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Maintenance of Genome Stability by Ubiquitination of DNA Repair Proteins in Mammalian Development and Disease

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Abstract

To maintain genome DNA, DNA repair machinery has been developed in cellular life cycle. Multiple DNA repair pathways such as base excision repair, nucleotide excision repair, DNA cross link damage repair, DNA single strand break repair and DNA double strand break repair including nonhomologous end joining and homologous recombination are regulated by protein signal cascade. Because of limited gene number, protein posttranslational modification signal has advantage to control cell dynamics during development and senescence. This chapter focuses on how DNA repair proteins molecular modification including phosphorylation and ubiquitination contribute to genome stability pathway during mammalian development and disease.

Keywords: DNA repair, BRCA1, FA pathway, NBS1, mammalian development, inherited disease

1. Introduction

Genome DNA is damaged by several environmental factors such as ionizing radiation (IR), ultraviolet (UV), environmental mutagen and metabolic products including reaction oxygen species (ROS). It is well known that IR induces base damage, DNA cross link and DNA strand breaks defined as, single strand breaks (SSB) and double strand breaks (DSB) [1] For instance, 1Gy gamma-ray irradiation induces 1000 SSBs and 40 DSBs per cells [2] Although base damage causes genome DNA mutation leading to cancer, DSB is a catastrophic damage that leads to severe chromosome breakage and cell death. To prevent this,
in mammalian cells, there are two major DSB repair pathway: nonhomologous end joining (NHEJ) repair [3] and homologous recombination (HR) repair [4] (Figure 1). NHEJ repair joint DNA damage ends directly and act as dominant repair pathway through cell cycle. HR repair is a precise pathway to repair completely with sister chromatid during S-G2 phase.

Figure 1. Schematic model of HR repair and NHEJ repair.
Both pathways cooperate to maintain genome DNA stability. Defect or depletion of related proteins of DNA repair result in hypersensitivity to the IR, severe developmental failure especially central nervous system and predisposition to the cancer. Recently, it is reported that abnormal expression of DSB repair proteins causes neurodegeneration, and small head phenotype called microcephaly. Neural stem cells and progenitors actively proliferate and produce ROS from mitochondria respiration [5, 6], which attack genome DNA. Decreasing of DNA repair activity is critical for cell survival. Furthermore, atomic bomb survivors show microcephaly when they are exposed in the womb [7]. DNA damage and centrosome amplification are critical for mammalian embryonic brain development [8, 9]. To regulate DNA repair machinery, several protein posttranslational modification systems such as phosphorylation, ubiquitination, SUMOylation, and NEDDylation are involved [10]. In this chapter, to identify how DNA repair signaling pathways are involved in mammalian development and disease, ubiquitination system in DNA repair machinery are focused on and discussed.

1.1. DSB NHEJ repair pathway

DNA-PKcs, Ku70, Ku80 are main components of NHEJ pathway and recruited to DNA damaged ends immediately when DSB occurred. Binding of Ku70/Ku80 to the DNA ends is important for protection from resection and recognition as telomere ends [11, 12]. DNA-PKcs act as a signal inducer by phosphorylation of several substrates [13]. DNA-PKcs also phosphorylates itself to activate this pathway. Subsequently, XRCC4 is recruited to damage sites as scaffold and then related proteins such as XLF, PAXX and Artemis are accumulated [14]. Artemis has endonuclease activity to resect DNA ends to facilitate DNA ligation. Polynucleotide kinase phosphatase (PNKP) is also recruited to DNA ends to remove 3'-P groups or add 5'-P residues for ligation [15, 16]. Finally, DNA ligase IV joint DNA ends. Because of broken ends by physical damage and resection by Artemis, NHEJ pathway sometimes generates DNA mutation and deletion. NHEJ pathway is not only important for DNA repair pathway, but also immune-systems, V(D)J recombination [17, 18]. Human patients with deficiency of Artemis, XLF, Ligase IV show severe combined immunodeficiency (SCID) and microcephaly phenotype. To investigate the role of DNA repair machinery in central nervous system, brain-specific conditional knockout mice of Ligase IV and PNKP were generated [19]. These mice show severe DNA damage and apoptosis in the cerebral cortex during embryonic development. This suggests that NHEJ repair machinery is important for genome maintenance of neural stem cells and progenitors during brain development.

1.2. DSB HR repair pathway

HR repair is a precise repair pathway that requires sister chromatid as DNA template. Ataxia telangiectasia mutated (ATM) and MRE11/RAD50/NBS1 (MRN complex) are accumulated to DNA damage sites as DNA damage sensor and ATM phosphorylates ATM itself (auto-phosphorylation) to activate HR signal [20, 21]. ATM is master regulator of DNA damage response signaling and has many substrates such as p53, SMC1, NBS1, MDC1, 53BP1 and CHK2. ATM regulates G1/S, S and G2/S cell cycle checkpoint. Ataxia telangiectasia (AT) patients show hypersensitivity to the IR, immunodeficiency, predisposition
to malignancy and progressive cerebellar neurodegeneration. MRE11 is responsible gene for AT like disorder (ATLD). ATLD patients show similar phenotype with AT. MRE11 has nuclease activity to generate 3’ ssDNA tails. Detail of NBS1 discussed below. After ATM activation, signal mediator such as BRCA1 and 53BP1 are accumulated depending on ubiquitination of histone protein by RNF8. RNF8 and RNF168 are key E3 ubiquitin ligase in HR pathway [22, 23]. Poly-ubiquitination of histone H1 by RNF8 is important for RNF168 recruitment to the DNA damage sites. Chromatin remodeling associates with DNA damage response to facilitate DNA repair. Histone protein modification is trigger of this process. NBS1 and ATM interact with E3 ubiquitin ligase RNF20 which mono-ubiquitinates H2B after DNA damage [24, 25]. RNF20 dependent H2B mono-ubiquitination is important process of DNA repair, because depletion of RNF20 by siRNA reduces accumulation of RAD51 and BRCA1 to the DNA damage sites. DNA exonucleases CtIP and Exo1 are recruited to damage sites to resect DNA ends [26]. Then, Replication protein A (RPA) and RAD52 binds to single strand DNA ends to protect DNA and replace with RAD51 and BRCA1 to promote DNA recombination [27, 28]. Simultaneously, cell cycle checkpoint proteins, p53, CHK1 and CHK2 activate to give repair time. HR factors are not only involved in DNA repair, but also meiosis.

Both DNA repair pathway are strictly regulated, and several E3 ubiquitination ligases are involved in these [29]. Defect of DNA repair machinery leads to chromosome aneuploidy and several diseases such as neurodegeneration, inflammation and cancer [30].

1.3. NHEJ and HR proteins and centrosomes

As mentioned earlier, NHEJ and HR proteins are important for DNA repair to maintain genome stability. In fact, defect of NHEJ and HR proteins leads to severe inherited disease such as immunodeficiency, neurodegeneration, developmental defect, predisposition to the malignancy. Recent reports uncover that NHEJ proteins and HR proteins localize centrosomes. Centrosome is an organelle consists of two centrioles surrounded by pericentriolar material (PCM) [31, 32]. γ-tubulin ring complex (γ-TuRC) attaches PCM to form microtubule extension. Centrosome plays pivotal role for the proper cell division [33]. Mammalian cells usually have one or two centrosomes depending on cell cycle. Ionizing radiation (IR) or some genotoxic reagents trigger centrosome amplification, which cause multipolar cell division and chromosome aneuploidy [8, 34–37]. Centrosome duplication is basically regulated cell cycle machinery. NHEJ factors such as DNA-PKcs localize centrosomes [38]. We found that DNA-PKcs or Ku70 deficient murine embryonic fibroblast (MEF) cells show slight centrosome amplification compared with complementary cells. Meanwhile, HR factors such as ATM, NBS1, BRCA1, BRCA2 and Rad51 localize centrosome and depletion of these factors show significant centrosome amplification [39]. The role of NBS1 and BRCA1 in centrosome maintenance is discussed in the following section. ATM phosphorylates centrosome protein CEP63 to regulate spindle assembly after DNA damage [40]. Inhibition of ATM in RAD51 deficient cells shows centrosome amplification which means that ATM and RAD51 interaction is important for centrosome proper duplication [41]. BRCA2 interacts with NPM to form BRCA2-NPM complex to maintain centrosome duplication and cell division [42]. CHK1 is one of key regulator for cell
cycle checkpoint to activate G2/M checkpoint. Depletion of CHK1 expression leads to centrosome amplification [41, 43]. After DNA damage, ATM- and Rad3-related (ATR) phosphorylates CHK1 to move to the centrosome from nucleus. ATR-dependent CHK1 translocation is important for centrosome duplication after DNA damage [44, 45]. Recent reports unveiled importance and molecular mechanism of HR factors in centrosome maintenance. However, function and physical means of NHEJ factors in centrosome still remain unclear.

2. Ubiquitination of DNA repair proteins and development

2.1. E3 ubiquitin ligase BRCA1

Breast and ovarian cancer gene, BRCA1 have multiple function in cell metabolism, including DNA repair, chromatin remodeling, microtubule maintenance and centrosome duplication. About 10% of women patients with breast cancer have inherited mutations in BRCA1 or BRCA2. BRCA1 forms heterodimer with BRCA1-associated RING domain (BARD1) to act as E3 ubiquitin ligase, which has several substrates including H2A, H2AX, RNA pol III, THIIE, NPM1, CtIP, ER-α and claspin [46–51] (Figure 2). Since BRCA1 can mono-ubiquitinates H2A and H2AX in vivo, it is believed that BRCA1 is required for chromatin remodeling after DNA damage [52, 53].

2.2. BRCA1 and centrosomes

BRCA1-BARD complex mono-ubiquitinates γ-tubulin at Lysine 48 and Lysine 344, which is the main component of centrosome [54–57]. Previously, we reported that Nijmegen breakage syndrome (NBS) gene and ATR gene products, NBS1 and ATR are involved in BRCA1 dependent γ-tubulin mono-ubiquitination to regulate centrosome duplication [58, 59]. Deficient of BRCA1 leads to centrosome amplification. Furthermore, BRCA1 and NBS1 are required for suppression of low dose rate IR dependent centrosome amplification [60]. This result suggests that BRCA1 keep genome integrity through cell cycle. So far, it is not known de-ubiquitinating enzymes (DUBs) of γ-tubulin. CP110 is a centriolar protein that regulates centrosome duplication. The level of CP110 is regulated by ubiquitination and de-ubiquitination by ubiquitin ligase complex SCFcyclinF and DUB USP33, respectively [61]. Destabilized CP110 levels by ubiquitination status lead to centrosome amplification and genome instability. Thus, balance of ubiquitination status is important. To identify DUBs of BRCA1-dependent γ-tubulin ubiquitination will contribute therapeutic strategies.

2.3. Mouse model of BRCA1

Since BRCA1 is involved in multiple cellular functions, complete defect of that leads to embryonic lethality. To identify the role of BRCA1 in mammalian development, conditional knockout mice were generated. Deletion of BRCA1 in mammary gland result in a phenotype of human basal like breast cancer [62, 63]. Central nervous system (CNS) specific BRCA1 knockout using nestin promoter resulted in microcephaly [64, 65]. Apoptotic cells were increased in brain layer structure during embryonic stage in BRCA1 brain specific KO mice. As another possibility, since genetic background such as Plk4 overexpression or genotoxic stress such as IR induce
centrosome amplification during CNS development result in microcephaly, centrosome amplification might be involved in microcephaly formation in BRCA1 deficient mouse brain [8, 66]. This result suggests that BRCA1 is important for genome maintenance in mammalian neural development.

2.4. Fanconi anemia (FA) pathway

Fanconi anemia (FA) is a hereditary disease clinically characterized as skeletal and visceral malformations, attrition of bone marrow stem cells [67, 68]. FA is firstly reported by Fanconi in 1927 and founded to be sensitive to DNA cross link damage by Sasaki et al. [69]. FA proteins pathway is important for inter cross link (ICL) DNA damage repair and HR repair [70, 71]. Currently, at least 21 FA proteins are reported. FANCD2 is a key player in FA pathway [72–75]. Mono-ubiquitination of FANCD2 at Lysine 561 by FA core complex is important event for activation of FA pathway. FA core complex consists by eight FA proteins (FANCA, B, C, E, F, G, L, M) and associated factors (FAAP100, FAAP24, FAAP20, MHF1 and MHF2). K561 mutated FANCD2 proteins cannot form DNA damage foci and localize to chromatin.
suggest that mono-ubiquitination of FANCD2 is essential event for DNA repair. FANCD2 forms heterodimer with FANCI, which is phosphorylated by ATR-ATRIP complex. Mono-ubiquitination of FANCD2 is de-ubiquitinated by USP1 after completion of DNA repair [76, 77]. Knockout mice of USP1 show FA like phenotype. This suggests that regulation of mono-ubiquitination level of FANCD2 is critical for DNA repair pathway [76, 77].

2.5. Mouse model of FA proteins

Knockout mice of FA genes show decreasing of fertility and chromosome breaks [78–80]. Fancg knockout mice show germ cell defects and decreasing of fertility. Fancg−/− cells display high sensitivity to the IR and DNA crosslink inducer mitomycin C (MMC). Fancd2−/− mice show more severe phenotype characterized by perinatal lethality microphthalmia and hypogonadism. Fancd2−/− mice are also prone to developing epithelial cancers than Fanca−/−, Fance−/− and Fancg−/− mice [78, 79, 81–84].

Figure 3. Ubiquitination of NBS1 by Skp2 is important for DNA repair pathway.
2.6. NBS1

Nijmegen breakage syndrome (NBS) is characterized by immunodeficiency, predisposition to the malignancy and IR hypersensitivity [85, 86]. Gene product NBS1 is 95 kDa protein and has several roles to maintain genome stability such as, HR repair, DNA replication initiation, cell cycle checkpoint, apoptosis, UV damage repair and centrosome duplication [58, 87–95]. NBS1 forms complex with MRE11 and RAD50 as MRN complex and act as DNA damage sensor and initiator [96]. Complete deletion of NBS1 proteins in mice leads to embryonic lethality. 70 kDa fragment of NBS1 protein expresses in NBS patient cells. NBS1 localizes to the nucleus and centrosomes. Depletion of NBS1 by siRNA in human osteosarcoma U2OS cells and murine embryonic fibroblast NIH3T3 cells show radio-sensitivity and centrosome amplification which suggest that NBS1 is required for DNA repair and centrosome duplication process. NBS1 is phosphorylated by ATM and ATR to activate G1/S checkpoint and G2/M checkpoint, respectively. NBS1 acts as DNA damage sensor and is important for ATM recruitment to the DNA damage sites. Ubiquitination of NBS1 by E3 ubiquitin ligase 3 Skp2 is required for interaction with ATM and activation [97] (Figure 3). Defect of Skp2 leads to decreasing of ATM foci formation at the DNA damage sites. Furthermore, NBS1 is involved in translesion DNA synthesis (TLS) [92]. After UV exposure, E3 ubiquitin ligase RAD18 recruited to the DNA damage sites and mono-ubiquitinates PCNA to initiate TLS. NBS1 controls RAD18 function because depletion of NBS1 results in decreasing of foci formation of pol eta and mono-ubiquitination of PCNA.

3. Concluding remarks

Genome DNA is attacked by several factors not only environmental stress but also metabolic stress to maintain cellular homeostasis. DNA repair and genome maintenance molecular mechanisms are strictly regulated by many enzymes. Since Goldstein and Ciechanover first reported about ubiquitin, the biological significance of this small peptide has been focused on several fields such as proteasome maintenance, translational signaling and DNA repair [98–100]. Ubiquitination of DNA repair factors are important for facilitates signaling cascade, because protein posttranslational modification is useful tool to diverse signaling pathway. DNA repair proteins defects cause several diseases such as immunodeficiency, neurodegeneration, growth defects and cancer progression. Furthermore, ubiquitination of DNA repair pathway is strong target for cancer therapy [101]. To understand of molecular pathway is necessary for clinical application.

Acknowledgements

The author thanks the members of Yoshihisa Matsumoto laboratory for critical discussion. This work was supported by the Uehara Memorial Foundation, the Takeda Science Foundation and the Kato Memorial Bioscience Foundation.
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References

[1] Iyama T, Wilson 3rd DM DNA repair mechanisms in dividing and non-dividing cells. DNA Repair (Amst). 2013;12(8):620-636

[2] Ward JF. DNA damage produced by ionizing radiation in mammalian cells: Identities, mechanisms of formation, and reparability. Progress in Nucleic Acid Research and Molecular Biology. 1988;35:95-125

[3] Lieber MR. The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. Annual Review of Biochemistry. 2010;79:181-211

[4] Kobayashi J, Iwabuchi K, Miyagawa K, Sonoda E, Suzuki K, Takata M, et al. Current topics in DNA double-strand break repair. Journal of Radiation Research. 2008;49(2):93-103

[5] Wood JW, Johnson KG, Omori Y. In utero exposure to the Hiroshima atomic bomb. An evaluation of head size and mental retardation: twenty years later. Pediatrics. 1967;39(3):385-392

[6] McKinnon PJ. Maintaining genome stability in the nervous system. Nature Neuroscience. 2013;16(11):1523-1529

[7] Wood JW, Johnson KG, Omori Y, Kawamoto S, Kehm RJ. Mental retardation in children exposed in utero to the atomic bombs in Hiroshima and Nagasaki. American Journal of Public Health Nations Health. 1967;57(8):1381-1389

[8] Shimada M, Matsuzaki F, Kato A, Kobayashi J, Matsumoto T, Komatsu K. Induction of excess centrosomes in neural progenitor cells during the development of radiation-induced microcephaly. PLoS One. 2016;11(7):e0158236

[9] Roque T, Haton C, Etienne O, Chicheportiche A, Rousseau L, Martin L, et al. Lack of a p21waf1/cip -dependent G1/S checkpoint in neural stem and progenitor cells after DNA damage in vivo. Stem Cells. 2012;30(3):537-547

[10] Lombardi PM, Matunis MJ, Wolberger C. RAP80, ubiquitin and SUMO in the DNA damage response. Journal of Molecular Medicine (Berl). 2017;95(8):799-807

[11] Taccioli GE, Gottlieb TM, Blunt T, Priestley A, Demengeot J, Mizuta R, et al. Ku80: product of the XRCC5 gene and its role in DNA repair and V(D)J recombination. Science. 1994;265(5177):1442-1445
[12] Takata M, Sasaki MS, Sonoda E, Morrison C, Hashimoto M, Utsumi H, et al. Homologous recombination and non-homologous end-joining pathways of DNA double-strand break repair have overlapping roles in the maintenance of chromosomal integrity in vertebrate cells. EMBO Journal. 1998;17(18):5497-5508

[13] Ma Y, Pannicke U, Schwarz K, Lieber MR. Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. Cell. 2002;108(6):781-794

[14] Koch CA, Agyei R, Galicia S, Metalnikov P, O'Donnell P, Starostine A, et al. Xrc4 physically links DNA end processing by polynucleotide kinase to DNA ligation by DNA ligase IV. EMBO Journal. 2004;23(19):3874-3885

[15] Chappell C, Hanakahi LA, Karimi-Busheri F, Weinfield M, West SC. Involvement of human polynucleotide kinase in double-strand break repair by non-homologous end joining. EMBO Journal. 2002;21(11):2827-2832

[16] Jilani A, Ramotar D, Slack C, Ong C, Yang XM, Scherer SW, et al. Molecular cloning of the human gene, PNKP, encoding a polynucleotide kinase 3'-phosphatase and evidence for its role in repair of DNA strand breaks caused by oxidative damage. Journal of Biological Chemistry. 1999;274(34):24176-24186

[17] Soulasingh-Sprauel P, Rivera-Munoz P, Malivert L, Le Guyader G, Abramowski V, Revy P, et al. V(D)J and immunoglobulin class switch recombinations: A paradigm to study the regulation of DNA end-joining. Oncogene. 2007;26(56):7780-7791

[18] Woodbine L, Gennery AR, Jeggo PA. The clinical impact of deficiency in DNA non-homologous end-joining. DNA Repair (Amst). 2014;16:84-96

[19] Shimada M, Dumitrache LC, Russell HR, McKinnon PJ. Polynucleotide kinase-phosphatase enables neurogenesis via multiple DNA repair pathways to maintain genome stability. EMBO Journal. 2015;34(19):2465-2480

[20] Shiloh Y, Ziv Y. The ATM protein kinase: Regulating the cellular response to genotoxic stress, and more. Nature Reviews Molecular Cell Biology. 2013;14(4):197-210

[21] Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular auto-phosphorylation and dimer dissociation. Nature. 2003;421(6922):499-506

[22] van Attikum H, Gasser SM. Crosstalk between histone modifications during the DNA damage response. Trends in Cell Biology. 2009;19(5):207-217

[23] Thorslund T, Ripplinger A, Hoffmann S, Wild T, Uckelmann M, Villumsen B, et al. Histone H1 couples initiation and amplification of ubiquitin signalling after DNA damage. Nature. 2015;527(7578):389-393

[24] Shema E, Tirosh I, Aylon Y, Huang J, Ye C, Moskovits N, et al. The histone H2B-specific ubiquitin ligase RNF20/hBRE1 acts as a putative tumor suppressor through selective regulation of gene expression. Genes & Development. 2008;22(19):2664-2676
[25] Nakamura K, Kato A, Kobayashi J, Yanagihara H, Sakamoto S, Oliveira DV, et al. Regulation of homologous recombination by RNF20-dependent H2B ubiquitination. Molecular Cell. 2011;41(5):515-528

[26] Sartori AA, Lukas C, Coates J, Mistrik M, Fu S, Bartek J, et al. Human CtIP promotes DNA end resection. Nature. 2007;450(7169):509-514

[27] McIlwraith MJ, Van Dyck E, Masson JY, Stasiak AZ, Stasiak A, West SC. Reconstitution of the strand invasion step of double-strand break repair using human Rad51 Rad52 and RPA proteins. Journal of Molecular Biology. 2000;304(2):151-164

[28] McIlwraith MJ, West SC. DNA repair synthesis facilitates RAD52-mediated second-end capture during DSB repair. Molecular Cell. 2008;29(4):510-516

[29] Nishi R. Balancing act: To be, or not to be ubiquitylated. Mutation Research. 2017;803-805:43-50

[30] McKinnon PJ. Genome integrity and disease prevention in the nervous system. Genes & Development. 2017;31(12):1180-1194

[31] Boveri T. Concerning the origin of malignant tumours by Theodor Boveri. Translated and annotated by Henry Harris. Journal of Cell Science. 2008;121(Suppl 1):1-84

[32] Nigg EA. Centrosome duplication: of rules and licenses. Trends in Cell Biology. 2007;17(5):215-221

[33] Doxsey S. Re-evaluating centrosome function. Nature Reviews Molecular Cell Biology. 2001;2(9):688-698

[34] Fukasawa K. Oncogenes and tumour suppressors take on centrosomes. Nature Reviews Cancer. 2007;7(12):911-924

[35] Ganem NJ, Godinho SA, Pellman D. A mechanism linking extra centrosomes to chromosomal instability. Nature. 2009;460(7252):278-282

[36] Godinho SA, Kwon M, Pellman D. Centrosomes and cancer: How cancer cells divide with too many centrosomes. Cancer and Metastasis Reviews. 2009;28(1-2):85-98

[37] Shimada M, Hirayama R, Komatsu K. High LET radiation amplifies centrosome over-duplication through a pathway of gamma-tubulin monoubiquitination. International Journal of Radiation Oncology, Biology, Physics. 2013;86(2):358-365

[38] Zhang S, Hemmerich P, Grosse F. Werner syndrome helicase (WRN), nuclear DNA helicase II (NDH II) and histone gammaH2AX are localized to the centrosome. Cell Biology International. 2007;31(10):1109-1121

[39] Niwa T, Saito H, Imajoh-ohmi S, Kaminishi M, Seto Y, Miki Y, et al. BRCA2 interacts with the cytoskeletal linker protein plectin to form a complex controlling centrosome localization. Cancer Science. 2009;100(11):2115-2125

[40] Smith E, Dejsuphong D, Balestrini A, Hampel M, Lenz C, Takeda S, et al. An ATM- and ATR-dependent checkpoint inactivates spindle assembly by targeting CEP63. Nature Cell Biology. 2009;11(3):278-285
[41] Dodson H, Bourke E, Jeffers LJ, Vagnarelli P, Sonoda E, Takeda S, et al. Centrosome amplification induced by DNA damage occurs during a prolonged G2 phase and involves ATM. EMBO Journal. 2004;23(19):3864-3873

[42] Wang HF, Takenaka K, Nakanishi A, Miki Y. BRCA2 and nucleophosmin coregulate centrosome amplification and form a complex with the Rho effector kinase ROCK2. Cancer Research. 2011;71(1):68-77

[43] Bourke E, Dodson H, Merdes A, Cuffe L, Zachos G, Walker M, et al. DNA damage induces Chk1-dependent centrosome amplification. EMBO Reports. 2007;8(6):603-609

[44] Griffith E, Walker S, Martin CA, Vagnarelli P, Stiff T, Vernay B, et al. Mutations in pericentrin cause Seckel syndrome with defective ATR-dependent DNA damage signaling. Nature Genetics. 2008;40(2):232-236

[45] Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB, et al. Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. Science. 2008;319(5864):816-819

[46] Chen A, Kleiman FE, Manley JL, Ouchi T, Pan ZQ. Autoubiquitination of the BRCA1* BARD1 RING ubiquitin ligase. Journal of Biological Chemistry. 2002;277(24):22085-22092

[47] Kleiman FE, Wu-Baer F, Fonseca D, Kaneko S, Baer R, Manley JL. BRCA1/BARD1 inhibition of mRNA 3' processing involves targeted degradation of RNA polymerase II. Genes & Development. 2005;19(10):1227-1237

[48] Starita LM, Horwitz AA, Keogh MC, Ishioka C, Parvin JD, Chiba N. BRCA1/BARD1 ubiquitinate phosphorylated RNA polymerase II. Journal of Biological Chemistry. 2005;280(26):24498-24505

[49] Sato K, Hayami R, Wu W, Nishikawa T, Nishikawa H, Okuda Y, et al. Nucleophosmin/B23 is a candidate substrate for the BRCA1-BARD1 ubiquitin ligase. Journal of Biological Chemistry. 2004;279(30):30919-30922

[50] Wu W, Nishikawa H, Hayami R, Sato K, Honda A, Aratani S, et al. BRCA1 ubiquitinates RPB8 in response to DNA damage. Cancer Research. 2007;67(3):951-958

[51] Eakin CM, Maccoss MJ, Finney GL, Klevit RE. Estrogen receptor alpha is a putative substrate for the BRCA1 ubiquitin ligase. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(14):5794-5799

[52] Wu W, Koike A, Takeshita T, Ohta T. The ubiquitin E3 ligase activity of BRCA1 and its biological functions. Cell division. 2008;3(1)

[53] Densham RM, Morris JR. The BRCA1 Ubiquitin ligase function sets a new trend for remodelling in DNA repair. Nucleus. 2017;8(2):116-125

[54] Parvin JD, Sankaran S. The BRCA1 E3 ubiquitin ligase controls centrosome dynamics. Cell Cycle. 2006;5(17):1946-1950

[55] Sankaran S, Parvin JD. Centrosome function in normal and tumor cells. Journal of Cellular Biochemistry. 2006;99(5):1240-1250
[56] Sankaran S, Starita LM, Simons AM, Parvin JD. Identification of domains of BRCA1 critical for the ubiquitin-dependent inhibition of centrosome function. Cancer Research. 2006;66(8):4100-4107

[57] Starita LM, Machida Y, Sankaran S, Elias JE, Griffin K, Schlegel BP, et al. BRCA1-dependent ubiquitination of gamma-tubulin regulates centrosome number. Molecular and Cellular Biology. 2004;24(19):8457-8466

[58] Shimada M, Sagae R, Kobayashi J, Habu T, Komatsu K. Inactivation of the Nijmegen breakage syndrome gene leads to excess centrosome duplication via the ATR/BRCA1 pathway. Cancer Research. 2009;69(5):1768-1775

[59] Shimada M, Komatsu K. Emerging connection between centrosome and DNA repair machinery. Journal of Radiation Research. 2009;50(4):295-301

[60] Shimada M, Kobayashi J, Hirayama R, Komatsu K. Differential role of repair proteins, BRCA1/NBS1 and Ku70/DNA-PKcs, in radiation-induced centrosome overduplication. Cancer Science. 2010;101(12):2531-2537

[61] Li J, D’Angiolella V, Seeley ES, Kim S, Kobayashi T, Fu W, et al. USP33 regulates centrosome biogenesis via deubiquitination of the centriolar protein CP110. Nature. 2013;495(7440):255-259

[62] Liu X, Holstege H, van der Gulden H, Treur-Mulder M, Zevenhoven J, Velds A, et al. Somatic loss of BRCA1 and p53 in mice induces mammary tumors with features of human BRCA1-mutated basal-like breast cancer. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(29):12111-12116

[63] McCarthy A, Savage K, Gabriel A, Naceur C, Reis-Filho JS, Ashworth A. A mouse model of basal-like breast carcinoma with metaplastic elements. Journal of Pathology. 2007;211(4):389-398

[64] Pao GM, Zhu Q, Perez-Garcia CG, Chou SJ, Suh H, Gage FH, et al. Role of BRCA1 in brain development. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(13):E1240-E1248

[65] Pulvers JN, Huttner WB. Brca1 is required for embryonic development of the mouse cerebral cortex to normal size by preventing apoptosis of early neural progenitors. Development. 2009;136(11):1859-1868

[66] Marthiens V, Ruijano MA, Pennetier C, Tessier S, Paul-Gilloteaux P, Basto R. Centrosome amplification causes microcephaly. Nature Cell Biology. 2013;15(7):731-740

[67] Ishiai M, Sato K, Tomida J, Kitao H, Kurumizaka H, Takata M. Activation of the FA pathway mediated by phosphorylation and ubiquitination. Mutation Research. 2017;803-805:89-95

[68] Pang Q, Andreassen PR. Fanconi anemia proteins and endogenous stresses. Mutation Research. 2009;668(1-2):42-53
[69] Sasaki MS, Tonomura A. A high susceptibility of Fanconi’s anemia to chromosome breakage by DNA cross-linking agents. Cancer Research. 1973;33(8):1829-1836

[70] Stingele J, Bellelli R, Boulton SJ. Mechanisms of DNA-protein crosslink repair. Nature Reviews Molecular Cell Biology. 2017;18(9):563-573

[71] D’Andrea AD. Targeting DNA repair pathways in AML. Best Practice & Research Clinical Haematology. 2010;23(4):469-473

[72] Ceccaldi R, Sarangi P, D’Andrea AD. The Fanconi anaemia pathway: new players and new functions. Nature Reviews Molecular Cell Biology. 2016;17(6):337-349

[73] Kee Y, D’Andrea AD. Molecular pathogenesis and clinical management of Fanconi anemia. Journal of Clinical Investigation. 2012;122(11):3799-3806

[74] Kim H, D’Andrea AD. Regulation of DNA cross-link repair by the Fanconi anemia/BRCA pathway. Genes & Development. 2012;26(13):1393-1408

[75] D’Andrea AD. Susceptibility pathways in Fanconi’s anemia and breast cancer. New England Journal of Medicine. 2010;362(20):1909-1919

[76] Nijman SM, Huang TT, Dirac AM, Brummelkamp TR, Kerkhoven RM, D’Andrea AD, et al. The deubiquitinating enzyme USP1 regulates the Fanconi anemia pathway. Molecular Cell. 2005;17(3):331-339

[77] Parmar K, Kim J, Sykes SM, Shimamura A, Stuckert P, Zhu K, et al. Hematopoietic stem cell defects in mice with deficiency of Fancd2 or Usp1. Stem Cells. 2010;28(7):1186-1195

[78] Yang Y, Kuang Y, Montes De Oca R, Hays T, Moreau L, Lu N, et al. Targeted disruption of the murine Fanconi anemia gene, Fancg/Xrcc9. Blood. 2001;98(12):3435-3440

[79] Reliene R, Yamamoto ML, Rao PN, Schiestl RH. Genomic instability in mice is greater in Fanconi anemia caused by deficiency of Fancd2 than Fancg. Cancer Research. 2010;70(23):9703-9710

[80] Parmar K, D’Andrea A, Niedernhofer LJ. Mouse models of Fanconi anemia. Mutation Research. 2009;668(1-2):133-140

[81] Cheng NC, van de Vrugt HJ, van der Valk MA, Oostra AB, Krimpenfort P, de Vries Y, et al. Mice with a targeted disruption of the Fanconi anemia homolog Fanca. Human Molecular Genetics. 2000;9(12):1805-1811

[82] Houghtaling S, Timmers C, Noll M, Finegold MJ, Huang JR, Meyn MS, et al. Targeted disruption of exons 1 to 6 of the Fanconi Anemia group A gene leads to growth retardation, strain-specific microphthalmia, meiotic defects and primordial germ cell hypoplasia. Human Molecular Genetics. 2003;12(16):2063-2076

[83] Koomen M, Cheng NC, van de Vrugt HJ, Godthelp BC, van der Valk MA, Oostra AB, et al. Reduced fertility and hypersensitivity to mitomycin C characterize Fancg/Xrcc9 null mice. Human Molecular Genetics. 2002;11(3):273-281

[84] Houghtaling S, Timmers C, Noll M, Finegold MJ, Jones SN, Meyn MS, et al. Epithelial cancer in Fanconi anemia complementation group D2 (Fancd2) knockout mice. Genes & Development. 2003;17(16):2021-2035
[85] Matsuura S, Tauchi H, Nakamura A, Kondo N, Sakamoto S, Endo S, et al. Positional cloning of the gene for Nijmegen breakage syndrome. Nature Genetics. 1998;19(2):179-181
[86] Komatsu K. NBS1 and multiple regulations of DNA damage response. Journal of Radiation Research. 2016;57(Suppl 1):i11-i17
[87] Matsuura S, Kobayashi J, Tauchi H, Komatsu K. Nijmegen breakage syndrome and DNA double strand break repair by NBS1 complex. Advances in Biophysics. 2004;38(Complete):65-80
[88] Tauchi H, Kobayashi J, Morishima K, van Gent DC, Shiraishi T, Verkaik NS, et al. Nbs1 is essential for DNA repair by homologous recombination in higher vertebrate cells. Nature. 2002;420(6911):93-98
[89] Sakamoto S, Iijima K, Mochizuki D, Nakamura K, Teshigawara K, Kobayashi J, et al. Homologous recombination repair is regulated by domains at the N- and C-terminus of NBS1 and is dissociated with ATM functions. Oncogene. 2007;26(41):6002-6009
[90] Iijima K, Muranaka C, Kobayashi J, Sakamoto S, Komatsu K, Matsuura S, et al. NBS1 regulates a novel apoptotic pathway through Bax activation. DNA Repair (Amst). 2008;7(10):1705-1716
[91] Kobayashi J, Tauchi H, Chen B, Burma S, Tashiro S, Matsuura S, et al. Histone H2AX participates the DNA damage-induced ATM activation through interaction with NBS1. Biochemical and Biophysical Research Communications. 2009;380(4):752-757
[92] Yanagihara H, Kobayashi J, Tateishi S, Kato A, Matsuura S, Tauchi H, et al. NBS1 recruits RAD18 via a RAD6-like domain and regulates Pol eta-dependent translesion DNA synthesis. Molecular Cell. 2011;43(5):788-797
[93] Tauchi H, Matsuura S, Kobayashi J, Sakamoto S, Komatsu K. Nijmegen breakage syndrome gene, NBS1, and molecular links to factors for genome stability. Oncogene. 2002;21(58):8967-8980
[94] Kobayashi J, Antoccia A, Tauchi H, Matsuura S, Komatsu K. NBS1 and its functional role in the DNA damage response. DNA Repair (Amst). 2004;3(8-9):855-861
[95] Morishima K, Sakamoto S, Kobayashi J, Izumi H, Suda T, Matsumoto Y, et al. TopBP1 associates with NBS1 and is involved in homologous recombination repair. Biochemical and Biophysical Research Communications. 2007;362(4):872-879
[96] Stracker TH, Petrini JH. The MRE11 complex: starting from the ends. Nature Reviews Molecular Cell Biology. 2011;12(2):90-103
[97] Wu J, Zhang X, Zhang L, Wu CY, Rezaeian AH, Chan CH, et al. Skp2 E3 ligase integrates ATM activation and homologous recombination repair by ubiquitinating NBS1. Molecular Cell. 2012;46(3):351-361
[98] Goldstein G, Scheid M, Hammerling U, Schlesinger DH, Niall HD, Boyse EA. Isolation of a polypeptide that has lymphocyte-differentiating properties and is probably represented universally in living cells. Proceedings of the National Academy of Sciences of the United States of America. 1975;72(1):11-15
[99] Schlesinger DH, Goldstein G, Niall HD. The complete amino acid sequence of ubiquitin, an adenylate cyclase stimulating polypeptide probably universal in living cells. Biochemistry. 1975;14(10):2214-2218

[100] Ciechanover A, Hod Y, Hershko A. A heat-stable polypeptide component of an ATP-dependent proteolytic system from reticulocytes. Biochemical and Biophysical Research Communications. 1978;81(4):1100-1105

[101] Hosoya N, Miyagawa K. Targeting DNA damage response in cancer therapy. Cancer Science. 2014;105(4):370-388