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Mini-review

DNA damage response – A double-edged sword in cancer prevention and cancer therapy

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ABSTRACT

Genomic stability depends on an efficient DNA damage repair system to keep the chromosomes intact. Unrepaired DNA damage not only causes cell cycle arrest, apoptosis, but also accumulates genome mutations. DNA damage response (DDR) exhibits a critical function on the protection against human cancer, as indicated by the high predisposition to cancer of individuals with germ-line mutations in DDR genes. However, a defective DNA repair is liked intimately with the unchecked proliferation and the intrinsic resistance to clinical DNA-damaging agents. Therefore, abrogation of specific proteins in DNA damage repair pathways is a promising strategy for developing targeted cancer treatments. It may sound paradoxical to inhibit DDR pathway for sensitization of clinical therapy because cancer promotion and malignant transformation are aided by deficient DNA repair pathways. Actually, DDR acts as a positive guardian of genomic stability to prevent from tumorigenesis. On the other hand, DDR also performs as a negative saboteur to resist chemo- and radiotherapy. In this regard, DDR functions as "a double-edged sword" in cancer prevention and cancer therapy. The defective DDR that makes cancer cells of high mutability should alternatively provide therapeutic opportunities that confer the lethality to cancer cells without harming normal cells.

DNA damage induces genomic instability and tumorigenesis

DNA damage, due to environmental factors or normal metabolic processes inside the cell, can compromise the cell's ability to carry out its regular function, which is appreciably prone to genomic instability [1–3]. Genomic instability as one of the most pervasive onset of tumorigenesis is linked intimately with oncogene activation and inactivation of certain tumor suppressors. Given the potentially devastating effects of genomic instability, cells have evolved the caretaking systems to maintain genomic integrity and prevent oncogenesis. A critical role of DNA damage repair in protecting humans against cancer becomes incontrovertible with the increasing studies showing that many of the human cancer predisposition diseases arise from germ-line mutations in DNA damage repair genes [4,5].

Generally, DNA damage is divided into two main types: 1) endogenous damage caused by reactive oxygen species (ROS) produced from normal metabolic byproducts, especially the process of oxidative deamination, as well as replication errors. 2) exogenous damage caused by external stresses such as ionizing radiation (IR), ultraviolet light (UV), hydrolysis or thermal disruption, certain plant toxins, human-made mutagenic chemicals, especially aromatic compounds [6]. The replication of damaged DNA before cell division can result in the introduction of wrong bases. Daughter cells that inherit these mismatch bases carry mutations from the original DNA sequence are unrecoverable. Faced with DNA damage, cells always elicit DNA damage response (DDR) comprising DNA damage recognition, signal transduction, transcriptional regulation, cell cycle control and DNA repair to attenuate DNA damage [7]. These signal transduction cascades facilitate faithful transmission of cellular genome in response to DNA damage threat by coordinating DNA repair, cell cycle arrest and apoptosis pathway. Actually, these DDR reactions are the complex network including specialized 'sensor' proteins to recognize DNA damage, 'transducer' proteins to recruit subsequent 'effector' proteins responsible for cell cycle arrest, apoptosis, transcription halt and DNA repair [8].

Abbreviations: DDR, DNA damage response; BER, base excision repair; MMR, mismatch repair; NER, nucleotide excision repair; TLS, translesion DNA synthesis; NHEJ, nonhomologous end joining; HR, homologous recombination; SSBs, single strand DNA breaks; DSBs, double strand DNA breaks; IR, ionizing radiation; TME, tumor microenvironment; CSCs, cancer stem cells; MLH1, MutL homolog 1; PMS2, postmeiotic segregation increased 2; MSH2, MutS homolog 2; UV, Ultraviolet; FA, Fanconi anemia; XPA, Xeroderma Pigmentosum complementation group A; BRCA1, breast cancer 1; MRE11, meiotic recombination 11; ROS, reactive oxygen species; ATM, ataxia telangiectasia mutated; NBS, Nijmegen breakage syndrome; PCNA, proliferating cell nuclear antigen; CDK, cyclin-dependent kinases; pRb, retinoblastoma suppressor protein; Mdm2, mouse double minute 2 homolog; PARP, poly (ADP-ribose) polymerase; CHK1, Checkpoint kinases 1; CDC2, cell division cycle protein 2; AP, apurinic/apyrimidinic; ICL, interstrand cross-link.

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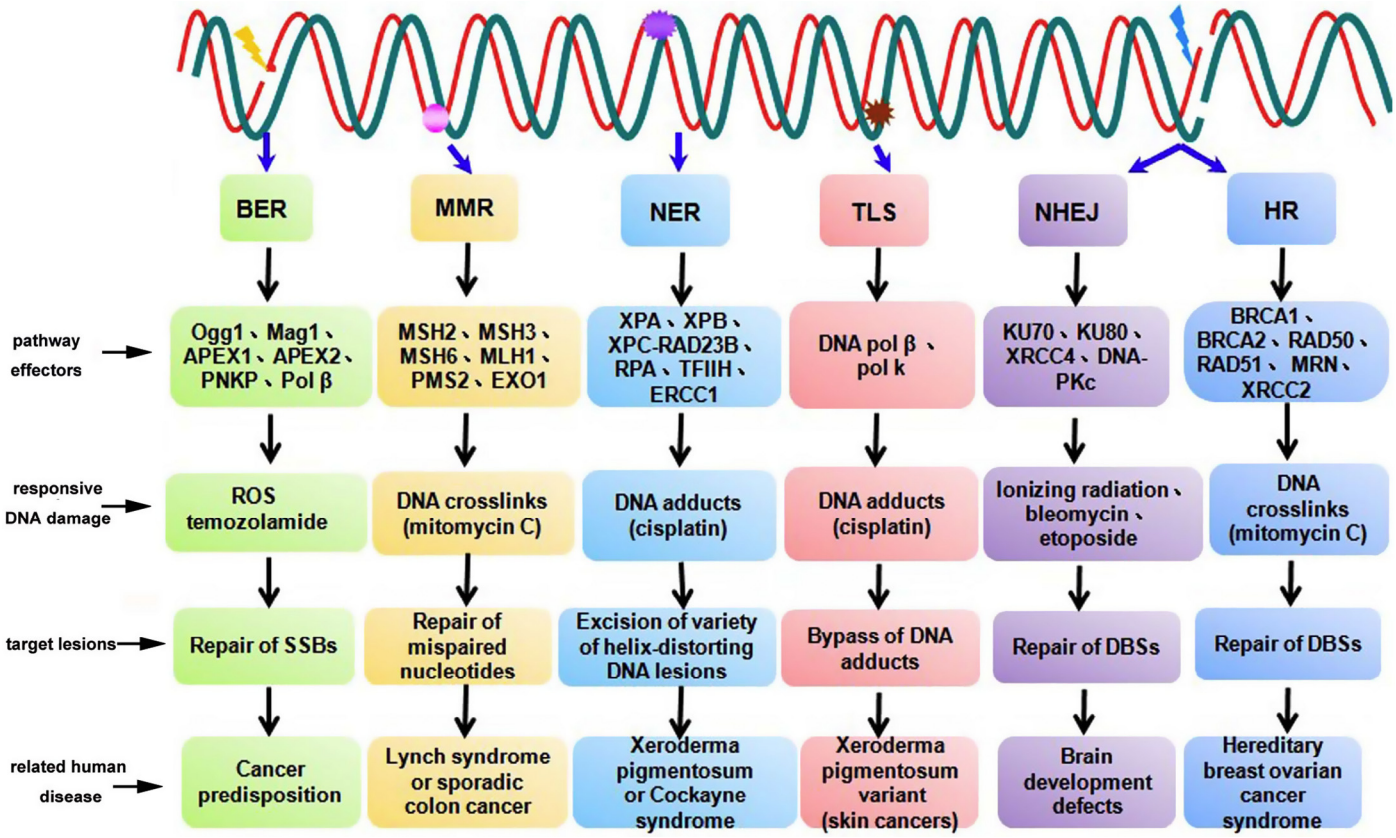

Fig. 1. The molecular mechanisms, the pathway effectors and the biological functions of six major DNA repair pathways: base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), translesion DNA synthesis (TLS), nonhomologous end joining (NHEJ) and homologous recombination (HR).

Since genomic stability is essential for faithful replication of the genome, and so is indispensible for cellular survival, cells have evolved a variety of mechanisms to protect genome integrity and repair any damaged DNA before trigger 'checkpoint' control [4,7,9]. Under normal physiological conditions, there are six major DNA repair pathways to counter DNA lesion, as shown in Fig. 1: base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), translesion DNA synthesis (TLS), nonhomologous end joining (NHEJ), homologous recombination (HR).

BER

In response to ROS produced during metabolism or environmental stress, DNA is normally subjected to single strand DNA breaks (SSB) and repaired by BER [10]. First, DNA glycosylases recognize and remove inappropriate bases to form apurinic/apyrimidinic (AP) sites. The resulting AP sites are processed by the AP endonuclease Ape1, leaving a 5'-deoxyribose phosphate, in turn by AP lyase, leaving a 3'-elimination product [11]. Finally, SSB can be repaired by either short-patch or long-patch BER. Notably, BER is important for removing damaged bases that otherwise cause DNA strand mutations by mispairing or lead to stall during DNA replication.

MMR

MMR removes mispaired nucleotides due to replication errors and repairs DNA adducts such as platinum-based chemotherapeutic agents [12,13]. Initially, the heterodimeric MutS homolog (MSH) complex recognizes the nucleotide mismatch, followed by its interaction with MutL homolog 1(MLH1)/postmeiotic segregation increased 2 (PMS2) and MLH1/MLH3 complexes. Several proteins including MSH2, MSH3, MSH6, MLH1, MLH3, PMS1, and PMS2 participate in the process of nucleotide excision and resynthesis. Tumor cells deficient in MMR are more likely to exhibit microsatellite instability than normal cells. Interestingly, an intact MMR pathway is required for cisplatin sensitivity rather than resistance as would be expected, indicating that the MMR pathway may guide cell to apoptotic death in response to DNA breaks caused by excision of adducts, thereby sensitizing cisplatin cytotoxicity in a manner independent of DNA damage repair.

NER

NER acts on a variety of helix-distorting DNA lesions caused mostly by exogenous sources [14,15]. A major function of NER facilitates the removal of pyrimidine dimers that are induced by UV. This pathway may also be particularly important in conferring resistance to platinum-based chemotherapy. Members of the NER pathway consist of Xeroderma Pigmentosum complementation group A (XPA), XPB, XPC, XPD, XPE, XPF, and XPG proteins. As for the other DNA repair pathway, these proteins cooperate to recognize and excise the damaged nucleotides, in turn, resynthesize and ligate the damaged DNA strand. NER includes two major branches: transcription-coupled repair and global genome repair. Global genome repair is a slow random process of inspecting the entire genome for damage, while transcription-coupled repair is a highly efficient repair of DNA damage that specifically blocks the progression of RNA polymerase II.

TLS

TLS is a DNA damage tolerance process that allows the DNA replication machinery to replicate DNA lesions such as thymine dimers or AP sites. It involves switching out regular DNA polymerases for