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Ku antigen interaction with apurinic/apyrimidinic sites: nonhomologous end joining vs base excision repair

Abstract

The apurinic/apyrimidinic (AP) site is considered to be a common lesion in genomic DNA. It is widely accepted that, irrespective of their origin, AP sites are further processed by the base excision repair (BER) machinery, being the central intermediate of this process. Under special conditions, proteins, which recognize AP sites, are able to form covalent adducts with DNA. By combination of the cross-linking technique with mass-spectrometry analysis, Ku antigen (Ku) - the central player in nonhomologous end joining (NHEJ), the pathway of double-strand break (DSB) repair - was identified as a protein reactive to AP sites. Moreover, Ku was shown to be a 5'-dRP/AP lyase that acts near DSBs in NHEJ. The recent studies have demonstrated involvement of Ku in the different stages of BER. Here we make an overview of Ku roles in the NHEJ and BER pathways of DNA repair.

Keywords: ku antigen, apurinic/apyrimidinic site, nonhomologous end joining, base excision repair

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Anastasiya A Kosova,[1] Olga I Lavrik,[1,2] Svetlana N Khodyreva[1,2]
[1]Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences, Russia
[2]Novosibirsk State University, Russia

Correspondence: Svetlana N Khodyreva, Institute of Chemical Biology and Fundamental Medicine SB RAS, 8 Lavrentiev Avenue, Novosibirsk, Russia 630090, Tel +73833635196, Fax +73833635153, Email svetakh@niboch.nsc.ru

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Abbreviations: AP, apurinic/apyrimidinic; BER, base excision repair; APE1, apurinic/apyrimidinic endonuclease 1; SS(B), single-stranded (break); DS(B), double-stranded (break); BHT, borohydride trapping; NHEJ, nonhomologous end joining; DNA-PK, dna-dependent protein kinase; dRP, deoxyribosophosphate; ROS, reactive oxygen species; Polβ, dna polymerase β

Introduction

The apurinic/apyrimidinic (AP) site is considered to be a common lesion in genomic DNA, arising at a frequency of 10,000 to 50,000 lesions per mammalian cell per day.[1] The number of AP sites can increase dramatically under stressful conditions such as X-ray or UV light irradiation and alkylating agent exposure. If unrepaired, AP sites present mutagenic and cytotoxic consequences to the cell.[2] The loss of DNA bases and attendant formation of AP sites in DNA occurs spontaneously as a result of hydrolytic cleavage of N-glycosylic bonds or through glycosylase-catalyzed removal of damaged bases during the early stage of base excision repair (BER).[3] The steady-state levels of AP sites in mammalian cells are in the range of approximately 1 site per 106 nucleotides.[4] Repair of AP sites is thought to be extremely rapid.[5] At the same time, it has been found that a part of AP sites can persist in genomic DNA for a rather long period.[6] This observation raised a question about nature of these slowly repaired AP sites and the mechanisms of prompt and dilatory repair. It is widely accepted that, irrespectively of their origin, AP sites are further processed by the BER machinery. In most cases, the repair of AP sites is initiated by hydrolytic cleavage 5' to an AP site catalyzed by apurinic/apyrimidinic endonuclease 1 (APE1).[7] AP sites also can be incised through β-elimination via the activity of DNA glycosylases and other enzymes with associated AP lyase activity.[3,7] In this case, strand incision occurs 3' to an AP site, generating α,β-unsaturated aldehyde (α,β-4-hydroxypenten-2-al) at the 3'-margin and phosphate at the 5'-margin, and this intermediate is further processed by the downstream BER enzymes.[7] This scenario appears to be realized in the case of isolated AP sites, which are generated under moderate level of DNA damage. But under some highly stressful conditions, e.g. exposure to ionizing radiation, AP sites can be a part of multiply damaged sites containing also oxidized bases, and single- or double-strand breaks (SSBs or DSBs).[8,9] Indeed, among additional types of damage produced by high linear energy transfer irradiation, AP sites, within 8-10bp of a DS end, were found to be most frequent.[10] One can suppose that specific protein(s) may take part in recognition and processing of AP sites in the context of complex damage. With this idea in mind, we screened cell extracts for proteins capable of binding AP site-containing DNA. The deoxyribose moiety in AP sites is in equilibrium between cyclic furanose and acyclic aldehyde forms.[4] The presence of an aldehyde residue allows AP sites to form Schiff-base intermediates. The formation of a Schiff base is a reversible reaction; however, the bonding of a protein to DNA can be stabilized by reduction of a Schiff base with sodium borohydride.[11] This approach is often called borohydride trapping (BHT). The resulting covalent protein-DNA adducts are stable in the subsequent analysis. Thus, the BHT technique in combination with mass spectrometry can be applied in searching for and identification of unknown proteins reactive to AP sites.[12]

Identification of unrecognized proteins capable of interaction with AP sites via formation of a Schiff-base intermediate includes the following steps. First, the preparative BHT of cell extract proteins with 32P-labelled AP DNA, which contains a biotin moiety, is performed. Second, the cross-linked protein is purified by affinity chromatography on streptavidin-coated paramagnetic beads and resolved by SDS-PAGE. A well-defined Coomassie stained protein band precisely corresponding to the radioactive label is excised from the gel, and the protein is subjected to in-gel trypsin digestion and MALDI-TOF-MS. Results from the MS analyses are searched against a database to identify the cross-linked protein. It should be pointed out that in this approach AP sites play two roles, the naturally occurring DNA lesion and the chemically reactive moiety.

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Using this approach, we have identified the polypeptide cross-linked to AP DNA as Ku80 subunit of Ku antigen.[13] The ability of Ku80 to interact with AP sites, the intermediates of the BER process, was unexpected and raised the question of biological role of found interaction. Ku is involved in nonhomologous end joining (NHEJ),[14] a DNA repair system, which does not process such lesions.

Discussion

Ku antigen

Ku antigen (Ku), consisting of two subunits with molecular masses about 70kDa (Ku70) and 83kDa (Ku80), is a eukaryotic DNA-binding component of DNA-dependent protein kinase (DNA-PK). The main function of Ku is participation in the DSB repair by NHEJ. Threading onto a DNA end like a bead on a string, Ku recognizes broken DNA ends and brings them together.[15] Ku serves as a platform for the assembly of the other NHEJ proteins around a DSB.[14] Interestingly, Ku is a moonlighting protein with many functions. In addition to the classical NHEJ, Ku participates in V(D)J recombination, telomere maintenance, replication and transcription regulation. It also has functions not directly associated with DNA repair, taking part in the regulation of apoptosis, cell adhesion, migration and invasion, and Rickettsia conorii and B19 parvovirus invasion.[14,16]

Ku interaction with AP sites

The majority of mammalian proteins, which are known to form a Schiff base with a baseless deoxyribose, belongs to the BER system. Interaction of proteins with AP sites via a Schiff base intermediate is characteristic of AP lyase activity, intrinsic for the BER proteins - bifunctional DNA glycosylases, which incise DNA backbone via β- or β, δ-elimination.[17] On the other hand, interaction of AP DNA with mammalian proteins not formally involved in BER, but capable of AP site cleavage, is well documented.[18–21] Interestingly, the interactions of proteins with AP sites via a Schiff-base intermediate without the concomitant DNA incision are also reported.[22,23] Considering the reversibility of the Schiff base formation, we can assume that these interactions provide the protective and/or regulatory function. With these ideas in mind, we tested the ability of DNA-PK, consisting of Ku and catalytic subunit, to cleave AP site located in the middle of the 32-mer blunt-ended DNA duplex. No detectable cleavage of AP sites by DNA-PK was observed. Instead, DNA-PK inhibited the AP site hydrolysis by APE1, which suggests the protective/regulatory function. In line with this assumption is stability of Ku80-AP DNA complexes formed in HeLa cell extract.[13]

Later Roberts with co-workers have shown that Ku displays biologically significant 5'-dRP/AP lyase activity near DS ends, particularly on the AP sites situated in the 5' SS overhang.[24] Both these activities are necessary for removing the groups, which block DNA repair during the preparation of DNA ends to ligation in NHEJ. More comprehensive analysis of substrate specificity of Ku's 5'-dRP/AP lyase revealed that Ku has drastically weaker AP lyase activity in the 3' overhang context as compared to the 5' overhang substrates.[25] The idea is the following. If AP site is on the dangling 5'-end of DNA, 5'-phosphate generated after the excision of this AP site can be used for ligation. But if AP site is on the dangling 3'-end, the α,β-unsaturated aldehyde is generated that prevents the ligation stage.

Another critical point for Ku's 5'-dRP/AP lyase activity is embedding an AP site into duplex context. The authors proposed an elegant scheme of "division of labor between NHEJ and BER" in repair of AP sites depending on the context surrounding them. The AP sites near the 5' end, which are not deeply embedded into duplex part of DNA, were considered to be relevant for direct NHEJ. Ku did not possess the AP lyase activity when an AP site was embedded in the duplex part of DNA for more than 3bp.[25] This observation is in agreement with our results.[13]

Interestingly, the authors considered the lysines in the N-terminal part of Ku70 as the main nucleophiles responsible for AP site cleavage; no cross-links with Ku70 were found for AP DNA with the AP site located within DS part of DNA that correlates with undetectable cleavage of AP sites.[25] At the same time, it has been found that the lysine(s) of Ku80 can substitute for the mutated lysines of Ku70 with only partial decrease in the Ku activity on the AP site in the 5' overhang.[24,25]

We extended the search for human proteins reactive to AP sites using the partial AP DNA duplex containing 5' and 3' dangling ends of 8nt (DDE-AP DNA) and mimicking clustered DNA damage.[26] In this case, the pattern of borohydride-dependent adducts included the predominant product of 100kDa along with less abundant one of 95kDa, which is characteristic for blunt-ended AP DNA. Using the previously developed protocol,[13] we searched for the candidate protein that forms this adduct.[26] Unexpectedly, two Ku80 isoforms with different molecular masses of 82652 and 93464Da were found in the list of candidate proteins. The last isoform has some biochemical properties, which resemble those of conventional Ku80, but cannot fully replace conventional Ku80.[27] The lower molecular mass isoform is known to be the main one,[27] but one cannot exclude the highly efficient cross-linking of the 93464 Da isoform with DDE-AP DNA. If the 100-kDa adduct is formed by conventional Ku80 isoform, one would expect the existence of another mode of protein interaction with DDE-AP DNA which, in turn, results in cross-linking to the other amino acid target(s). Unfortunately, in this case the peptide mass-mapping approach is unable to discriminate isoforms of cross-linked protein. To confirm the identity of the cross-linked polypeptide, we used Ku purified from HeLa cells. Purified Ku containing the conventional Ku80 isoform, like Ku in the extract, formed two cross-linking products - the predominant of 100kDa and less abundant of 95kDa - thereby indirectly confirming the proposal about different modes of Ku binding with AP DNA (positioning of bound AP DNA), which depend on the structure of AP DNA ends. It is of great interest to determine whether this found effective interaction of Ku80 polypeptide with AP sites results in their cleavage.

Ku in BER

In most cases, cells and mice with deleted Ku exhibit the phenotypes that can be expected upon disruption of NHEJ, for example hypersensitivity to clastogenic agents and immunosuppression.[14] Therefore, this suggests functioning of Ku70 and Ku80 only within Ku heterodimer to repair DSBs arising under the action of DNA damaging agents or during V(D)J recombination.[16] However, deletion of either Ku70 or Ku80 results in different phenotypes in contrast to ones expected under NHEJ disabling. This observation suggests that Ku70 and Ku80 may function outside the Ku heterodimer. Supportive to this idea is the ability of free Ku70 to bind DNA.[28] Interestingly, deletion of Ku70 or Ku80 causes different sensitivity of mice fibroblasts to genotoxins, which cause base lesions and SSBs - DNA lesions repaired by BER.[29] In addition, interaction of Ku with AP sites - the central intermediates of BER - has been demonstrated,[13,24–26] although the model DNAs used in these four

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works were represented by short linear DNA duplexes that mimic NHEJ substrates. The aforementioned observations indirectly testify to possible involvement of the Ku heterodimer and/or its separate subunits in the BER process. Recently, two comprehensive studies concerning the involvement of Ku70 and Ku80 polypeptides in the BER process have been published.[30,31]

Based on the known mechanisms of DNA damages caused by different genotoxic agents and pathways and proteins involved in the damage repair, the authors proposed four working models that suggested successive exclusion of the possible effects of NHEJ and proved direct influence of Ku80 on the BER process.[30] To this end, the genotoxic screen in wild type, ku80$^{-/-}$ and lig4$^{-/-}$ cells of the number of DNA damaging agents producing DNA lesions, which are characteristic for the repair by the NHEJ, BER or both systems, combined with the analysis of DSB formation (γ-H2AX foci) revealed that Ku80-deleted cells are hypersensitive to the genotoxins generating base lesions and SSBs. This suggests that Ku80-deleted cells are defective at BER. *In vitro* repair of the specific BER substrates by nuclear extracts revealed that the extracts deleted for Ku80, but not Lig4 or Ku70, exhibited reduced BER capacity. In addition, ectopic expression of Ku80 in ku80$^{-/-}$ cells rescued this deficiency. Moreover, overexpression of 8-oxoguanine DNA glycosylase and poly (ADP-ribose) polymerase-1 - the proteins involved in the repair of lesions generated by reactive oxygen species (ROS) - can also rescue hypersensitivity of Ku80-deleted cells to ROS. Thus, by the detailed step-by-step analysis the authors proved the idea that Ku80 deletion negatively impacts multiple BER functional processes, with Ku80 acting outside the Ku heterodimer. In the next work, the study of the Ku subunit functions outside the DNA-PK holoenzyme (not related to NHEJ) was extended.[31] The dose response analysis to methyl methane sulfonate revealed that depletion of Polβ by RNA interference in ku80$^{-/-}$ fibroblasts increased the cell sensitivity, while Polβ over expression rescued sensitivity of ku80$^{-/-}$ cells.

Since ku80$^{-/-}$ cells have decreased capacity to repair AP sites,[30] the authors proposed that free Ku70 may inhibit the APE1 activity, and, therefore using the cell lines deleted for Ku70, Ku80 or both, they tested the cell sensitivity to an APE1 inhibitor.[31] It has been found that the absence of either free Ku70 or free Ku80 sensitizes the cells, while the absence of both polypeptides does not. Again, ectopic expression of mouse Ku80 in ku80$^{-/-}$cells rescued this sensitivity. In addition, overexpression of APE1 rescued the deletion of Ku80 in the sensitivity test. This suggests that the separate Ku subunits specifically interact with AP sites unlike the Ku heterodimer. By *in vitro* experiments based on cross-linking of AP DNA to proteins and on the DNA competition approach, it was demonstrated that both individual subunits are able to preferentially bind AP site-containing DNA. The Ku heterodimer, although being capable of binding to AP DNA as revealed by the cross-linking of AP DNA probe to both subunits, did not exhibit a preference in recognition of AP DNA as compared to regular DNA. Free Ku70 and its N-terminal fragment, but not free Ku80, inhibited the APE1 activity. Interestingly, the interference of free Ku80 and free Ku70 is not fully reciprocal. Both Ku70 and Ku80, when present alone, make cells hypersensitive to an APE1 inhibitor, that can be achieved by competition with APE1 for AP site binding, while *in vitro* individual Ku80 does not inhibit AP site cleavage. Thus, in cells, the influence of Ku70 and Ku80 outside the Ku heterodimer on AP site repair appears to be more sophisticated. In any case, the imbalance between Ku70 and Ku80 may impair the BER process in cells under some conditions. For example, deviation from equimolar ratio of Ku70 and Ku80 in lymphocytes with ageing was demonstrated.[32]

Another interesting issue concerning the impact of free Ku subunits on the BER process is how the separate subunits and the Ku heterodimer bind with AP sites in the context of "uninterrupted" DNA. The Ku heterodimer is known to efficiently bind with DS ends of DNA duplex threading onto a DNA end like a bead on a string.[15] According to the crystallographic data, the DNA binding loop in the Ku heterodimer is formed by the polypeptide chains of both subunits that encircle DNA.[15] Both the photo-crosslinking[33] and crystal structure data[15] suggest that the DNA end enters the binding channel from the Ku80 side and then extends to the Ku70 side. But the way of the Ku heterodimer binding with DNA in the absence of DS ends is still unknown, although participation of the Ku70 SAP domain, not involved in the loop formation, is shown.[15,34] For free Ku70 it has been demonstrated *in vitro* that the N-terminal domain (amino acids 1-115) is responsible for inhibition of the APE1 activity on AP DNA substrate with DS ends.[31] This is in line with preferential binding of the N-terminal domain with AP sites in blunt-ended DNA substrate as judged by the cross-linking experiments.[31] However, it is still unknown whether the same type of binding is realized in the context of cellular DNA in the absence of closely spaced DS ends.

Conclusion

Thus, Ku appears to participate in the repair of AP sites, but the mechanisms have not been fully understood yet. On the one hand, Ku can bind to AP sites embedded into DS DNA and protect them from cleavage by other proteins,[13] with the binding mechanism depending on the structure of DNA ends.[26] On the other hand, Ku cleaves AP sites near broken DNA ends, if they interfere with the ligation of a DSB during NHEJ.[24,25] The recent studies proposed that free Ku70 and free Ku80 may participate in BER outside the holoenzyme, with Ku70 being bound to AP sites thereby inhibiting the initiation of the BER process by APE1.[30,31] Further studies are required to completely understand the interrelation of the Ku roles in the NHEJ and BER pathways.

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Conflict of interest

The author declares no conflict of interest.

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