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# Unveiling the non-repair face of the Base Excision Repair pathway in RNA processing: A missing link between DNA repair and gene expression?

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ABSTRACT

The Base Excision Repair (BER) pathway, initially studied as a mere DNA repair pathway, has been later found to be implicated in the expression of cancer related genes in human. For several years, this intricate involvement in apparently different processes represented a mystery, which we now are starting to unveil.

The BER handles simple alkylation and oxidative lesions arising from both endogenous and exogenous sources, including cancer therapy agents. Surprisingly, BER pathway involvement in transcriptional regulation, immunoglobulin variability and switch recombination, RNA metabolism and nucleolar function is astonishingly consolidating. An emerging evidence in tumor biology is that RNA processing pathways participate in DNA Damage Response (DDR) and that defects in these regulatory connections are associated with genomic instability of cancers. In fact, many BER proteins are associated with those involved in RNA metabolism, ncRNA processing and transcriptional regulation, including within the nucleolus, proving a substantial role of the interactome network in determining their non-canonical functions in tumor cells. Maybe these new insights of BER enzymes, along with their emerging function in RNA-decay, may explain BER essential role in tumor development and chemoresistance and may explain the long-time mystery. Here, we would like to summarize different roles of BER pathway in human cells. First, we will give a short description of the classical BER pathway, which has been covered in detail in recent reviews. We will then outline potential new roles of BER in gene expression and RNA metabolism. Although recent works have provided tremendous amount of data in this field, there are still lot of open questions.

## 1. Relevance of the canonical BER pathway and open questions

The BER pathway (Fig. 1) is an essential DNA repair system in higher eukaryotes and gene deletions of the core BER factors (apurinic/apyrimidinic endonuclease 1 – APE1, DNA polymerase β − Polβ, X-ray repair cross-complementing 1 – XRCC1, DNA ligase I − LigI and DNA ligase III − LigIII) results in embryonic or early post-natal lethality [1]. The pathway is comprised of five major steps, in which enzymatic and non-enzymatic components cooperate to carry out a highly integrated set of reactions: i) recognition and excision of the damaged base; ii) incision of the resulting AP site to generate a nick on the DNA backbone; iii) processing of the nick ends; iv) filling of the nucleotide gap; and v) sealing of the nick (Fig. 2).

Different specific DNA glycosylases scan the DNA substrate, recognize, through a flipping out mechanism, and excise the damaged base in a lesion-specific manner. Two kinds of DNA glycosylases are known: mono- or bi-functional, depending on their mechanism of action. While monofunctional DNA glycosylases (e.g. the uracil-DNA glycosylase − UNG) simply cleave the C1′-N-glycosidic bond, generating an AP-site, bifunctional enzymes also possess an associated β-lyase activity (e.g. the 8-oxoguanine DNA glycosylase − OGG1) deputed to cleave the DNA backbone leaving a 3′-α,β-unsaturated aldehyde blocking group. An additional family of DNA glycosylases, represented by the human NEIL1 and NEIL2 enzymes, is also able to operate a β,δ-elimination reaction, leaving a 3′-phosphate nick [2]. Higher eukaryotes are provided with a vast array of DNA glycosylases with a significant redundancy in their damage selectivity for this reason, single knockout of several DNA glycosylases is not lethal *per se*, although an accumulation of unrepaired DNA lesions occurs [3].

The glycosylase-catalyzed reaction generally produces an AP-site, which is immediately processed by APE1 in metazoans. APE1 cleaves at the 5′ termini of the abasic site, generating a nick on the DNA backbone

*Abbreviations:* AP-site, apurinic/apyrimidinic site; APE1, apurinic/apyrimidinic endonuclease 1; BER, Base Excision Repair; DDR, DNA damage response; miRNA, microRNA; ncRNA, non coding RNA; NIR, Nucleotide Incision Repair; PARP, poly(ADP-ribose) polymerase; RBP, RNA binding protein; rNMPs, ribonucleotides; ROS, reactive oxygen species; SSBR, Single Strand Break Repair

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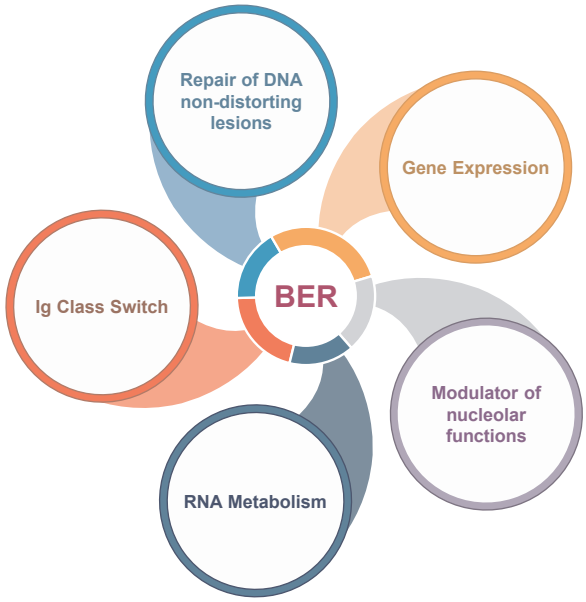


**Fig. 1.** BER exerts different functions in human cells.
Schematic representation of different biological functions of Base Excision Repair (BER) pathway in human cells including DNA repair player of alkylated and oxidative DNA lesions; regulator of expression of genes involved in response to genotoxicants; regulator in RNA metabolism, control of nucleolar function and regulation of immunoglobulin Class Switching together with AID.

and producing a 3′-OH and a 5′-dRP (deoxyribonucleotide-phosphate) termini. Usually, APE1-incision activity is sufficient to generate the DNA ends required for the completion of the DNA repair process. Once further oxidation of the DNA termini or base-excision operated by bifunctional glycosylases occurs, other end-processing enzymes may be involved, such as tyrosyl-DNA phosphodiesterase 1 (TDP1), aprataxin (APTX) or polynucleotide kinase 3′-phosphatase (PNKP). The dRP-lyase activity of Polβ, along with APE1 3′-phosphodiesterase activity, contributes to the "end-cleaning" process, ultimately generating a single-nucleotide gap that can be efficiently filled in and re-ligated [4].

BER is then completed via a "short-patch" (SP) or a "long-patch" (LP) pathways, depending on the 5′-moiety generated. In the SP-BER, Polβ is engaged to replace the missing nucleotide, and then is followed by the XRCC1-LigIII complex, which is responsible for the ligation of the nick [5]. In the presence of a 5′-moiety refractory to the Polβ lyase activity, low ligation efficiency, or during the S-phase of the cell cycle (i.e. when replication-associated proteins are more abundant), BER can be completed through the LP-BER which involves a strand displacement-dependent gap filling process [1]. Replicating polymerases, such as DNA polymerase δ and ε, act in concert with the sliding clamp PCNA (proliferating cell nuclear antigen) in the LP-BER, generating a stretch of 2–12 nucleotides, which is removed by the flap endonuclease 1 (FEN1). Finally, intervention of the PCNA-associated DNA Ligase I seals the nick [6].

Notably, BER protein components are involved in at least two subpathways, namely Single Strand Break Repair (SSBR) and Nucleotide Incision Repair (NIR) [7]. SSBs are generated by different sources including reactive oxygen species (ROS), radiomimetic drugs, ionizing radiation, topoisomerase-mediated DNA cleavage or they are unavoidable intermediates generated during BER processing. The SSBR pathway initiates through recruitment of the poly(ADP-ribose) polymerase PARP1, which recognizes exposed SSBs and modulates the repair process through enzymatic ADP-ribosylation of protein substrates. Tight connection between BER and SSBR has been highlighted by the observation that many BER proteins (e.g. XRCC1, Polβ) interact with PARP1 [6] and by the fact that PARP1 has been shown to orchestrate the BER processing of uracil and AP-sites [8]. Interestingly, it has been recently demonstrated that APE1 has glycosylase-independent NIR activity on particular modified bases, see below. Although very intriguing, the physiological impact of the NIR pathway is still under investigation, as within the intracellular milieu the presence of specific DNA glycosylases would likely dampen the efficiency of the NIR process on DNA.

Overall, BER is currently regarded as a dynamic intertwining of different enzymes and auxiliary proteins that operate in a highly coordinated manner to allow temporal and spatial modulation. The relevance of this coordination is remarked by several observations, which still deserve further studies:

- imbalanced expression of BER components has been linked to genomic instability. In particular, overexpression of core elements of the pathway is a hallmark of cancer progression and resistance to therapy. Increased expression of a single BER factor may result in competition or in excessive enzymatic activity, which is not compensated by equimolar amounts of other BER proteins. This has been formally demonstrated, in the case of APE1 [9–11] and Polβ [12].
- abortive intermediates of the pathway are intrinsically cytotoxic since unprotected intermediates (e.g. SSBs) are much more toxic than the initial damaged base [13]. Therefore, the fine-tuning and coordination of the pathway is possibly the result of an evolutionary tradeoff between the rapid repair of mutagenic lesions and the potentially hazardous intermediates that such repair may generate.

In order to explain mechanisms evolved to optimize the repair efficiency of the BER pathway, several models have been proposed including those of the 'passing the baton' and the 'BERosome' [7,8,14]. Despite the apparent divergence amongst models that have been put forward to explain the complexity of BER, each of them probably describes different aspects of a unique and highly dynamic integrated process. However, it is clear how it is modulated through a complex network of more or less stable DNA-mediated or protein-protein interactions, among BER enzymes and non-enzymatic scaffold proteins (e.g. XRCC1, PCNA) and PTMs (Post-translational modifications). Phosphorylation, acetylation, methylation, SUMOylation, as well as ubiquitination of almost every BER component have been suggested to play a role in the modulation of the pathway [7].

An emerging concept in this field is the role of some non-canonical regulatory proteins as BER modulators. Several proteins, apparently unrelated to the pathway, have recently been discovered as novel unexpected coordinators of BER [15]. p53, for instance, has been implicated in the modulation of both APE1 and Polβ [6], whereas our laboratory discovered nucleophosmin (NPM1) as a modulator of the APE1 enzymatic activity [16]. Additional regulation of the BER pathway is also achieved through evolutionarily acquired disordered extensions of some BER components [17,18]. These accessory proteins were proposed to be important for stabilizing large complexes, "repairsome", by providing extended interaction surface area [19].

An interesting link between DNA damage sensing and modulation of BER protein amount has been recently demonstrated. Indeed, BER proteins amount, which is generally abundant with a relatively long half-life, is constantly oscillating in response to the DNA damage load at the steady-state level. This equilibrium is strictly controlled by the ubiquitin-proteasome system [4]. It is possible that the high level of them (such as APE1 and Polβ) observed in several tumors is the result of perturbations of this equilibrium. Understanding these aspects will shed light on the role of BER proteins in cancer development.

## 2. NIR activity of APE1 on non-canonical substrates

In the last decade, Nucleotide Incision Repair (NIR) pathway has been described as a new function of APE1 which works as back up of BER pathway ensuring a correct removal of damaged bases as a result of oxidative stress [20–25]. NIR activity by APE1 consists of an incision at

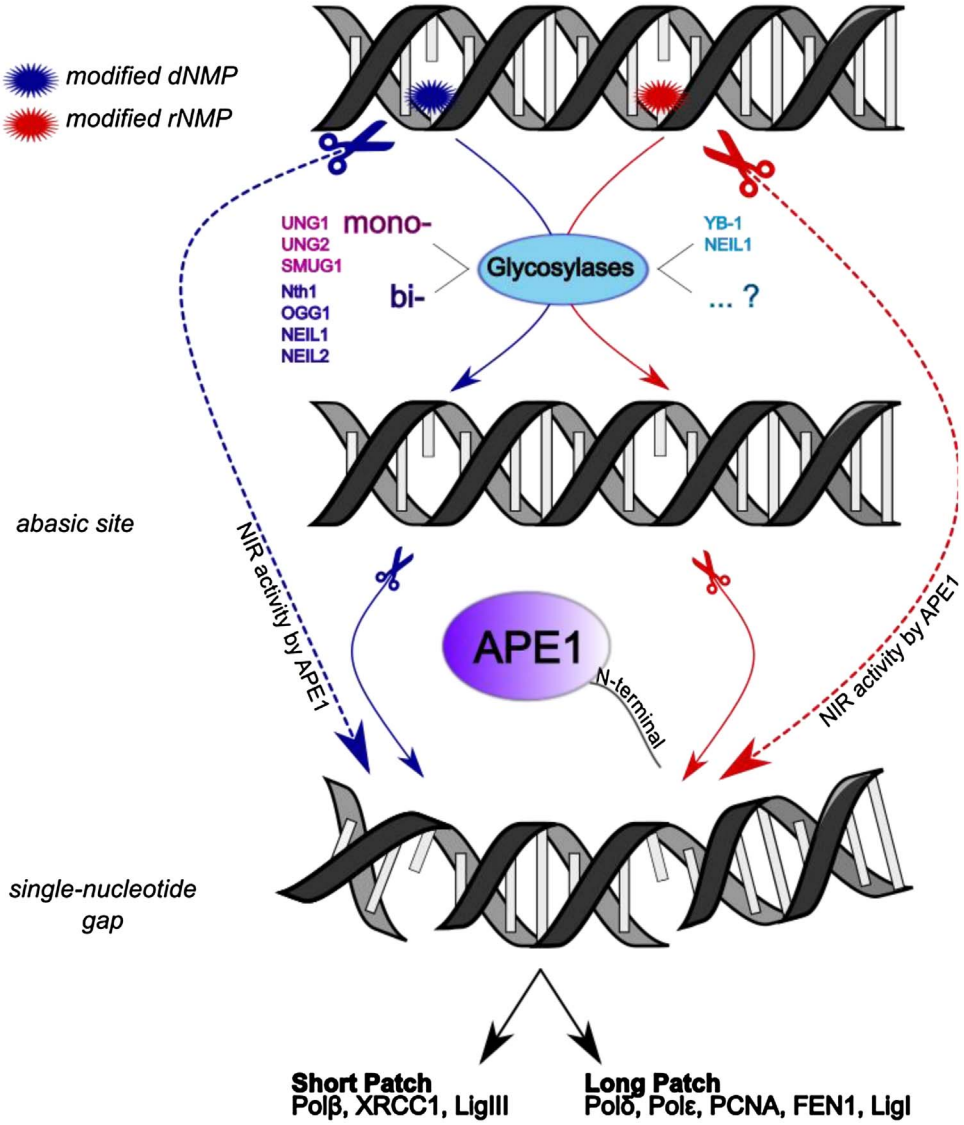


**Fig. 2.** Schematic representation of consecutive BER steps during the repair of different DNA lesions. BER is endowed to repair different lesions including modified dNMPs (blue star) and modified rNMPs (red star). Different types of mono- and bi- functional glycosylases exist in order to recognize damaged dNMPs, such as oxidized dNMPs, uracil, etc., and generate deoxy-abasic sites, which are subsequently processed by APE1. At the same way, an oxidized rNMPs, embedded in DNA, could be recognized by specific glycosylases such as YB-1 and NEIL1, and be converted in ribo-abasic sites, efficiently processed by APE1. For both types of damages, APE1 possesses a NIR activity in which APE1 cleaves directly the lesion bypassing the glycosylases action. BER pathway is finally terminated by different specific enzymes depending on whether the Short Patch or Long Patch pathways.

the 5′ next to a oxidatively damaged base in a DNA glycosylase–independent manner, providing a proper 3′-OH group for further processing [20]. After the removal of the dangling damaged nucleotide by a flap endonuclease [26,27], DNA backbone can be efficiently repaired by a DNA polymerase. In this way, the NIR action avoids the generation of potentially toxic AP-intermediates [28]. Several uncanonical substrates are processed by APE1 through NIR activity, including 5,6-dihydro-2′-deoxyuridine (DHU) [20,28], 5,6-dihydrothymidine (DHT) [20,28], 5-hydroxy-2′-deoxyuridine (5OHU) [20,28], 5-hydroxy-2′-deoxycitidine (5OHC) alpha-2′-deoxynucleosides (αdA, αdT and αdC) [20,28–31], the majority of which are generated under ionizing radiation (IR) and exposure to certain drugs. This non-canonical activity of APE1 could explain how, on the contrary to what is observed in APE1 deficient cells [32–34], the lack of DNA glycosylases does not sensitize cells or mice to oxidative agents and IR [35–37]. Although NIR pathway plays an important role as a back-up of BER, experimental working conditions, such as salts and pH conditions, seem to affect the NIR function of APE1. The optimal conditions for NIR activity are very similar to those required for the 3′– > 5′ exonuclease activity by APE1, characterized by a pH around 6.4–6.8, and a KCl concentration of 50 mM [20]. Moreover, NIR is more active to 100-fold lower $MgCl_2$ concentration compared to that of the canonical AP-endonuclease activity [20]. Interestingly, the N-terminal domain of APE1 deputed to modulate protein-protein interaction and indispensable to redox activity but not AP-endonuclease activity [38], is contrarily essential for the NIR activity; indeed the lack of the first 33 N-terminal aminoacids of the protein produces a 20-fold-decrease of APE1 NIR activity [20]. Moreover, Timofeyeva et al. demonstrated that Lysine in position 98 contributes significantly in the 5′-phospodiester bond hydrolysis of DNA substrate, but not in the dissociation of the enzyme-product complex [21]. Interestingly, the substitution of this amino acid influences the APE1 NIR activity more than BER, demonstrating that the APE1 active site involved in NIR and BER pathways is the same, but different conformational requirements are responsible for APE1 NIR or BER activities [21].

## 3. Unusual involvement of BER enzymes in the regulation of gene expression

Generation of single base modifications is not only a harmful DNA modification caused by genotoxic agents but it may have important regulatory functions also at the basis of epigenetic mechanisms. For instance, 5-methylcytosine and Uracil, which are enzymatically generated during epigenetic regulation of gene expression and in antibody diversification processes, respectively, are the most well-known examples of this phenomenon. Very recently, a number of studies pointed to 8-oxoG (8-oxo-7,8-dihydroguanine) modification as a new epigenetic mark with a relevant role in the control of gene expression [39]. Generation of 8-oxoG on different promoters regulates the activity of

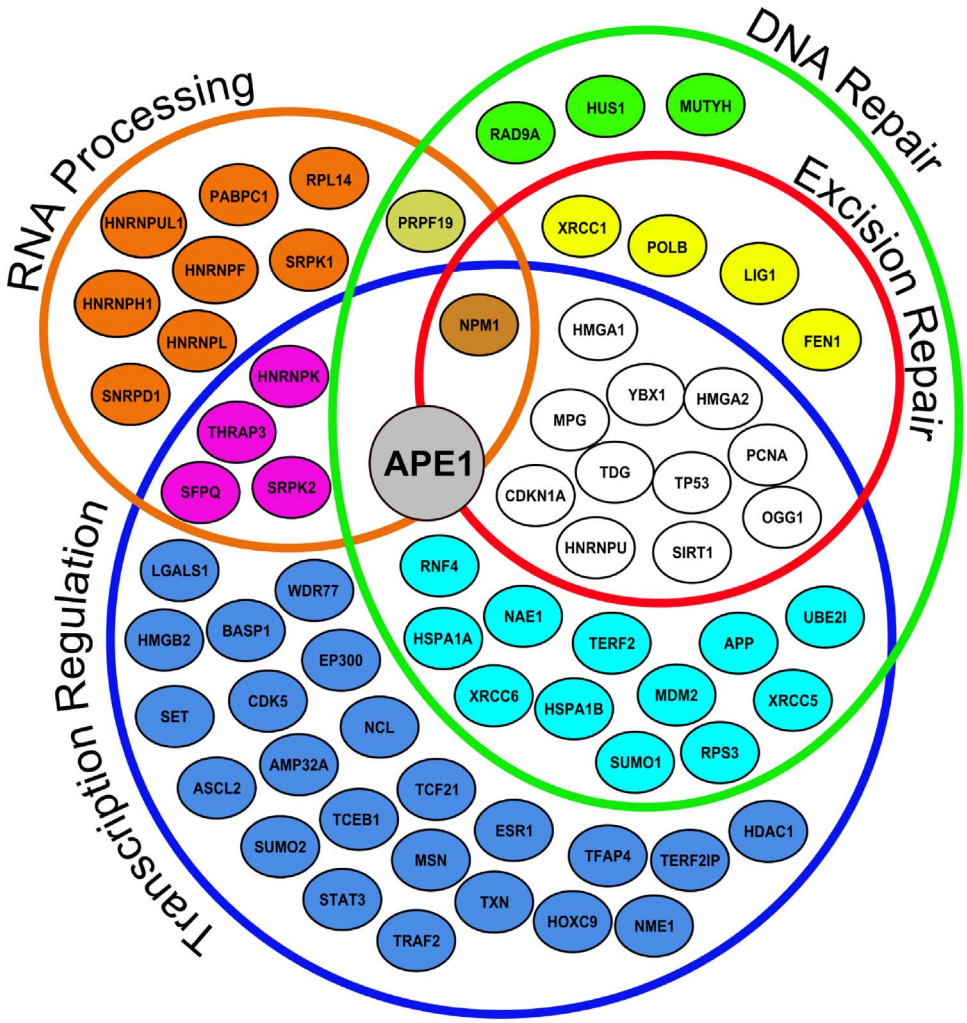


**Fig. 3.** APE1 protein interactors are highly interconnected.
The top four functional annotation clusters of APE1 interactors identified by DAVID enrichment analysis based on gene ontology terms of biological processes. Protein interactors that are found in more than one cluster are colored accordingly.

several transcription factors (e.g. Hif1α, STAT1, NF-κB and MYC) in conjunction with OGG1 protein and, in turn, regulates the expression of important genes involved in cancer development, such as VEGF [40], SIRT-1 [41] and inflammatory genes such as TNF-α and CXCL2 [42]. Interestingly, this last role of OGG1 on inflammatory genes may explain the reduced inflammatory response in $Ogg1^{-/-}$ mice [43].

Canonical epigenetic mechanisms seem to crosstalk with new DNA damage epigenetic marks. In fact, it has been recently shown that demethylation of histone H3 at Lys9 by LSD1 de-methylase, through generation of $H_2O_2$, promotes oxidation of estrogen-receptor responsive promoters in breast cancer cell lines with a consequent OGG1-dependent promoter activation [44]. In a similar way, also Myc-induced, retinoic acid-induced and androgen receptor-induced transcription has been proved [45–47] demonstrating that the transcriptional function of OGG1 is a much more general non canonical function than previously thought. OGG1, in complex with 8-oxoG free base, has been recently suggested to play a role in signal transduction as a new Guanine Exchange Factor (GEF) for Ras, Rac and Rho GTPases [48–50]. These findings open new completely unpredicted perspectives for this unusual DNA-repair enzyme in controlling gene expression.

Another well-known enzyme of the BER pathway having important function in transcriptional regulations is APE1 [11,51]. APE1 plays a role in the regulation of expression of human genes during oxidative stress conditions and it is important for cancer biology, through indirect- and direct-mechanisms [52]. Thus, besides providing a crucial role in the genome stability maintenance, APE1 acts also as a master regulator of cellular response to genotoxic damage via indirect mechanisms. Indeed, by regulating the expression of several tumor related genes, through the stimulation of DNA binding activity of transcription factors such as NF-κB, Egr-1, Hif-1α, Nrf1, APE1 can influence the onset of inflammatory and metastatic progression [11]. Through the redox-mediated activation of NF-κB and Hif1α, for example, APE1 indirectly drives IL-8 and VEGF expression, respectively, thus acting as a key regulator of inflammatory and tumor-associated neo-angiogenesis processes. Moreover, APE1 has been implicated in chemoresistance, considering its ability to stimulate the expression of the multi-drug resistance gene MDR1 through the interaction with Y-box-binding protein 1 (YB-1) [53], and its regulatory abilities on the PTEN tumor suppressor [54,55]. We recently characterized a direct role of APE1 in the transcription of SIRT1 gene through the binding of nCaRE-sequences present on its promoter, demonstrating that BER-mediated DNA repair promotes the initiation of transcription of SIRT1 gene upon oxidative DNA damage [41]. A recently published paper gave a definitive prove to our previous findings and suggested a novel role of APE1 in epigenetic regulation, through modulating in a redox-mediated manner the DNMT1 expression and causing consequent suppression of Oct4 and Nanog expression through specific promoter methylation [56]. The epigenetic role of 8-oxoG modification was further supported by a recent publication showing a regulatory function of BER enzymes on specific gene expression by controlling the topological superstructure of G-quadruplex containing promoters, such as those of *VEGF* and *NTHL1* genes [57], as also discussed in another article of this issue by A. Fleming and C. Burrows. All these studies highlight a new unsuspected function of oxidative DNA lesions as novel epigenetic mechanisms of gene regulation through the action of BER enzymes.

Moreover, despite the previous consistent research into APE1

molecular mechanisms in DNA damage repair, only recently it has been hypothesized that this protein may play an unsuspected though important function in RNA metabolism impacting on the post-transcriptional control of gene expression [17,58,59].

Overall, these pioneering studies hold the promise to change the focus of scientific research from investigating the canonical roles of BER enzymes in DNA repair to the study of their function in gene regulation highlighting the BER peculiarity for eukaryotic cells. Overall, these studies will contribute to open the DNA repair world to RNA universe.

## 4. BER enzymes and RNA metabolism: unexpected findings from interactomics studies

Emerging evidences have pointed out that DNA damage repair and RNA metabolism are more closely related than previously thought. In addition, ncRNAs and miRNAs act at multiple levels of DNA damage response regulation and have been proposed as novel anticancer therapeutic targets [59]. DNA repair enzymes, in particular a large cohort of BER proteins, have been implicated in RNA metabolism and in transcriptional regulation of genes suggesting that DNA damage repair and RNA pathways are tightly inter-regulated [59].

A number of recent interactomic studies significantly contributed to open new scenarios for the comprehension of non-canonical functions of BER proteins, including understanding their unusual distribution in the nucleolar compartment [17,60,61] (Antoniali et al., submitted). The APE1-interactome network, characterized in part in our laboratory and in different literature works, actually comprises more than 100 different protein species whose functions are related to four biological pathways intimately interconnected: DNA repair, Excision Repair, RNA processing and Transcriptional Regulation (Fig. 3).

Actually, the major focus is on APE1, SMUG1 and PARP1, as prototypical examples [17,59,62–64]. In this review, in particular, we highlight current knowledge of APE1 in controlling RNA metabolism. Interested readers are referred to the aforementioned references for further details about SMUG1 and PARP1.

## 5. BER enzymes and miRNA regulation: a new paradigm in gene expression?

We recently found that many ncRNAs, few miRNAs and some functional RNAs are directly bound by APE1 in cancer cells (Antoniali et al., submitted). Furthermore, preliminary analysis from our laboratory indicated a potential role of APE1 in miRNA biology through an effect on the Microprocessor complex. These observations prompt a new model that links DNA damage responses and the modulation of target genes, and highlight how APE1 may regulate gene expression through its direct binding and/or processing of specific RNA. Therefore, studying APE1 new function in miRNAs processing may represent a novel field of investigation in cancer biology, which may be linked to its role during cancer progression.

MicroRNAs (miRNAs) are small non-coding RNA that function as a guide in RNA silencing of most protein-coding transcripts thereby being critical regulators of nearly all physiological and pathological processes. As a consequence, a delicate temporal/spatial balance between miRNAs and their targets is central to achieve the appropriate biological outcome and, it is not surprising, that any deregulations of miRNA biogenesis and expression have been linked to a broad spectra of pathological features of human diseases including cancer [65]. Understanding whether APE1 regulation of target genes of genotoxic response, could be mediated through miRNA processing will definitively increase our knowledge regarding its role in tumor progression and chemoresistance.

An increasing number of evidences indicate that miRNA post-transcriptional maturation, rather than transcription, is often perturbed in cancer. The accumulation of miRNAs precursor forms and the corresponding depletion of mature forms have been evidenced in human cancers compared to normal tissue [66], strongly indicating that the impairment of key steps in miRNA biogenesis could be the underlying cause. RNA binding proteins (RBPs) are crucial components in the determination of miRNA function and stability, as they control different steps of miRNA biogenesis, localization, degradation and activity.

Mechanisms regulating mammalian miRNA biogenesis are quite complex and comprise a series of biochemical steps converting a primary miRNA transcript (pri-miRNA) into a biologically active mature form [65,67]. The canonical miRNA biogenesis pathway is characterized by two subsequent ribonuclease reaction steps. First, in the nucleus, where the transcription by RNA polymerase II takes place, pri-miRNAs are recognized and cropped into hairpin-structure precursors (pre-miRNAs) by the Microprocessor complex minimally composed by the nuclear RNase III Drosha and the RNA binding protein DGCR8 (DiGeorge critical region 8)[68]. Subsequently, pre-miRNAs are actively exported by Exoportin-5 in the presence of its Ran-GTP co-factor into the cytoplasm [69] where a second-round ribonuclease reaction mediated by another RNase III enzyme, Dicer, generates a mature ~22nt duplex miRNA [70]. Only one strand of this miRNA duplex is loaded onto the RNA-induced silencing complex (RISC) whereas the other is usually degraded. Mature miRNAs function as guides by base pairing the RISC complex to its target mRNAs, whereas the Argonaute (Ago) family proteins serve as effectors by recruiting factors that induce translational repression, mRNA deadenylation and mRNA decay [71].

In the last decade, as scientists began to characterize a larger fraction of miRNA genes, it appeared that the complexity and pleotropic nature of miRNAs have been underestimated [72]. The multiple steps of miRNA maturation could potentially provide a variety of molecular options revealing a complex dynamic in miRNA processing. Recent studies have pointed out alternative pathways for maturation of certain miRNAs that deviate from the canonical miRNA biogenesis pathway bypassing one of the RNase III cleavage steps [72–74]. This is the case of the mirtrons, pre-miRNA hairpins generated by splicing and debranching of short hairpin introns, and other small nucleolar RNAs (snoRNAs), transfer RNAs (tRNAs), tailed endogenous shRNA, long hairpin RNAs (hp-RNAs) derived from short interspersed nuclear elements (SINEs) that bypass the cleavage step of Drosha [75–77]. To date, miR-451, an erythropoietic miRNA conserved in vertebrates, is instead the only Dicer-independent miRNA identified [78].

Furthermore, there is still a great uncertainty regarding the exact composition of the miRNA-processing complex. Although the core components, Drosha and DGCR8 are required for the biogenesis of almost all miRNAs, the Drosha complex contains numerous auxiliary factors including the DEAD-box RNA helicase p68 (DDX5) and p72/p82 (DDX17) which selectively promote the activity of Drosha processing over certain pri-miRNAs. Dicer is instead associated with TAR RNA-binding protein (TRBP) and the kinase R-activating protein (PACT) [67]. Several studies have further revealed a number of further RNA binding proteins that are required for miRNA biogenesis. These modulators have been shown to positively or negatively regulate miRNA biosynthesis by directly binding miRNA terminal loop region, thus affecting Drosha and/or Dicer interaction with pri-miRNA or pre-miRNA. More importantly, deregulation of RBPs expression and activity has been linked to several malignancies. Among the panel of factors identified for example: DDX1, BRCA, ARS2, DR5, ADAR1, hRNP A1, KSRP, Lin 28, SMADs, YAP, ERα, ERβ, wtp53 and mutant p53 [79,80]. Of note, included in this list of RBPs, there are few DNA damage response (DDR) proteins [81].

Remarkably, several groups pointed to a specific miRNA-RBP interplay in response to external stimuli including DNA damage. Different enzymes involved in DDR have been shown to participate in miRNA processing and maturation (Fig. 4). Up-regulation of specific miRNAs such as miR-16-1, miR-143, miR-206 and miR-145 has been shown to be induced in a p53-dependent manner after DNA damage. p53 is able to interact with the Drosha complex through p68 increasing pri-miRNA biogenesis. Interestingly, transcriptionally inactive p53 mutants disrupt

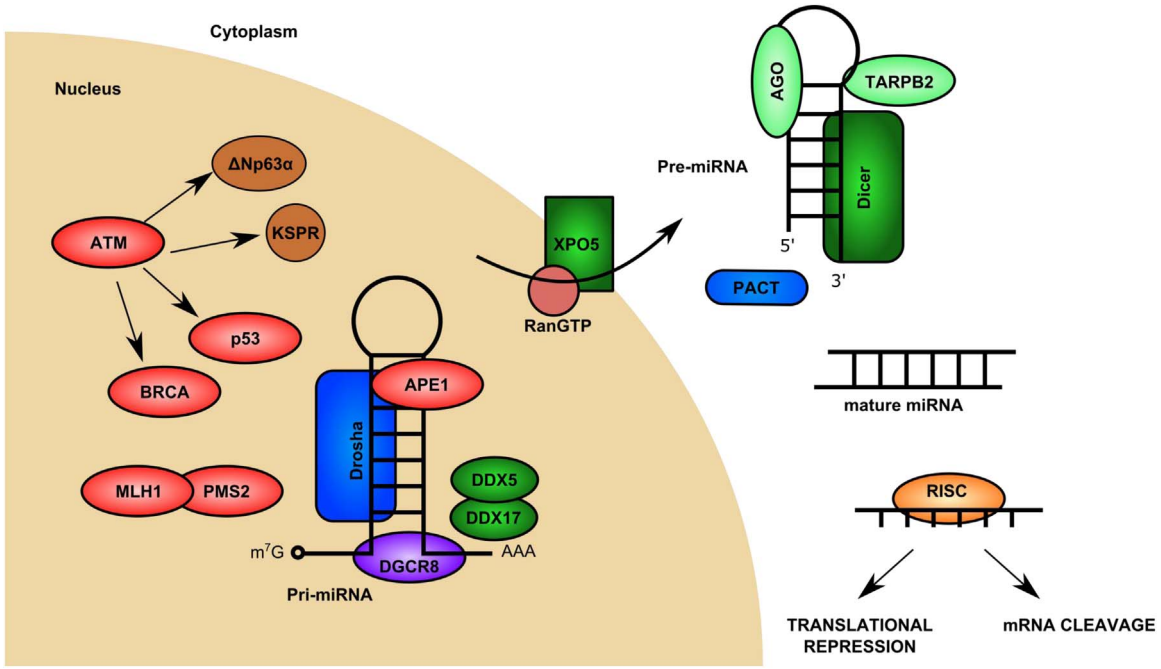


**Fig. 4.** Is BER involved in miRNA processing?
Regulation of miRNA biogenesis pathway by DNA damage response (DDR) proteins. Several DNA repair enzymes influence the processing of a subset of miRNA by recognizing specific miRNA features or by associating with key components of the miRNA maturation pathway. Red boxes indicate DDR proteins involved in miRNA biogenesis.

Drosha and p68 complex suppressing miRNA processing activity of Drosha by sequestering p68 cofactor [79,82].

Additionally, BRCA1, a key player in DSBs (Double Strand Breaks) response, has been recently shown to increase the expression of let-7a-1, miR-16-1, miR-145, and miR-34a through a direct binding of p68 RNA helicase in Drosha complex [83].

ATM, a crucial kinase in DDR, regulates miRNA expression in response to DNA damage through the phosphorylation of different targets including, KSPR [84], p53 [84,85], ΔNp63α [86] and BRCA1 by indirectly promoting the processing of a subset of pri-miRNAs [83].

MMR pathway can also mediate miRNA processing. The heterodimer MLH1-PMS2 (MutLα) has been shown to positively regulate the processing of miR-422a and other miRNAs by specifically stimulating the Drosha/DGCR8-catalyzed processing of pri-miRNAs to pre-miRNAs [87].

Different studies have also suggested a possible involvement of BER proteins in miRNA processing, particularly those proteins found to be multifunctional enzyme with unique features such as: YB-1, Poly(ADP-ribose) polymerases (PARPs) and APE1.

YB-1 is a multifunctional protein participating in a variety of DNA/RNA-dependent events such as DNA replication and RNA-processing events including mRNA transcription, splicing, translation and stability. Interestingly, in light of its interaction with different DNA repair enzymes, it is considered as a non-canonical BER protein [88]. In addition, genome-wide analysis of YB-1-RNA interaction in glioblastoma cell line unraveled a novel role of YB-1 in the regulation of miRNA biogenesis during tumorigenesis. Wu et al., recently demonstrated that YB-1 interaction with the loop region of pre- and pri-miR-29b-2 interferes with Drosha and Dicer cleavage step. Interestingly, down-regulation of miR-29b-2 expression as a consequence of this missed recruitment of Drosha and Dicer to miR-29b-2 precursor due to YB-1 blockage, has crucial implication in glioblastoma proliferation [89].

Recent data suggest that miRNA biogenesis can be also modulated by post-translational modifications of each member of the Argonaute family by PARPs [90,91]. Indeed, poly(ADP-ribose) modification of key RNA regulatory proteins has been documented for every step of RNA metabolism including miRNA biogenesis. There are five specific PARPs that can be considered RBPs because of the presence of RNA binding domain in their sequence (i.e. CCCH zing finger and RRMs, RNA recognition motif): PARP7, PARP12, PARP13, PARP10 and PARP14. In particular, it has been observed that, upon stress condition, an increased PARP13 activity near the Argonaute/miRNA complex might result in the disruption of the electrostatic interaction between miRNA and its mRNA target with a consequent mRNA cleavage relief [91].

APE1 possible involvement in miRNA biogenesis was previously only speculative based on different findings. It has been demonstrated that APE1 can directly bind, *in vitro,* structured RNA molecules through its 33 amino acids N-terminal domain [92] and, more interestingly, that APE1 is endowed with RNA-processing activity over single-stranded RNA, regulating for example c-Myc mRNA level and half-life in tumor cells [93] and, of note, it can cleave pre-miR10b and pre-miR-21 interfering with Dicer processing *in vitro* [94]. In addition, to further support APE1 involvement in RNA processing it has been also demonstrated its 3′-RNA phosphatase and 3′-exoribonuclease activities [95].

As a supplementary indirect observation, it has been recently found that APE1 down-regulation is associated with alteration in miRNAs expression, which are involved in pathways relating to developmental and regulation of cellular processes, cell signaling and cancer [96].

Very recently, in order to improve our knowledge on APE1 possible involvement in miRNA maturation, by using a combination of different unbiased high-throughput approaches at the transcriptomic and proteomic levels, we demonstrated that APE1 is involved in miRNome regulation by acting on early phases of miRNAs processing (Antoniali et al., submitted). We found more than 1000 APE1-bound RNA among which many ncRNAs and notably pri-miRNAs that are directly bound by APE1 in cancer cells. In particular, we showed that APE1 endonuclease activity over pri-miR-221/222 mediates the regulation of the tumor suppressor PTEN, a known target of these miRNAs [97]. Moreover, we evidenced, for the first time, that APE1 associates with the Drosha microprocessor complex during oxidative stress suggesting a possible contribution of APE1 in RNA-decay pathways controlling miRNAs precursors stability in the genotoxic cell response. Therefore, since APE1 is an interacting partner of Drosha and of p53 [98] and hRNPA1 (Antoniali et al., submitted), both proteins described as modulator of Drosha-mediated cleavage, we may speculate that APE1 endoribonuclease activity is part of inducible mechanisms regulating

the processing of miRNA biogenesis in the nucleus especially during oxidative stress or genotoxic damage. This is further support by the observation that oxidative stress promotes APE1/Drosha interaction and that APE1-kd is associated to increase oxidation levels of precursors miRNAs. These findings, together with previous data that APE1 silencing is associated with increased RNA oxidation [99], would support a major role of APE1 in the RNA-decay mechanisms of precursors pri-miRNAs.

Of note, not only RNA-binding factors can influence miRNA processing, but also post-transcriptional modification such as RNA-editing may change both maturation and expression of miRNAs. Adenosine to inosine (A-to-I) RNA-editing within the hairpin region of miRNA precursors is among the major effective mechanism described to alter the primary sequence of RNA. A-to-I miRNA editing is mediated by adenosine deaminases acting on RNA (ADAR) protein, ADAR1 and ADAR2, having consequences in miRNA biogenesis both at the level of Drosha and Dicer [100]. Recently, Wang et al. demonstrated that also oxidation represents another miRNA post-transcriptional modification with remarkably pathological outcomes. They proposed a new model in which ROS may modulate cellular events by oxidatively modifying miRNAs, as in the case of miR-184, which after oxidation changed its binding proprieties from native targets to new ones [101].

In light of our previous data, demonstrating that APE1 has endoribonuclease activity over abasic RNA [99], we should therefore reinterpret the roles of APE1 in modulating cellular responses to genotoxic stresses and in the pathogenesis of human diseases, taking into account the new role of this multifunctional protein in RNA biology. Our data demonstrate that APE1 is involved in specific miRNA processing and highlight a new mechanism of miRNA regulation with profound relevance in tumor biology.

In conclusion, recent advances in miRNA maturation pathways have demonstrated that the multiple stages of miRNA biogenesis could serve a multitude of regulatory options in control of miRNA-dependent gene regulation. These findings have changed the conventional concept of miRNA processing and have shown an additional level of complexity in the miRNA network. miRNAs are often deregulated in human pathologies including cancer; frequently this change is a consequence of impaired transcription rate and/or miRNA processing. RBPs and their interacting modulators mostly account for these observed changes in miRNAs processing and activity.

Further investigations on the additional mechanisms that control the processing of miRNAs under various cellular conditions and the role of DNA repair proteins will extend our knowledge on miRNA function in both physiological and pathological processes. These findings will also offer a molecular basis for diagnostic and therapeutic strategies based on miRNA biology.

## 6. New insights about BER involvement into removal of modified ribonucleotides embedded in DNA

A “new type of damage”, abundantly explored in the very last years, is the presence of ribonucleotides monophosphate (rNMPs) within genomic DNA. It has been studied how the additional presence of a reactive 2′-hydroxyl group on the sugar ring may: i) alter the DNA physical properties, reducing its elasticity [102,103] and structure in a sequence dependent manner [104–108]; ii) induce DNA replication or transcription arrest making the DNA backbone prone to hydrolysis triggering a persistent genomic instability [103,108,109]. This incorporation occurs quite frequently into the cell [110,111], potentially during every DNA replication reaction [110]. It has been estimated that a few thousands of rNMPs are embedded in budding yeast genome [110] and over a million in mouse genome [112]. The higher amount of the cellular pool of ribonucleotides (rNTPs), compared to their corresponding deoxyribonucleotides (dNTPs) [110] counterparts, combined to an incomplete elimination of RNA primers used in the generation of Okazaki fragments [113] and an imprecise 3′-exonucleolytic proofreading activity of replicative DNA polymerases [113–117] are some of the major causes of the rNMPs incorporation into genomic DNA. Moreover, another potential significant, yet poorly characterized, source of rNMPs incorporated in DNA is oxidative stress. Specifically, ROS, among which the hydroxyl radical ‘OH is the most reactive, can attack all components of DNA, including the deoxyribose giving rise to ribose [118], both *in vitro* and *in vivo*. Moreover, oxidation can occur not only in DNA but also in the nucleotides pool and then rNMP may be incorporated into neo-replicated DNA. During last years, several approaches have been developed [119], including Ribose-seq, in order to map rNMPs sites into genomic DNA [111]. By using these methods, it has been discovered that the incorporation of rNMPs has a widespread but not random distribution in chromosomal DNA of budding and fission yeast [111] and their number, per nuclear chromosome, seems to be proportional to the chromosome size [111].

It is imperative that mis-incorporated rNMPs should be efficiently and rapidly repaired by the cell, otherwise the effect on genome stability and cell survival can be disastrous. Processing of single rNMPs embedded in DNA is guided by the Ribonucleotide Excision Repair (RER) pathway in which the leading initiating enzyme is RNase H2 [120] deputed to incise the phosphodiester linkage at 5′ end of rNMPs [121]. Conditions in which human *RNASEH2* is mutated, are associated with a neurological auto-inflammatory childhood disorder named Aicardi-Goutières Syndrome (AGS), characterized by an over production of IFNγ [122–124]. It has been demonstrated that AGS patients, having altered RNase H2 activity, may accumulate rNMPs in DNA, which could induce a chronic, low-level DNA damage response signaling that stimulates innate immune pathways [125]. Moreover, RNase H2-null murine embryonic fibroblasts (MEFs) accumulate over 1 million rNMPs in their genomic DNA, activating a p53-dependent damage response, whereas null-RNase H2 are embryonic lethal [121]. While, under normal physiologic conditions, the involvement of functional RER pathway in repairing the rNMPs incorporated in DNA is known [112,120] information is scanty about possible back-up mechanisms, provided by other DNA-repair pathways, when RER is functionally impaired. In the absence of RNase H2, Topoisomerase I cleavage [126] followed by nick processing by Srs2–Exo1 can remove some rNMPs [127,128]. Paired and mispaired rNMPs in DNA can also be targeted by the nucleotide excision repair (NER) in bacteria [129] but likely not in mammalian cells [130], and by the mismatch repair (MMR) systems [131,132]. About this last pathway, it was hypothesized the incorporation of ribonucleotides into mismatching damaged DNA could be interpreted as a putative “benefic” role, verifiable in a signal for the activation of MMR pathway [133].

However, nothing is currently known about the mechanisms, if any, responsible for repairing modified rNMPs embedded in DNA such as abasic or oxidized rNMPs. Future studies are required to address this issue.

## 7. Open questions and future perspectives

Based on the observations described so far, many open questions remain to be addressed:

- Considering that many BER enzymes are catalytically active in many different RNA substrates, are their main functions linked to RNA-decay processes or in the editing processes?
- May the role of BER enzymes, both mRNA and ncRNA, affect the protein translational machinery thus contributing to gene expression regulation through post-transcriptional mechanisms?
- It is unknown whether abasic RNA may derive from enzymatic processing of modified (i.e. oxidized, alkylated) RNA. Are there specific BER glycosylases responsible for recognition and processing of these substrates?
- Is the BER involved in processing modified ribonucleotides embedded in human genome, which are not repaired through canonical

RER?

- Based on the emerging role of 8-oxoG as a new epigenetic mark, do BER proteins work as novel epigenetic regulators?
- Pondering the many evidences about the relevance of non-canonical function of BER proteins, should we reinterpret the overall biological function of BER and their role in cancer and neurodegeneration?

Answer to these questions may help us to better understand the role of BER pathway in different pathological processes from neurodegeneration to cancer development moving from an old tolemaic and reductive vision, which considers BER only a mere DNA repair pathway, to a more galileian theory which regards also its essential function in RNA biology and thus may explain its unpredicted role in gene expression.

## Conflicts of interest

None declared by the author.

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