Biochemistry (Moscow), Vol. 67, No. 7, 2002, pp. 730-736. Translated from Biokhimiya, Vol. 67, No. 7, 2002, pp. 882-889.

REVIEW

Role of Excision Mechanisms of DNA Repair in Induction of Apoptosis

V. A. Tronov*, E. M. Konstantinov, and I. I. Kramarenko

Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, Moscow, 119991 Russia; fax: (095) 938-2156; E-mail: tronov@center.chph.ras.ru

Received September 27, 2001
Revision received December 13, 2001

Abstract—DNA repair and apoptosis lead to principally different final results: the first mechanism removes damages from DNA, restoring genome integrity; the second mechanism eliminates potentially dangerous cells harboring DNA lesions. The cells deficient in mismatch repair (MMR) demonstrate inceased resistance (viability) to DNA-damaging agents due to decreased ability to undergo apoptosis. This means that mechanism of MMR both restores structure of DNA and generates a signal for apoptosis. DNA breaks and single strand gaps, which are temporarily produced by excison mechanism during DNA repair, are suggested to be the initial signals for apoptosis. However pathway involved in such signaling at least partially is independent of p53 function.

Key words: excision repair, DNA breaks, apoptosis

Molecular events resulting in cell death as the final cell response to various damages of DNA have been studied in numerous works during the last decade [1-4]. The relationship of the primary signal with cell death is well studied in the case of a signal from the cell surface (e.g., the binding of FasR with FasL) [5]. In the case of the initiating DNA damage this relationship is more difficult to be followed partially because of the complexity of the phenomenon: DNA-damaging agents also interact with other components of the cell, such as RNA, lipids, proteins. However, using a set of isogenic cell lines different in the ability to repair the only type of DNA damage just the damage of DNA has been shown to be the initial cause of the cell death [6, 7].

The cause–effect relations between the DNA damage and the cell death are outlined in Fig. 1. In this scheme the phenomena of cell viability/tolerance, chromosome aberrations, mutagenesis, etc. are not considered. The scheme shows three pathways of development of the DNA damage to the final event of the cell death. The number *1* in Fig. 1 designates a "non-repair" pathway of development of the DNA damage. Tumor suppressor p53 plays the key role in this pathway. This pathway is studied better than the other pathways presented in the scheme. The results of these studies are presented in many reviews [8-11]. Note two specific features of this pathway. The first concerns the type of DNA damage. In our case these are DNA breaks. This type of damages is thought to be a sufficient signal to trigger apoptosis. The signal is mediated by p53 [12, 13]. The second specific feature concerns the DNA repair. Its absence in this pathway suggests that the signal transduction and initiation of p53-dependent apoptosis need no repair [14]. However, the breaks are a substrate for the repair, whereas p53 marks disorders in the DNA structure and transactivates some genes accelerating the repair [15, 16]. The repair of DNA breaks can be considered as a particular case of the nucleotide excision repair (see below) which is included into the independent pathway of the signal transduction (*2* in the scheme).

The idea of a signal translation via the repair by the second pathway is known from the late 1980s [17]. We and other authors have followed this pathway of translation of the primary signal induced by ionizing radiation [18],

Abbreviations: ERCC) excision repair cross complementing protein; FEN) flap endonuclease; hMLH) human MutL homolog (the homolog of the MutL protein of *E. coli*); hMSH) human MutS homolog (the homolog of the MutS protein of *E. coli*); hPMS) human post-meiotic segregation (the homolog of a protein responsible for the post-meiotic segregation in yeasts); HNPCC) hereditary non-polyposis colorectal carcinoma; HSSB) human single-strand binding protein; PARP) poly(ADP ribose) polymerase; PCNA) proliferating cell nuclear antigen; RPA) replication protein A; TFIIH) human transcription factor II.

* To whom correspondence should be addressed.

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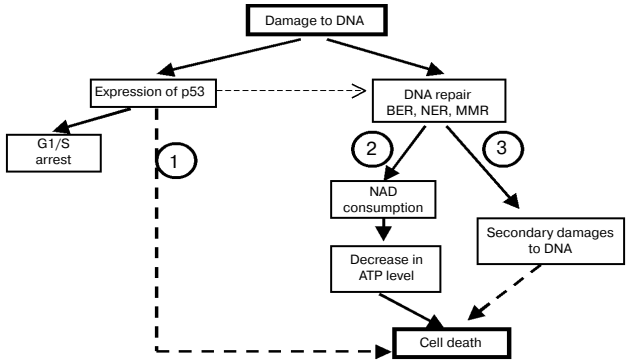

Fig. 1. Scheme of three pathways which connect a genotoxic stress with a cytotoxic cell response. The dotted line shows intermediate stages not presented in the scheme. Each pathway is considered in the text.

etoposide [19], and by oxidative stress [20]. In this pathway the repair mainly contributes to the induction of apoptosis by decreasing the intracellular levels of NAD^+ and ATP due to activities of the repair system components [21]. It should be emphasized that the "de-energization" level of the cell can determine the type of the cell death, apoptosis or necrosis [20, 22].

The purpose of this review is to consider the third pathway of development of the cytotoxic effect. This pathway is associated with generation of secondary damage during the DNA repair which either is not repaired or its repair is difficult. This pathway suggests that chemically modified bases in DNA can be the primary damage. Such damage is a source of mutations and is a substrate for four repair mechanisms in mammalian cells (Fig. 2): the base excision repair (BER); the nucleotide excision repair (NER); a direct biochemical repair; and the mismatch repair (MMR), the repair of mispairs, deletions and excess insertions. The first three repair mechanisms function before the initiation of replication and, therefore, can also occur in resting cells. The MMR system can function after the cell has passed even one replication cycle, i.e., the MMR occurs only in proliferating cells. Each repair mechanism is considered below in connection with its possible involvement in the induction of apoptosis.

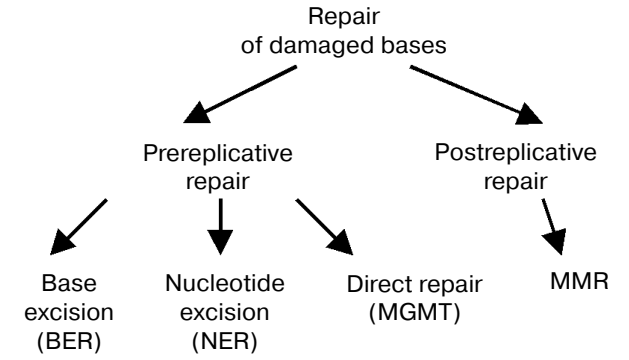

Fig. 2. Four repair mechanisms of damaged DNA bases in the cell.

PREREPLICATIVE EXCISION REPAIR

Base excision repair (BER) is started with an activation of specific glycosylases which hydrolyze the N-glycosidic bonds and eliminate the damaged bases without disturbance of the sugar-phosphate skeleton of DNA [23]. This results in the generation of an apurinic/apyrimidinic site (AP). The AP can inhibit the activity of DNA-polymerases, but the enzyme often rounds the AP and inserts the non-complementary nucleotide into the DNA molecule synthesized [24] that causes mutations. In *Escherichia coli* such a nucleotide is most often represented by dATP. Therefore, the so-called "A-rule" has been postulated: DNA-polymerase makes a non-template insertion of adenine into the daughter strand opposite the AP [25]. Eucaryotic polymerases are sometimes out of this rule [26].

The AP can be repaired. This can involve AP-endonuclease which makes a break in either 5′- or 3′-position from the AP and removes the sugar residue. The gap produced is filled in with DNA-polymerase β (Fig. 3). The gap size varies within some nucleotides and depends on two circumstances: the presence of the phosphodiesterase activity in the AP-endonuclease and the type of polymerase involved in the resynthesis. The polymerase β fills in very short gaps [27], whereas the polymerases δ and ε fill in gaps by the nick-translation mechanism, with PCNA as a processing factor [28]. In this case a flap is produced of some (⩽6) nucleotides [29], which is eliminated by flap-endonuclease (FEN-1) [30, 31]. The substrate range of the BER is limited by a diversity of glycosylases initiating this type of repair.

Obviously, the BER with excision of short regions of DNA is characterized by the low probability of mistakes and by the short lifetime of the gaps. Therefore, the contribution to apoptosis of this type of repair is not high. This may be a reason for the small number of publications considering apoptosis in association with functions of the BER system [32].

Nucleotide excision repair (NER) is characterized by a wide spectrum of types of damage removed: thymine dimers, photoproducts, adducts of thymine interaction with psoralen, cis-platinum adducts, etc. The NER universality is provided by a great number of proteins involved in the damage recognition and in binding to damaged sites. The NER repair complex includes at least

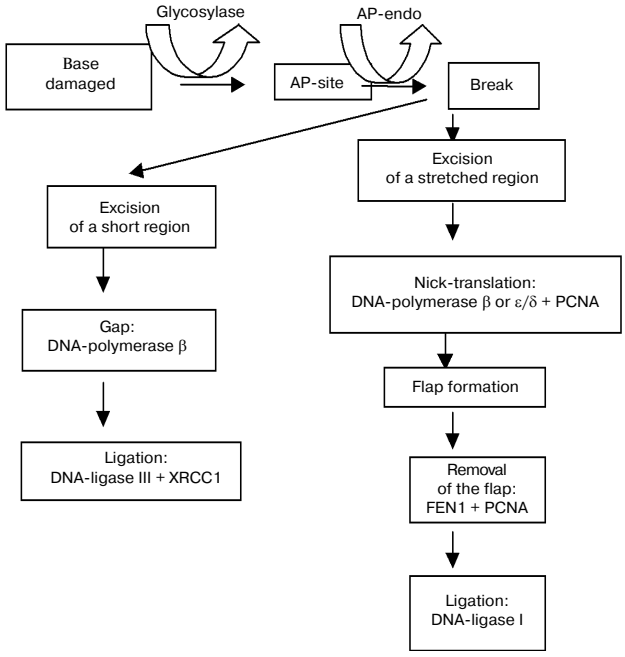

Fig. 3. Two pathways of DNA repair by the base excision repair (BER) mechanism in eucaryotic cell.

16 polypeptides [1]. The majority of enzymes in the human NER system have been identified in studies on the cells of a patient with xeroderma pigmentosum (the XP-syndrome). Therefore, the names of these enzymes often include the abbreviation XP. The first group of these enzymes is responsible for initial operations of the NER: recognition, binding, and incision. This group includes the following proteins: XPA (p31) which is responsible for the damage recognition; RPA/HSSB (p70) which binds to the damaged DNA; TFIIH/XPB/ERCC3 (p89) which produces an excision complex and has helicase activity; XPF/ERCC4 (p112) which makes the 5′-break; ERCC1 (p33) which interacts with XPF; XPG/ERCC5 (p135) which makes the 3′-break and has the FEN activity.

Due to the repair complex activity, a single-strand flap is produced which contains 27-29 nucleotides including the nucleotide damaged [33]. The flap can be removed during in the incision stage with a resulting production of a gap [34]. This gap can be filled in with involvement of DNA-polymerase δ or ε together with the PCNA factor which promotes the dissociation of the excision complex from DNA [35]. The breaks at the insertion ends are ligated by DNA-ligase. Thus, the excision of a stretched region by the BER and the excision by the NER are different only in the length of the flap produced which includes ⩽6 or 27-29 nucleotides, respectively.

As in the case of BER, a signal for apoptosis at the NER can be generated during the repair synthesis. Because the length of the excision gap is more than 20 nucleotides, in the case of high local density of damage a number of gaps can fuse into one gap. And the generation of respectively stretched regions of the single-strand DNA increases the probability of their being attacked by nucleases and of their converting double-strand breaks.

Some of cis-platinum-induced DNA damages are diadducts and produce crosslinks between the bases of complementing strands of DNA [36]. Such damage can be repaired through the generation of a temporary double-strand break. If not repaired, these stop the replication. Such a block can fix non-canonical structures in DNA resulting in a "structural stress". All this leads to the apoptosis induction by cis-platinum in both proliferating and resting cells [37]. The dependence of apoptosis on PARP suggests that the DNA breaks resulting during the excision repair in the cell are involved in the induction of apoptosis [38].

POSTREPLICATIVE REPAIR

The MMR mechanism is responsible for a very important function of marking and correction of non-canonical base pairs G–T, G–A, C–A, etc., formed during the replication. Such mismatched (MM) pairs are generated occasionally at the rate of 1/10,000 as a result of DNA-polymerase mistake [39]. Moreover, during the replication of DNA regions which contain repeated sequences of a number of bases (microsatellite DNAs) the enzyme sometimes "slips" and omits some bases [40]. As a result, the strand synthesized on the template is the omitted number of nucleotides shorter than its pattern. And the DNA duplex produces in the initial chain a loop resembling the Greek letters α or Ω [41]. In the case of an excess insertion of nucleotides during the replication, such a loop is produced in a newly synthesized chain. The three types of damages mentioned disturb the regular structure of the duplex and are a substrate for the MMR. It has been shown that in *E. coli* only the daughter strand is corrected because the repair system can discriminate it from the mother strand by the level of base methylation [42]. The existence of such a discrimination mechanism has also been shown in mammalian cells [43], but the mechanism is believed to be universal, which is determined by "geography" of location of breaks near the MM initiating the repair in the daughter strand [44].

The MMR system first described 1975 for *E. coli* [45] was afterwards also detected in human cells [46]. Although in higher organisms the MMR system is significantly more complicated, these systems are fundamentally very similar, suggesting a high evolutionary conservatism of the MMR mechanism. All proteins of the MMR identified in human are homologs of the corresponding proteins in *E. coli* or *Saccharomyces*, and this is

represented by their names. The most important proteins are hMSH2, -3, -6; hMLH1 and hPMS1 and -2.

One of two heterodimers, MutSα (hMSH2–hMSH6) and MutSβ (hMSH2–hMSH3), is bound to the MM-containing DNA. Each dimer has its own range of the substrate competence: MutSα has an affinity for single MMs produced by a pair of non-complementary bases and for loops produced by an insertion/deletion of ⩽12 bases [47]. MutSβ recognizes MMs produced by two or more unpaired bases but is unable to recognize and repair an insertion/deletion of a single base. In general, the recognition mechanism of insertions/deletions of more than 20 nucleotides by the MMR system is still unclear. It seems that such damages can be efficiently repaired by other mechanisms (e.g., by recombination) [48, 49]. On binding to DNA, the heterodimer marks the damage and activates the generation and binding of the initiating repair complex MutLα (hMLH1–hPMS2). This reaction is accompanied by hydrolysis of ATP and requires PCNA to be involved [50]. The repair complex includes the endonuclease FEN1 and helicase which remove from DNA the MM-containing single-strand fragment. DNA-polymerases δ or ε fill in the gap and the boundary breaks are ligated with DNA-ligase (Fig. 4). Obviously, this mechanism is error free. Under normal conditions, it 1000-fold decreases the level of spontaneous mutations during replication [51, 52]. However, the result can be changed if a MM is generated by a genotoxic agent.

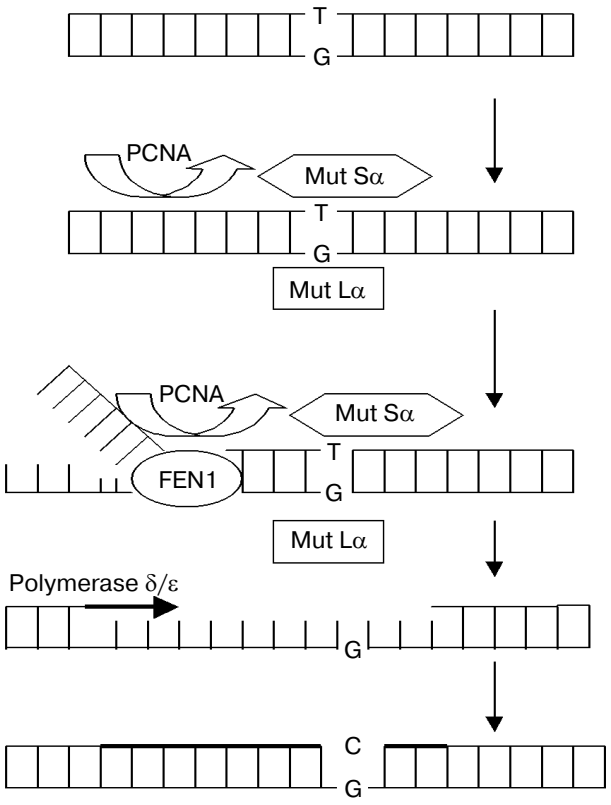

Fig. 4. Successive stages of repair of the G–T mispairs by the mismatch repair (MMR) mechanism.

MMR and apoptosis. It has been shown in many works that the bases modified by alkylating agent, cis-platinum, the purine analog 2-CldA induced apoptosis [7, 37]. In some cases apoptosis depended on p53 but it always depended on the functioning of MMR. The interrelation of apoptosis and MMR attracted sharply increased interest after the finding of correlation between MMR deficiency and the human hereditary non-polyposis colorectal carcinoma (HNPCC) [53-55]. Mutations in one of five genes of the MMR system in humans decrease its efficiency and increase the risk of some malignancies [53].

On the cell level a decrease in the MMR efficiency is accompanied by an increase in the cell resistance to DNA damage [56]. The MMR-deficient cells were resistant to cis-platinum and displayed a decreased ability for apoptosis [57]. The MMR-deficient CHO cells and human lymphoblasts also had a decreased ability for apoptosis induced with an alkylating agent N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) compared to the wild type cells [58]. In the same work the suppression of activity of the MutSα heterodimer which is responsible for recognition of the methylated guanine (O^6-MeG) in DNA made the cells insensitive to signals for apoptosis. All this suggests that the normally operating MMR mechanism generates a signal for apoptosis of damaged cells. So far the nature of this signal is not known in detail. Based on recent studies on the O^6-MeG repair and on the death of cells with this damage, it was suggested that gaps and breaks produced in DNA with the MMR involvement should play the key role in the induction of apoptosis [56, 59-61].

Repair of O^6-methylguanine and a signal for apoptosis. O^6-MeG is produced in DNA under the influence of alkylating agents, is characterized by high mutagenicity and carcinogenicity [59], and initiates apoptosis [58, 62]. In various cell lines and under various conditions, the MNNG-induced apoptosis can occur before the entrance of the cell into the cycle [32] and after the termination of two and more replication cycles [58, 60]. Therefore, it is suggested that in both cases the signal which triggers apoptosis in the O^6-MeG-containing cells is the same, although the repair systems dealing with the damage are different.

The specific and unique feature of O^6-MeG is its direct repair with the involvement of methylguanine-DNA-methyltransferase (MGMT). The enzyme transfers the methyl group from the nucleotide onto the cysteine residue in its active site [63, 64]. This results in the repair of guanine, whereas the enzyme is irreversibly inactivat-

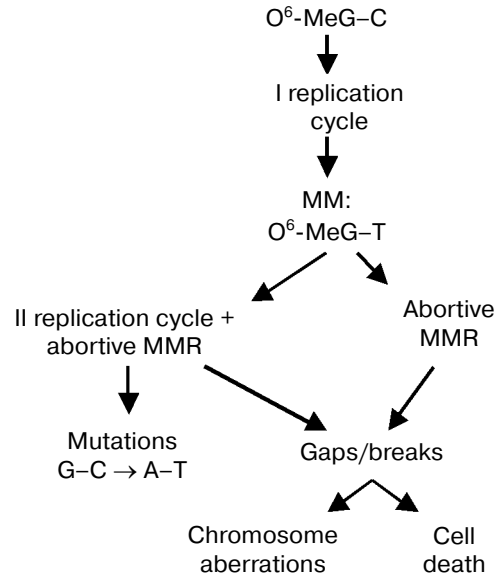

Fig. 5. A hypothetic pathway of the O^6-methylguanine transformation during MMR into the cytotoxic effect via the secondary damage of DNA: a double-strand break (DB) or a single-strand gap.

ed. This pathway is absolutely error free, but the repair volume is limited by number of the enzyme molecules and by the expression of the *mgmt* gene.

The events on the entrance of the O^6-MeG-containing DNA into the replication phase can be presented based on the hypothesis that DNA-polymerase takes the modified guanine as adenine [65]. The MMR which starts functioning after the first replication cycle becomes abortive, because during the filling the excision gap polymerase reproduces the mismatched pair O^6-MeG-T. In some of the sites a return to the O^6-MeG-C pair is possible. The second replication cycle inevitably results in a transversion of G–C → A–T (the succession is as follows: G–C + MNNG → O^6-MeG-C + I replication cycle → O^6-MeG-T + II replication cycle → A–T). The presence of such mutations associated with the production of O^6-MeG is shown elsewhere [66-68].

The abortive MMR repeated many times after the first replication cycle promotes a long-term existence not only of the MM but also of the excision gap in DNA (Fig. 4). Such damage is itself a signal for apoptosis and can be converted into a double-strand break under the influence of endonucleases. The double-strand break is generally thought to cause both chromosome aberrations and apoptosis. Double-strand gaps were recently found in CHO cells 24 h after the treatment with MNNG, near before the beginning of apoptosis [60].

The relationship between the DNA damage and apoptosis is shown in Fig. 5. Note, that till the initial damage of O^6-MeG is maintained in DNA, it can be directly repaired with MGMT. This means that the cell response to damage can depend on the ratio between the mistake-free repair due to MGMT and the MMR activity which generates the signal for apoptosis. In tissues with a low level of MGMT and the MMR deficiency mutant cells can be accumulated that increases the risk of malignant transformation.

In conclusion, consider two questions associated with the problem under discussion. The scheme presented in Fig. 5 can be realized in proliferating but not in resting cells [69]. This is supported by the absence of apoptotic death in non-dividing cells treated with MNNG [70]. Nevertheless, the resting cells can repair alkylated bases including O^6-MeG by the excision mechanism [28]. Evidently, the pre-replicative repair also generates breaks in DNA. Although this mechanism is less error prone and operates with a high rate (because it operates in the SOS-regimen), it induced an early (6 h) apoptosis in HeLa cells treated with MNNG or with methylmethane sulfonate [32]. Obviously, the contribution of each repair mechanism to the cytotoxic damage of DNA depends on the cell type, their proliferative state, and on the damage type. The solution of this question is important for development of a rational approach to chemo- and radiotherapy of tumors and, therefore, needs further studies.

The second question concerns the mechanism of the signal translation from the apoptosis-inducing damage (DNA gaps and breaks). A classic mediator of the signal for such damages is p53 [12, 13]. However, although the MNNG-induced apoptosis was accompanied by an increased expression of p53, its suppression by the product of the gene 16E6 of the papilloma virus was followed only by a little delay of apoptosis [58]. The independence of apoptosis on p53 was also found for CHO cells treated with MNNG [60]. The apoptosis independence of p53 is the reason for searching for other pathways of the signal translation. In particular, a decrease in the expression of the antiapoptotic protein Bcl-2 is considered [60]. A decrease in the Bcl-2 level promotes an activation of proapoptotic proteins Bad and Bax [71] and facilitates the release from mitochondria of cytochrome *c* which is a factor of the caspase activation [72, 73]. In this scheme it remains unclear how the breaks and gaps in DNA are related with the decrease in the Bcl-2 level without the involvement of the transactivating ability of the p53. In general, the identification of p53-independent pathways of the apoptosis development is important because the majority of tumor-producing cells in humans have mutations in the *p53* gene [74].

The work was supported by the Russian Foundation for Basic Research.

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