of its role in conserving stability by preventing genome mutation	p53 is generally wild-type and expressed in ER positive breast cancer	TP53 mutation or p53 mutated gene signature is prognostic for poor disease-free survival	ERa upregulates TP53 and stabilizes p53. Generally suppresses p53 transcriptional function. p53 upregulates ESR1 Modulates ERa induced transcription	[116–124]
PCNA	Is a cofactor of DNA polymerase delta	N/A	N/A	PCNA interacts directly with ERa to modulate its transcriptional function in normally proliferating cells	[125]
RAD17	Binds to chromatin prior to DNA damage and is phosphorylated by ATR after the damage, recruits the RAD1-RAD9-HUS1 checkpoint	Higher levels in breast cancer; high RAD17 protein correlated with ER negative; RAD17 sometimes lost in ER negative, but due to loss of 5q11 locus	High RAD17 mRNA prognostic of increased lymph node metastasis	RAD17 mRNA isupregulatedbyestrogenin anERa dependent manner	[126,127]

3.4. Nucleotide excision repair (NER) pathway

Helix-distorting lesions induced by platinum-based chemotherapeutics and particularly UV irradiation are repaired by NER [69]. NER is divided into two subpathways including global-genome NER (GG-NER), which occurs by recruiting RPA/XPA and XPC/RAD23B complexes to the damaged location, and transcription-coupled-NER (TC-NER), which is initiated by a complex of XPG and CSB and their recruitment to sites of RNA polymerase stalling. The process of GG-NER and TC-NER follows by recruitment of transcription factor II H (TFIIH). Then, the helicases XPB and XPD unwind a 30 nucleotide fragment around the lesion. The complexes XPF/ERCC1 and XPG then exhibit nuclease activity at the 5′ and 3′ ends of the damaged site, respectively. Finally, the damaged site is restored by complexes consisting of DNA-Polδ/ε, RFC, and PCNA or, DNA-Polδ/ε and XRCC1 [70]. NER deficiency and its potential in the etiology of breast cancer was investigated in a study by Latimer et al. [71], who showed a significant deficiency of NER capacity in stage I breast tumors relative to normal disease-free epithelial tissue, as tested by the functional unscheduled DNA synthesis assay. In tumor samples, the expression of 20 genes in NER pathway was decreased compared to normal tissue. These results were also further validated at the protein level for five NER gene products. As such, the authors concluded that NER deficiency might have a key role in the etiology of sporadic breast cancer. Additionally, it was also suggested that polymorphisms in particular genes in the NER pathway, such as XPD, ERCC2, and ERCC5, may increase the risk of breast cancer in subjects [57,58,72–78].

3.5. DNA mismatch repair (MMR) pathway

Yet another DNA repair machinery is mismatch repair (MMR) which recognizes and eliminates bases mis-incorporated during replication, recombination, or repairing other DNA damages. MMR also takes care of erroneous bases ignored during DNA polymerase proofreading [79]. These types of DNA damage are either detected by the MutSa complex, which recognizes small mismatches, generated by Msh2/Msh6, or the MutSb complex, which recognizes large mismatches and insertion loops, generated by Msh2/Msh3. The MutLa complex is formed by MLH1 and PMS2 and links MutS to the PCNA/RFC complex. Following binding, the exonuclease Exo1 is recruited to the MutS/MutLa complex and the damage gap is removed by DNA Polδ [80]. Similar to other DNA repair pathways, variance in MMR genes may predixpose individuals to breast cancer. Commonly occurring SNPs in MMR genes have also been reported to contribute to breast cancer risk due to their pivotal role in maintaining genome stability and integrity [81,82]. The phenotype of microsatellite instability (MSI), which is defined as the instability in sequence motifs of dinucleotide repeats, is observed in the defects of MMR pathway. Recent studies have implicated MSI and MMR deficiency in breast cancer [83]. In fact, MSI and/or losses of heterozygosity (LOH) have been noted in 83% of skin samples obtained from patients with invasive ductal breast carcinoma [84]. In addition, genetic alterations in key MMR genes, hMLH1 and hMSH2, have been shown to be related with sporadic breast cancers displaying MSI [81,85].

4. DNA damage response in breast cancer

Any destructive damages in the DNA structure trigger phosphorylation-driven signaling cascades or so called, DDR [86]. In fact, DDR maintains genome stability and integrity through three main steps with three key players: sensors, which detect damages; transducers, which convey the damage signal; and effectors, which repair the damages [86]. Sensing of a DNA lesion leads to cell cycle arrest and an attempt to repair such damages; otherwise, in cases of irreparable damage, cell proceeds toward apoptosis. The DDR signaling takes place through three members of the phosphoinositide 3-kinases (PI3K)-like protein kinases family including, ATM, ATR and DNA-PKcs [87]. While ATM is recruited to damage site following detection of DSBs, ATR is recruited after sensing of SSBs. On the other hand, DNA-PKcs is induced by detection of DSBs, autophosphorylates and mediates DSB repair via

NHEJ [87]. Signals from transducers activate and phosphorylate downstream effectors including BRCA1, p53-binding protein 1 (53BP1) and CHK1, and spread DDR signaling away from the site of lesions to the effectors such as p53 and cell division cycle 25 (CDC25) phosphatases [88]. Subsequently, p53 takes the cell fate decision, i.e. to either undergo cell-cycle arrest and DNA repair or proceed toward apoptosis [89]. As mentioned before, about 5–10% of breast cancer cases are part of hereditary cancer susceptibility syndrome resulting from mutations, alternation in expression, amplification, and methylation in high penetrance susceptibility genes, which often contribute to DDR or cell cycle regulation. In spite of huge efforts in the identification of breast cancer susceptibility genes, only 30–50% of hereditary breast cancer cases can be explained by alternation in particular genes [90]. This might be explained by a mixed impact of unidentified genes, multiple low-penetrant genes, and novel high-penetrant genes resulting in an increased risk of breast cancer. Therefore, genes and proteins implicated in DDR and in the maintenance of genome stability and integrity are appropriate candidates as controlled risk factors and as probable susceptibility genes for familial and sporadic breast cancers [90]. Table 1 explains the functions of important DDR genes including ATR, ATM, DNA-Pcs, BRCA1/2, and p53 and the associations of these altered genes with pathogenesis of breast cancer.

5. Development of new treatment modalities by targeting DNA repair defects in breast cancer

Surgery, radiation, hormonal- and chemo-therapy are the most important therapeutic strategies for patients with breast cancer [128]. Usually, a combination of these modalities is employed to prevent locoregional recurrence or metastasis. Intrinsic DDR impairment of tumor cells, and following impairment in the induction of apoptosis necessitate the use of radiation and chemotherapeutics in the therapy. The high rate of proliferation in cancer cells, in comparison with normal cells, is an essential characteristic that makes them vulnerable to DNA damage exposure occurring during S phase of the cell cycle. Inhibition of DDR induction, which is mediated by most chemotherapeutic agents might increase the efficacy of radiotherapy and DNA damaging agents. Khongkow et al. [129], have recently studied the involvement of FOXM1 in paclitaxel drug action and resistance in breast cancer. The forkhead transcription factor FOXM1 has an important role in DDR, and its overexpression is associated with genotoxic drug resistance in breast cancer [130]. They showed that FOXM1 deletion suppresses cell viability and sensitizes breast cancer cells to paclitaxel-induced senescence. FOXM1 was further shown to regulate the expression of the microtubulin-associated kinesin KIF20A at the transcriptional level. Finally, the authors suggested paclitaxel targets the FOXM1-KIF20A axis, which induces the formation of abnormal mitotic spindle and mitotic catastrophe. Deregulation of FOXM1 and KIF20A expression may thus lead to paclitaxel resistance. In other study by Asakawa et al. [131], sixty primary breast invasive ductal carcinoma patients received neoadjuvant chemotherapy with cyclophosphamide and epirubicin, two drugs that induce DSBs, followed by treatment with docetaxel. The authors made a correlation between focus formation of BRCA-1, RAD51, and γH2AX before treatment and RAD51 focus formation following treatment with mean tumor volume reduction and tumor response rate. These repair proteins dramatically responded to cyclophosphamide and epirubicin treatment. This study is of significant importance, since understanding and measuring DDR competence can be used for prediction of tumor response to chemotherapeutics in an attempt to exclude non-responder patients. Targeting specific DDR proteins by small molecules is another important strategy to develop treatment modalities. A number of molecules targeting Chk1 and Chk2 for example, are currently undergoing clinical trials [90]. Therefore, understanding the DNA damage and repair pathway is the key to understanding breast cancer tumorigenesis and designing novel superior chemotherapeutics.

6. Conclusion and perspectives

We have mainly discussed how defective components in different DNA repair machineries, including homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER) and finally DNA mismatch repair (MMR) can contribute to the risk of breast cancer. This review highlighted the importance of DNA repair pathways in breast cancer pathogenesis, from development to progression and prognosis. As such, further studies focusing on cellular DNA repair machinery will enhance our understanding of breast cancer etiology and help to design therapeutics specifically targeting the defective pathway in individual patients.

Conflicts of interest

None declared.

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