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Review

BCL10 in cell survival after DNA damage

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ABSTRACT

The complex defense mechanism of the DNA damage response (DDR) developed by cells during long-term evolution is an important mechanism for maintaining the stability of the genome. Defects in the DDR pathway can lead to the occurrence of various diseases, including tumor development. Most cancer treatments cause DNA damage and apoptosis. However, cancer cells have the natural ability to repair this damage and inhibit apoptosis, ultimately leading to the development of drug resistance. Therefore, investigating the mechanism of DNA damage may contribute markedly to the future treatment of cancer. The CARMA-BCL10-MALT1 (CBM) complex formed by B cell lymphoma/leukemia 10 (BCL10) regulates apoptosis by activating NF-κB signaling. BCL10 is involved in the formation of complexes that antagonize apoptosis and contribute to cell survival after DNA damage, with cytoplasmic BCL10 entering the nucleus to promote DNA damage repair, including histone ubiquitination and the recruitment of homologous recombination (HR) repair factors. This article reviews the role of BCL10 in cell survival following DNA damage.

1. Introduction

Over the lifetime, DNA within cells is affected by many in vivo factors and the local environment, resulting in DNA damage. Under normal circumstances, this damage can be addressed by a variety of intracellular DNA repair pathways to maintain normal cell proliferation and apoptosis. The intracellular DNA damage response (DDR) pathway is a complex protein network and an important mechanism for maintaining genome integrity. Intracellular DDR defects can cause many diseases, such as tumor development, neurodegenerative diseases, and immunodeficiency [1,2] (Fig. 1). After first sensing damage, the DDR network transmits and extends the damage signal, ending with an activation checkpoint to terminate the cell cycle that ultimately leads to the repair of damaged DNA or the induction of apoptosis when the damage cannot be repaired [1–3]. Cancer is considered to be a major human health issue worldwide. An important characteristic of cancer cells is genomic instability, which is primarily caused by changes in chromosome number and/or structure and microsatellite instability (MIN). Therefore, the DDR has become an important target in cancer drug development. The high mortality rate and difficulty of treating malignant tumors represent major obstacles. Chemotherapy is one of the primary methods used in the treatment of malignant tumors. Most chemotherapeutic drugs used to treat DNA damage are primarily used to inhibit tumor cell growth and kill tumor cells by directly or indirectly causing tumor cell double-strand breaks (DSBs), thereby inactivating essential genes or inducing apoptosis [4,5]. Radiation therapy also functions by damaging DNA and causing tumor cell death. However, cancer cells can repair damaged DNA through a variety of DNA repair pathways and inhibit apoptosis to improve their own viability and enhance tolerance to radiotherapy and chemotherapy [6]. Therefore, an in-depth understanding of the DDR and its association with tumor activity is essential to elucidate the underlying mechanisms of cancer resistance and to develop effective treatment strategies.

Since the first description of the BCL10 protein in 1999, many

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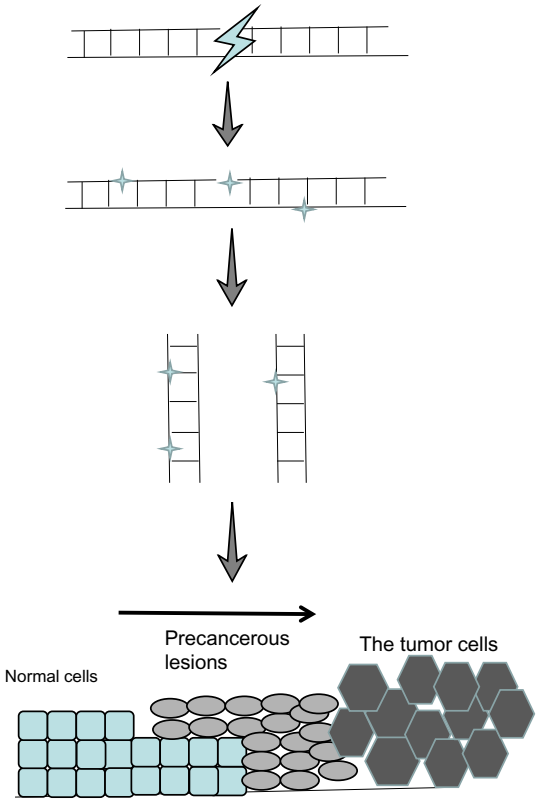

Fig. 1. Link between DNA damage repair and cancer. DNA damage from endogenous and exogenous sources. Damaged cells with the ability to repair DNA are subsequently incorrectly repaired and duplicated. Finally, mutations confer a selective advantage for clonal expansion and premalignant field defects, ultimately resulting in tumor transformation.

studies have demonstrated that it induces the key characteristics of innate and adaptive immune signaling downstream of the caspase recruitment domain (CARD) scaffold protein. The BCL10 protein that was cloned from the t(1;14)(p22;q32) breakpoint of mucosa-associated lymphoid tissue (MALT) lymphoma regulates apoptosis and is associated with the progression of this disease. Translocation related to BCL10 is also recurrent in low-grade MALT lymphoma [7,8]. BCL10 mediates the development of a variety of tumors. A defect in BCL10 is the cause of malignant mesothelioma (MESOM), which is an invasive tumor of the pleural serosa [9]. In a variety of solid tumor types, such as ovarian cancer, head and neck squamous cell carcinoma, cervical cancer, breast cancer, and renal clear cell carcinoma, BCL10 is commonly involved in promoting the growth and invasion of cancer cells [10–14]. In lymphoid cells, BCL10, which includes both a CARD and a C-terminal serine and threonine-rich domain that remains in the cytoplasm, activates the transcription factor NF-κB downstream of various immune receptors, such as the TCR, the B cell receptor, C-type family lectin receptors, NK-cell receptors, G protein-coupled receptors and Ig family receptors [15–19].

The purpose of this review is to discuss the role of BCL10 in the DDR to promote the survival of damaged cells. First, the types, repair methods and clinical significance of DNA injury are introduced. Second, evidence demonstrating that BCL 10 is involved in the formation of the CARMA-BCL10-MALT1 (CBM) complex is discussed. Third, the importance of BCL10 and RNF8/RNF168 in the repair of DNA damage by histone ubiquitination and the induction of homologous recombination (HR) repair at the site of DNA damage is described.

2. Types, repair pathways and clinical significance of DNA damage

DNA is unstable, and drastic changes in the environment or the production of byproducts of normal cell metabolism, as well as the destruction of chemical bonds in DNA can cause changes in DNA. A number of disruptive elements may cause single-strand breaks (SSBs), double-strand breaks (DSBs), or interstrand cross-links in cellular DNA. DNA damage can generally be divided into two categories: single-base changes and structural distortions. Although there are multiple types of DNA damage, one type of damage factor can often lead to multiple types of DNA impairment, depending on the magnitude and type of its damaging effects and dose, as well as the cell cycle state. Although DSBs rarely occur, they are the riskiest type of DNA damage because an unrepaired DSB is sufficient to induce cell death. The primary pathways of DNA repair are the single-strand break repair (SSBR) and double-strand break repair (DSBR) pathways. The primary mechanisms of these repair pathways are nonhomologous end joining (NHEJ), HR, nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and trans-injury synthesis [20]. SSBR primarily involves BER and MMR, whereas DSBR primarily involves HR and NHEJ. HR requires homologous chromatids as a template to allow for synthetic DNA repairs; thus, this process occurs only in late S and G2 phases [21]. In contrast, NHEJ directly links only broken DNA ends together. Thus, HR is a relatively faultless repair mechanism, while NHEJ is an error-prone repair mechanism [22]. Therefore, HR is the best mechanism to repair DSB injuries.

The investigation of the DNA damage repair process led to the development of a poly(ADP-ribose) polymerase (PARP) inhibitor for the treatment of breast cancer-associated gene 1/2(BRCA1/2)-deficient breast cancer and ovarian cancer that has been widely reported. PARPs are a class of nuclear enzymes that ubiquitously modulate poly-ADP ribosylation in eukaryotic cells and play a crucial role in DNA damage reconstruction and the maintenance of genomic stability. PARPs can detect DNA SSBs and transmit the information to the machinery involved in SSB repair [26]. A number of studies have shown that PARP inhibitors can effectively kill BRCA1/2-defective tumor cells, leading to the proposal of the new concept of “synthetic lethality” [23]. The PARP protein family is composed of 17 enzymes, among which PARP1, the best-studied member, has been shown to be involved in the cellular response to DNA damage through multisite ADP ribosylation. PARP-1 is activated after DNA damage and has an important role in SSB repair, although defects in this protein do not cause problems in nonmalignant cells [24–26]. In cells treated with PARP inhibitors, DNA mutations will only cause cell death due to a higher error rate in tumor cells with an impaired HR repair pathway (such as those with a BRCA1/2 deficiency) [27](Fig. 2). Among the known DDR pathway inhibitors, PARP inhibitors are currently the most widely studied. Because BRCA1/2 mutant cells are more susceptible to SSBs than normal cells, these cells have been shown to be extremely sensitive to PARP inhibitors and be highly susceptible to DNA-disrupting platinum agents such as cisplatin [28,29]. To date, the Food and Drug Administration (FDA) has approved olaparib, rucaparib, and niraparib for the advanced clinical treatment of ovarian and/or breast cancer. Olaparib is a well-known PARP inhibitor that has been demonstrated to induce lethality in BRCA1/2-defective tumor cells [30,31]. Numerous basic experiments and early clinical trials have confirmed that PARP inhibitors can significantly strengthen the effect of chemotherapy in patients with BRCA1/2 mutations. Furthermore, PARP inhibitors have been shown to exhibit relatively low toxicity and have clinical effects that are not limited to BRCA-deficient cancers, with activity also observed against non-BRCA mutation cancers with HR pathway dysfunction [32]. In addition, these agents present promising therapeutic prospects for refractory tumors such as melanomas, making it possible for PARP inhibitors to be used as effective and specific antitumor drugs.

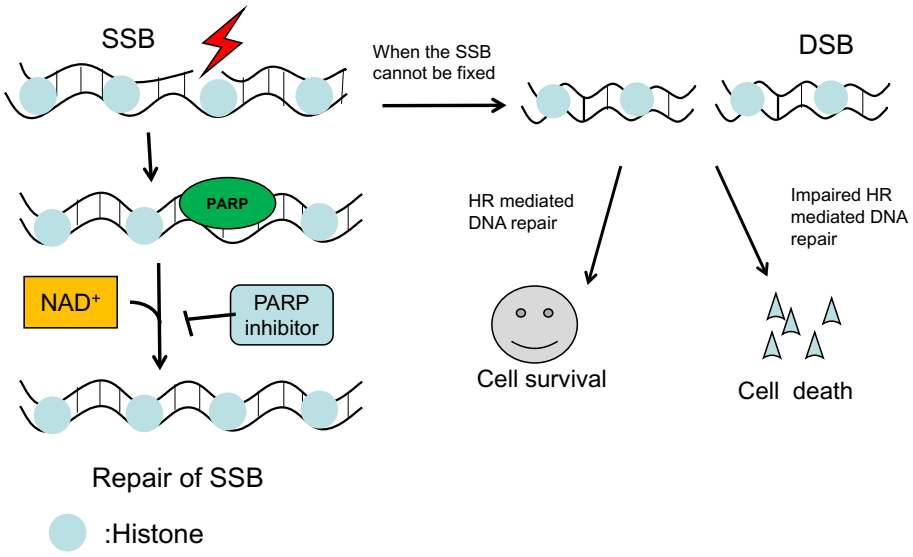

Fig. 2. The mechanism through which PARP inhibitors cause cell death without affecting normal cells. PARP is an important factor for sensing single-strand DNA damage and participates in DNA repair. When PARP is inhibited by inhibitors in normal cells, SSBs can be converted into DSBs by HR repair without errors, whereas in HR repair-defective tumor cells, the damaged DNA cannot be correctly repaired and causes cell death.

3. CBM complexes formed by BCL10 are involved in the activation of NF-κB induced by DNA damage and prevent apoptosis

NF-κB is a family of transcription factor proteins consisting of 5 subunits that regulate cell proliferation and survival. In resting cells, NF-κB and IκB form complexes that exist in an inactive form in the cytoplasm. IκB kinase (IKK) activates IκB phosphorylation when cells are stimulated by extracellular signals, resulting in NF-κB translocation to the nucleus. Free NF-κB is subsequently rapidly translocated to the nucleus and binds to specific exposed κB sequences to induce related gene transcription. IKK consists of two catalytic subunits (IKK-α and IKKβ) and a regulatory subunit (IKK-γ), also known as NF-κB essential modulator (NEMO), and a variety of upstream signaling pathways control IKK activation. Many scaffold proteins play pivotal roles in the activation of NF-κB stimulated by different receptors. CARD- and membrane-associated guanosine kinase-like domain (CARMA) proteins are a family of scaffold proteins containing CARDs that play key roles in the recruitment and activation of IKK. There are three members of the CARD and CARMA family: CARMA1, CARMA2, and CARMA3 [33]. CARMA proteins are encoded by three different genes that exhibit diverse tissue expression profiles, although they share the same set of structural domains [33]. Under different stimuli, every CARMA protein can form complexes with BCL10 and MALT1, and the function of these CBM complexes is to activate NF-κB signaling [13,34,35]. CARMAl is a backbone protein that changes its conformation after antigen receptor activation and recruits the downstream signaling pathway components BCL10 and MALT1. The mutual recognition of CARMAl and the adaptor protein BCL10 is mediated by the CARD domain. BCL10 and MALT1 form a complex in the cytoplasm, while CARMAl binds to MALT1 through its coiled-coil domain [36–38]. The interaction of these three proteins stabilizes the CBM complex. Importantly, BCL10 integrates the process of positive and negative regulation to control CBM complex function and dynamic assembly, disassembly and destruction [39]. IKKβ is a component of the heterotrimeric NF-κB regulatory IKK complex that is ubiquitinated and degraded by CBM, which induces NF-κB nuclear translocation and activates target gene transcription [40].

One of the major methods of cancer treatment is chemotherapy. Many chemotherapeutic drugs are considered to act as DNA damage agents that inhibit tumor growth by interfering with the apoptotic or necrotic pathways of cancer cells. The ataxia telangiectasia-mutated (ATM) protein kinase is activated after DNA damage and associates with NEMO and receptor-interacting protein 1 (RIP1) to form a cytosolic complex [41]. DNA damage induces the translocation of activated ATM to the cell membrane and cytoplasm, which catalyzes the release of IKK mono-free radicals and activates the NF-κB pathway through ATM-TRAF6-cIAP1 module formation [42]. In addition, the DNA damage signal also stimulates ATM-dependent NEMO phosphorylation, which in turn activates the TAK1 and ELKS-TAK1 interaction, leading to IKK and NF-κB activation [43]. Interestingly, many DNA damage agents also activate the transcription factor NF-κB family, which induces the expression of anti-apoptotic proteins, thereby preventing cancer cells from undergoing apoptosis and making them resistant to chemotherapy. A complex of CARMA3 and TRAF6 has been shown to mediate GPCR- and EGFR-induced NF-κB activation [44]. Therefore, the hypothesis that DNA damage-induced NF-κB activation originates from the formation of the CBM complex should be tested [45]. The results of this study demonstrated that CBM complex-mediated, DNA damage-induced NF-κB is activated in hematopoietic or non-hematopoietic cells in an ATM-dependent manner. In hematopoietic cells, CARMA1 forms a CBM complex with MALT1 and BCL10, whereas in nonhematopoietic cells, CARMA3 associates with MALT1 and BCL10 to form a CBM complex [45]. In addition, defects in the major components of the CBM complexes, including CARMA and BCL10, directly block NF-κB activation caused by genotoxic reagent-induced DNA damage [45]. The PKC family of kinases promotes the phosphorylation of CARMA family proteins and induces the binding of CARMA proteins to downstream signaling factors of BCL10 and MALT1 to form a CBM complex. Therefore, members of the PKC family of kinases play pivotal roles in CBM complex-mediated NF-κB activation in response to multiple stimuli [10]. However, DNA damage-induced NF-κB activation is independent of the PKC kinase family, indicating that the CBM complex may be activated through another unidentified pathway after DNA damage [45]. It has been shown that CARMA3 overexpression is associated with K63 polyubiquitination, which may regulate NF-κB activation [46]. Based on the observed DNA damage-induced polyubiquitin of K63 junctions and the role of TARF6 in the DNA damage-induced activation of NF-κB, it has been demonstrated that DNA damage-induced activation NF-κB requires the involvement of TARF6 [41] for the activation of CBM complexes [45]. In addition to NF-κB signaling, the CBM complexes also inhibit innate antiviral immune responses by preventing MAVS oligomerization in mitochondria and inhibiting IRF3-type I IFN expression [46]. Knockout of CBM proteins blocks NF-κB activation in ovarian cancer and inhibits the NF-κB-mediated invasion of ovarian cancer cells, indicating that CBM proteins regulate tumorigenesis [47]. The CBM complex may also affect cell death induced by the DDR because the CBM complex regulates the growth factor-mediated induction of the NF-κB pathway [13,48]. These results demonstrate that CBM complexes can promote survival-related signal transduction and

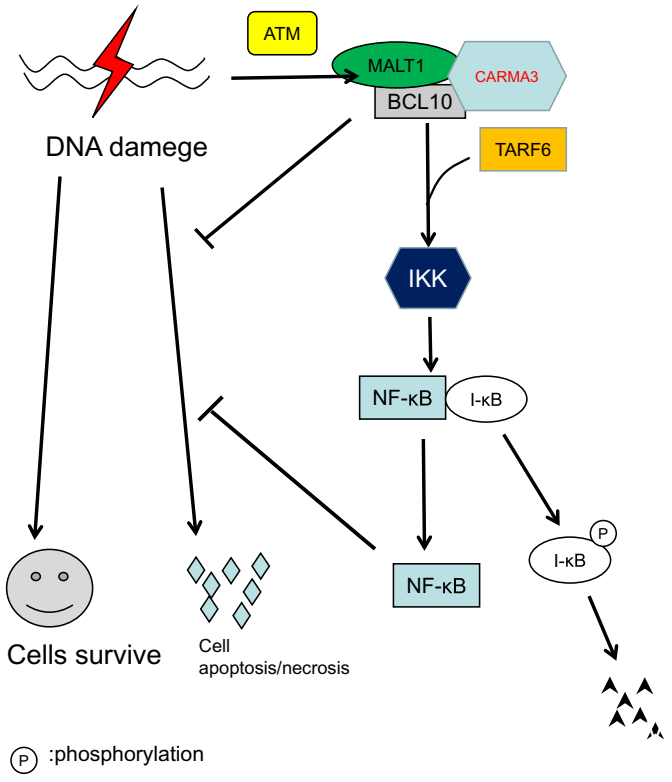

Fig. 3. The CBM complex can inhibit apoptosis. After DNA damage, the formation of CBM complexes is dependent on ATM. CBM complexes promote the activation of IKK with the participation of TARF6. NF-κB is separated from IκB, resulting in NF-κB activation. Activated NF-κB enters the nucleus to bind specific sequences and induce the transcription of genes to prevent cell apoptosis or necrosis. CBM complexes may also directly facilitate the survival of DNA-damaged cells.

antagonize DNA damage-induced apoptosis. Inhibition of CARMA3 doubles the number of apoptotic cells after DNA damage and prevents BCL10-induced apoptosis (Fig. 3). Furthermore, CARMA3 in the CBM complex may be one of the key factors involved in this process, as the role of CARMA3 is to promote tissue repair through the radiation-induced DDR [45]. Interestingly, the overexpression of CARMA3 in many tumor cell types is associated with malignant behavior of cancer cells [48,49].

4. BCL10 plays an important role in multiple DSB repair processes

4.1. RNF8/RNF168-mediated ubiquitination of histones is regulated by BCL10 in the DDR

Only half of the genome of eukaryotes consists of DNA, with the rest consisting almost entirely of histones. In addition to the packaging and organization of chromosomes, the histones that make up nucleosomes (the core of chromatin and the basic repeated protein subunits) are thought to act as true partners in all nuclear processes involving DNA. Each histone impacts DNA and other histones through its orbicular structure region, but the N- and C-terminal ends are exposed. Cells can modify the conformation of nucleosomes through different histone modifications, including ubiquitination, methylation, and phosphorylation, which bind DNA to other interacting proteins and ultimately affect the biological functions of cells, such as gene expression and DNA damage repair. In recent years, it has emerged that histone ubiquitylation recruits related effective factors to DNA damage sites to regulate the timing and efficiency of the DNA repair process [9]. During the DNA repair process, a series of response proteins, including RNF8 and RNF168 (two E3 ubiquitin ligases), have been confirmed to recruit DNA damage-induced repair proteins [9]. Ubiquitin (Ub; consisting of 76 amino acids) is a required protein for this process in species ranging from yeasts to humans. Ubiquitination is a three-step enzymatic process in which ubiquitins are gradually linked to specific proteins. However, histone ubiquitination is distinguished from the degradation associated with general protein ubiquitination. During the HR repair process, the subtle and complex networks of DSB repair signals largely depend on posttranslational modifications (PTMs) [50], particularly reversible phosphorylation and ubiquitination.

BCL10 is typically present in the cytoplasm, but recent studies have shown that BCL10 is primarily located in the nucleus in breast cancer cells, which is associated with tumor invasion and poor prognosis [47]. The observed subcellular localization of BCL10 in breast cancer cells, which was investigated using indirect immunofluorescence staining, contrasted with the primarily cytoplasmic localization of BCL10 observed in lymphocytes. Research has shown that BCL10 is present in large nuclear foci in breast cancer cells [47], and this nuclear localization may play a novel role in facilitating cell transformation and carcinogenesis [51]. The nuclear domains of BCL10 are similar to those of cryptogenic γ-H2AX, a phosphorylated form of histone H2AX foci that has been identified in unirradiated mammalian cells [52,53]. BCL10 takes part in the DDR, and persistent DSBs that surround eroded telomeres are indicated by large γ-H2AX foci [54–56]. The experimental finding that BCL10 knockdown significantly decreases the number of constitutive γ-H2AX foci indicates that BCL10 may take part in the maintenance and/or function of these foci [54–56]. γ-H2AX plays a role as a marker of DSB damage and also serves as a bridge to other repair factors at DNA damage sites during DSB repair. Interestingly, the key factors involved in DSB repair in the HR repair mode (BRCA1) and the key factor in the NHEJ repair mode (MRN complex) cannot aggregate at a DSB site to exert their functions in the absence of γ-H2AX [54–56].

When breast cancer cells are exposed to ionizing radiation, BCL10 colocalizes with ubiquitin in multiple lesions in early and late stages, suggesting that BCL10 may play a key role in DNA repair-related protein ubiquitination [51]. Ubiquitination has been reported to be crucial in the process whereby a number of repair factors are recruited to sites of DNA damage [57]. The E3 ubiquitin ligases RNF8 and RNF168 play crucial roles in DNA damage-induced ubiquitin foci by acting as positive regulators of the signaling cascade at the site of DNA damage, and these proteins can become inactivated to a great enough extent to severely impair the ability of a cell to respond to DNA damage [51]. The response to DSBs is triggered by the phosphatidylinositol 3-kinase-associated kinase ATM, which accumulates immediately following MRN (MRE11/RAD50/NBS1)-dependent DNA damage [58]. The histone variant H2AX is phosphorylated on serine 139 upon ATM activation and is then referred to as γ-H2AX, which marks the nucleosome surrounding DNA damage and serves as an anchoring platform for subsequent aggregation of downstream signaling proteins at the DSB site [59,60]. Mediator of DNA damage checkpoint 1 (MDC1) is a significant checkpoint mediator that directly concatenates to γ-H2AX in the early reactions of the DDR and amplifies the damage signal by accumulating ATM in an NBS1-dependent manner [61,62]. The ATM-mediated phosphorylation of MDC1 facilitates its oligomerization [63,64], after which it binds to the ring finger protein RNF8. The N-terminal forkhead-associated (FHA) domain of RNF8 combines with the ATM-phosphorylated TQXF motifs in MDC1 and guides RNF8 to the DSB site [65–67]. At DNA damage sites, BCL10 is also enriched and phosphorylated in an ATM-dependent manner [9]. RNF8 is the first E3 ligase recruited to a DSB site by MDC1, which is necessary to assemble repair proteins at DNA damage sites. The repair factors BRCA1 and 53BP1 (p53 binding protein 1) are recruited by the ligase activity of the C-terminal RNF8 RING finger domain, which acts in concert with the E2 enzyme UBC13 [68]. The hypothesis that RNF8-dependent signaling is crucial for the cellular response to DNA damage has been verified by

some experimental results showing an impaired G2/M checkpoint under low doses of ionizing radiation (IR) and hypersensitivity to IR induced by depletion of RNF8 [65–68]. Overall, the available results indicate that RNF8 plays a central role in the ubiquitination of histones after DNA damage. RNF8 cooperates with phosphorylated MDC1 to relocate to DSBs and ubiquitinate histones at the site of DNA lesions. Numerous repair factors, RNF168, HECT domain and RCC-like domain-containing protein 2 (Herc2), 53BP1 and BRCA1 cooperate with the upstream factor RNF8, the activity of which tethers these downstream proteins to damaged chromatin to convert the repair signal for DNA damage in cells [69].

UBC13 is a ubiquitin-conjugating enzyme that is primarily used for K63-linked ubiquitination and works together with RNF8 and RNF168 to adjust the DDR [68,70–73]. UBC13 is also involved in NF-κB signaling [74–76], and the formation of a CBM complex in the cytosol is one of the indispensable steps in the NF-κB signaling pathway. UBC13-TRAF6 ubiquitinates NEMO to form a K63-linked ubiquitin chain after the formation of the CBM complex, and this chain collects the subsequently activated I-κB-kinase complex and acts as an anchor. The activated I-κB-kinase complex phosphorylates I-κB proteins to target these proteins for proteasomal degradation. Thus, UBC13 and BCL10 are involved in the activation of NF-κB. Some recent studies have reported that these proteins exhibit a new intersection in the DDR in which phosphorylated BCL10 facilitates UBC13 binding to RNF8, which in turn participates in the ubiquitination of BCL10 [9]. Previous evidence suggests that the targets of RNF8-UBC13 at DSBs are histone H2A and H2AX because they are ubiquitinated in an RNF8-dependent manner in response to DSBs [65,67]. RNF8 is coupled to the ubiquitin-conjugating enzyme UBC13 to catalyze the ubiquitination of K63-linked histones H2A and H2AX, thereby facilitating the formation of ionizing radiation-induced foci (IRIF) of 53BP1, BRCA1-RAP80 and FK2 and enhancing G2/M DNA damage checkpoints [65–68]. The UBC13/RNF8 ubiquitin ligase complex may control the formation of foci under the DDR in Rap80/Abraxas/BRCA1/Brcc36 complexes.

It was shown in an groundbreaking study that RNF168 mediates the initial ubiquitination of histone H2A at K13–15 depending on RNF8, although RNF8 is not active at nucleosome H2A [77]. K13-15 of H2AX is activated by RNF168 in an RNF8-dependent manner, promoting the polyubiquitination of K63 linkages on H2AX and other DDR factors by RNF8 and other E3 ligases. RNF8-dependent, RNF168-mediated monoubiquitination of H2AX on K13 and K15 requires the binding of protein X, which should previously have been ubiquitinated by RNF8. Although experimental results have shown that BCL10 does not bind to protein X, after its ubiquitination, BCL10 promotes the binding of RNF168 and the E2 ligase-like UBC13 to RNF168, conferring E3 ubiquitin ligase activity upon RNF168 [9]. Similar to the RNF8 E3 ubiquitin ligase, RNF168 collaborates with UBC13 to ubiquitinate histones located close to DSBs [72,73]. RNF168 ubiquitination of H2A and H2AX depends on RNF8, which increases the local concentration of ubiquitin conjugates to the threshold required for the retention of 53BP1 and BRCA1 [72,73]. On the whole, RNF168 amplifies and/or stabilizes the transient and/or unstable ubiquitin conjugates generated by RNF8, which allows the threshold required for the completion of the DSB-induced chromatin response to be reached. It is interesting that overexpression of RNF8 rescues cellular phenotypes in cells exhibiting slight or moderate downregulation of RNF168 [73], indicating that high RNF8 activity can maintain unstable ubiquitin conjugates to compensate for a weaker, but not absent, RNF168 response. The ubiquitination of BCL10 allows RNF168 to conduct monoubiquitination of H2AX and to further conduct multiubiquitination through the complex containing RNF8 and RNF168. This activity is unexpected for RNF8/RNF168, which is required for BCL10 to remain at the DNA damage site [51]. It is worth noting that mutations in RNF168 are closely associated with radiosensitivity, immunodeficiency dysmorphic features and learning difficulties (RIDDLE) syndrome, which is characterized by the repair of DSB cell defects. Cells from RIDDLE patients are unable to

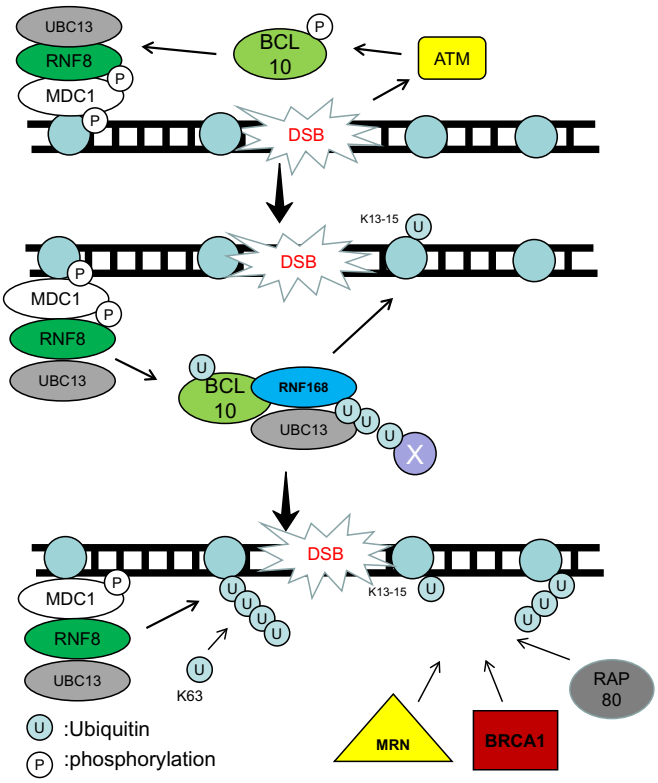

Fig. 4. BCL10 regulates the ubiquitination of histones in DNA damage repair by interacting with UBC13, RNF8 and RNF168. Upon DNA damage, ATM phosphorylates BCL10, promotes the binding of BCL10 to RNF8 and simultaneously presents UBC13 to RNF8. After ubiquitination induced by the RNF8/UBC13 complex, BCL10 binds to RNF168 and promotes UBC13 binding to RNF168, activating the RNF168 E3 ligase. RNF168 activates H2AX monoubiquitination at K13-15 in an RNF8-dependent manner, enabling RNF8 and other E3 ubiquitin ligases to perform polyubiquitination at K63 in H2AX and other DDR factors. RNF8-dependent and RNF168-mediated monoubiquitination of K13-15 in H2AX requires a ligand protein X, which should be have been previously ubiquitinated by RNF8. Fully ubiquitinated H2AX modifies the chromatin region around the DSB site as a platform for further deposition of DSB signals and other factors required for DNA repair.

recruit 53BP1 and BRCA1 at irradiation-induced DNA damage sites (IRIFs), but integration can be achieved through the expression of exogenous RNF168 [78]. The E3 ubiquitin ligases RNF8 and RNF168, which are binding targets of downstream effectors of BRCA1 and 53BP1 in the recruitment of DDR pathways, catalyze the formation of non-proteolytic polyubiquitin chains induced by DNA damage. A specific flow chart is provided show how BCL10 regulates the ubiquitination of histones in DNA damage repair by interacting with UBC13, RNF8 and RNF168. (Fig. 4) The accumulation of RNF8/RNF168 at DNA damage sites is extremely important for the selection of repair pathways required to ensure genomic stability in cells, which highlights the central role of these pathways in the coordination of DDR and repair pathways. Thus, BCL10 plays an active role in DSB repair by interacting with RNF8/RNF168 to further promote cell survival.

4.2. BCL10 recruits HR repair factors to participate in DNA damage repair

The HR pathway is consistently recognized as the best repair mechanism for DSBs. Even during normal cell proliferation, DNA replication forks often halt when the template chain is damaged, and the stalled fork may split to produce DBSs that can be repaired by HR. The mechanism of HR, which is used to repair DNA damage without errors by swapping with complete homologous sequences (such as the sister chromatid), is the key to resolving a stalled fork [79]. BRCA1 is an

indispensable tumor suppressor gene whose encoded protein plays an important role in the HR repair pathway [80]. The BRCT domain of BRCA1, which is thought to be crucial in the DSB repair process [81,82], forms at least four distinct complexes, designated A, B, C, and D according to the different proteins they interact with, and these complexes play distinct roles at different levels of HR [83]. These complexes can sense DNA damage, regulate cell cycle checkpoints and recruit DNA repair enzymes to harmonize the interference between DNA repair pathways and numerous cell processes [84]. BRCA1 and BRCA2 are fundamental to effective HR in mammalian cells [85–89]. Without these proteins, replication-related DNA fragments may be repaired through an error-prone mechanism, such as NHEJ or microhomology-mediated end joining, in which crude reconnections can destroy the ends [87–91]. Based on the physical interaction between its structural domain and various proteins, BRCA1 plays a significant role in a variety of cellular programs, and its protein products are widely expressed and participate in many basic physiological processes [92,93]. During DSB repair by HR, H2AX near the site of chromosomal DNA damage is first phosphorylated by PI3K family members (ATM/ATR/DNA-PK) [94]. Subsequently, a series of response proteins, including the two ubiquitin ligases RNF8 and RNF168, are recruited to the site of DNA damage to control the repair process [78]. RNF8 and RNF168 mediate the polyubiquitination of H2A and H2AX near DSBs, and the polyubiquitination signal further recruits downstream response proteins (such as RAP80, BRCA1 and 53BP1) to perform DNA repair at DNA damage sites [95–99]. The choice between HR and NHEJ is a complex and not fully understood problem that will require further investigation in the future. However, it has been shown that 53BP1 is necessary for the NHEJ pathway, while BRCA1 is necessary for the HR pathway and that the two repair pathways are antagonistic. Suppression of 53BP1 in cells with impaired BRCA1 activity can partially restore cell viability by allowing DSBs to be repaired through the HR pathway [78]. At the beginning of the HR repair pathway, 5′ to 3′ nucleolytic activity resects blunt-ended DNA to expose 3′-overhang single-stranded (ss) DNA tracts, generating the substrate for HR [79]. BRCA1 may regulate this crucial step to restrict HR to the post-replicative G2 phase of the cell cycle, during which a duplicated sister chromatid is available as a template for the repair of its damaged partner [100–103]. Rad52 and Rad51 are specific endonucleases that resolve Holliday structures and play important roles in HR [104]. The interaction between RPA and Rad52 modulates Rad52 activity, which is necessary for the interaction of Rad51, Rad52 and Rad54 at a 3′ overhang and for subsequent steps. The ss-DNA immediately binds to replication protein A (RPA), which is then swapped by Rad51, with Rad54, BRCA2 and PALB2 being crucial during this exchange process. Rad51 further promotes the invasion of sister chains and the formation of Holliday junctions, inducing the repair of damaged DNA using intact sister chromatids as templates. Among these proteins, the interaction between RPA and Rad52 is the most important, which not only plays a role in regulating the activity of Rad52 but is also necessary for Rad51. Rad52 and Rad54 form a complex on the 3′ protruding end and are involved in subsequent steps [105]. Consequently, the HR repair pathway is a highly complex and regulated process.

BCL10, together with CARMA 1 and MALT 1, forms the CBM complex. This complex connects T cell receptor signals with the typical IKK/NF-κB pathway. However, studies have revealed a new function of BCL10 apart from the CBM complex in the DDR in which BCL10 modulates RNF8/RNF168-mediated ubiquitination to regulate the synthesis of BRCA1. BCL10 knockout can induce cellular radiosensitivity and control DSB repair through HR repair. The results of a study by Ismail et al. showed that BCL10 plays an essential role in the HR pathway for repairing DNA damage, similar to the key role of BRCA1 in HR [51]. Another important result is that both HR- and NHEJ-mediated DSB repair pathways are disrupted when BCL10 is inhibited [9]. BCL10 is known to interact with the key human enzyme UBC13 for homologous recombination for DSB repair [74,106]; thus, a

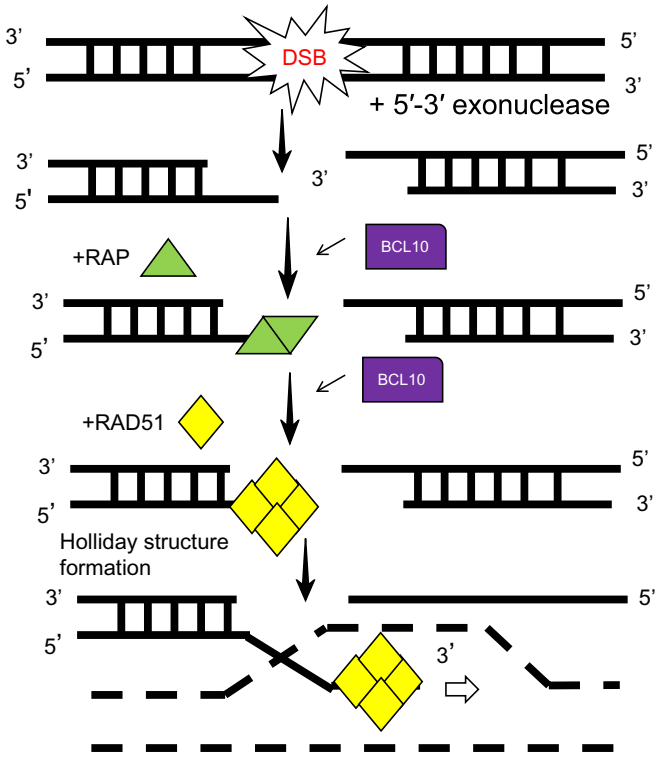

Fig. 5. BCL10 directly participates in HR and promotes the initial recruitment/accumulation of crucial HR proteins. The general scheme of homologous recombination in eukaryotes is as follows: a 5′-3′ exonuclease generates free 3′ ends; RAP immediately binds to the free 3′ ends; and RPA is subsequently swapped by Rad51. BCL10 directly guides RPA, RAD51 and BRCA1 to the DSB site to participate in the HR repair process. The 3′ end of the hydrolyzed DNA strand (solid line) is incorporated into the intact double-stranded DNA with a homologous sequence (dotted line), after which the gap in the DNA is filled and ligated, and the Holliday structure is produced.

number of studies have been performed to explore whether BCL10 is further involved in other aspects of HR repair. The excision of the DSB tip is one of the primary responses in the HR repair pathway, and RPA and CtIP recruited to DNA damage sites perform this excision step. Experimental results have shown that BCL10 influences the relocalization and recruitment of RPA to DNA damage sites to promote the formation of Holliday junctions, which is an important step in the HR pathway. Furthermore, infrared-induced formation of HR protein foci, including RAD51 and BRCA1, is decreased in BCL10-knockdown cells. Therefore, BCL10 may directly participate in HR and promote the initial recruitment/accumulation of crucial HR proteins (such as BRCA1, RAD51, and RPA) to DSB sites [51](Fig. 5).

RAP80, a BRCA1-A complex subunit and an ubiquitin-binding protein that specifically distinguishes and binds to K63-linked ubiquitinated proteins (such as DNA damage at histones H2A and H2AX), guides the BRCA1-A complex and BRCA1-dependent HR factors (such as RAD51) to DSBs [107,108]. Because the BCL10-dependent assembly of the RNF8/RNF168 ligase complex is crucial for the K63-linked ubiquitination of H2AX, BCL10 is required for the recruitment of HR factors (including RAP80 and BRCA1) to DNA damage sites [9]. Although BCL10 activates NF-κB through the CBM signaling complex, the function of BCL10 has been demonstrated to be independent of the CBM complex in HR-mediated DNA damage repair [9]. It is unclear how BCL10 affects the recruitment of important factors involved in the HR repair of DNA damage, and further research on this topic is needed. In summary, similar to BRCA1, BCL10 not only plays an important role in multiple stages of the HR repair pathway, it also affects important factors such as BRCA1. Thus, there may be a specific connection

between these proteins.

5. Conclusions and future perspectives

Based on the points discussed above, we conclude that BCL10 plays an important role in mediating the DDR at multiple sites. The CBM complex composed of BCL10, CARMA and MALT1 is necessary to promote survival signals opposing apoptosis induced by DNA damage. BCL10 can participate in histone ubiquitination by interacting with RNF8/RNF168 and can induce HR factors to participate in the initial HR repair process at DNA damage sites. Loss of BRCA 1 may lead to delayed or even interrupted repair of DNA damage, and the failure of BCL10 to participate in DNA damage repair also greatly reduces the efficiency and efficacy of DNA repair, which may eventually lead to failure of repair and even cell death.

Since the discovery of BRCA1/2, their roles as key factors in the HR repair pathway have been demonstrated by numerous experimental results, and the efficacy of PARP inhibitors against defective BRCA1/2 proteins has been widely recognized. Synthetic lethality, as a newly proposed concept in the treatment of cancer, has become a novel direction for anticancer drug research. Among the synthetic lethal gene pairs that have been discovered, PARP/BRCA is currently the most widely studied. Based on the important role of BCL10 in the HR repair pathway, it is necessary to further study whether BCL10-deficient tumors can be treated using PARP inhibitors such as BRCA1 to broaden the clinical application of PARP inhibitors. Based on the induction of tumor cell death by DNA damage under treatment with radiotherapy and chemotherapy, knockdown of BCL10 may increase the efficacy of radiotherapy and chemotherapy, which will give rise to new ideas and directions for clinical comprehensive cancer therapy in the future. A great deal of genetic and biochemical evidence has revealed the molecular mechanism of the CBM complex in activating NF-κB following DNA damage, which may be a molecular basis for the development of cancer treatment strategies targeting the CBM complex. This knowledge also provides a new direction for the treatment of cancers showing chemotherapeutic resistance due to the inhibition of tumor cell apoptosis. The role of BCL10 in the DDR, either alone or as a component of the CBM complex, is promising. In the context of existing cancer biomarkers such as p53, HER2, and BRCA1, whether BCL10 can be used for the early diagnosis of cancer, in single-targeted treatment and as a predictive and prognostic biomarker for well-organized therapy needs to be further explored.

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