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Inhibition of nucleotide excision repair by arsenic

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Inhibition of DNA repair is one proposed mechanism for the co-mutagenicity/co-carcinogenicity of arsenic. This review summarizes the current literature on the effects of arsenic compounds on nucleotide excision repair (NER). Several possible mechanisms for the observed NER inhibition have been proposed. Modulation of the expression of NER proteins has been considered to be one possibility of impairing the NER process. However, data on the effects of arsenic on the expression of NER proteins remain inconsistent. It is more likely that arsenic inhibits the induction of accessory or other key proteins involved in cellular control of DNA repair pathways, such as p53. For example, arsenic affects p53 phosphorylation and p53 DNA binding activity, which could regulate NER through transcriptional activation of downstream NER genes. Although it is important to study possible direct inactivation of NER proteins by arsenic binding, indirect inactivation of proteins having thiol residues critical to their function or zinc finger proteins cannot be negated. For example, nitric oxide (NO) induced in arsenic-treated cells serves as a specific inhibitor of NER, possibly through NO-induced S-nitrosylation of proteins related to DNA repair. Poly(ADP-ribose) polymerase-1, a zinc finger protein implicated in both NER and base excision repair (BER), deserves special attention because of its involvement in NO production and its broad range of protein substrates including many repair enzymes.

arsenic, carcinogenesis, DNA repair, nucleotide excision repair, p53, nitric oxide, PARP-1, protein binding

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1 Introduction

1.1 Arsenic and its co-carcinogenicity

Inorganic arsenic (arsenite and arsenate) is a ubiquitous environmental contaminant that has long been classified as a human carcinogen but its carcinogenic effects have not been conclusively demonstrated in laboratory animals [1–3]. Most of the animal experiments showed negative results and some reported a decrease in tumor induction by arsenic alone [1–4]. Unlike classical carcinogens, arsenic fails to induce point mutations in bacterial or mammalian cells [3–7]. By contrast, considerable evidence has pointed to arsenic promoting mutagenesis/carcinogenesis, both in *in vivo* bioassays and in *in vitro* cell culture systems. At non-toxic concentrations, co-mutagenic effects of arsenic with X-rays, ultraviolet (UV) radiation, or alkylating agents have been repeatedly observed [3–7]. Therefore, it is reasonable to consider that arsenic acts as a co-carcinogen, although some arsenic compounds have been shown to act as complete carcinogens in a few animal models [1]. This co-mutagenicity/co-carcinogenicity of arsenic might explain the lack of tumor development in most laboratory animals challenged with inorganic arsenic alone and the relative ease with which tumors were initiated when arsenic compounds were administered before, during, or after exposure to a potent carcinogen (an initiator). The co-carcinogenic mechanism might also shed light on human studies. Exposure to multiple carcinogens represents the environmental conditions for humans better than controlled exposure to a single carcinogen under laboratory settings. Co-exposure to cigarette smoking and arsenic has been shown to be linked to elevated rates of lung cancer in several epidemiological studies [8].

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1.2 Relevance of DNA repair inhibition to arsenic co-carcinogenicity

The integrity of genomic DNA is continuously challenged by endogenous and exogenous DNA damaging agents. Various DNA repair pathways have evolved in prokaryotic and eukaryotic organisms to protect their DNA, including direct reversal, excision repair, post-replication and recombination repair [9–11]. It is generally considered that inorganic arsenic neither affects DNA directly nor forms adducts with DNA. However, there is mounting evidence that inorganic arsenic and its metabolites may inhibit DNA repair pathways, especially base excision repair (BER) and nucleotide excision repair (NER) [3–7,12–15], leading to increased cancer risk. Other potential mechanisms for arsenic carcinogenesis/co-carcinogenesis are also under investigation including epigenetic changes by histone modifications, DNA methylation and micro RNA expression elicited by arsenic [7,16,17].

2 Nucleotide excision repair (NER)

NER is the most important and versatile DNA repair pathway for removing bulky DNA adducts and helix-distorting lesions induced by environmental carcinogens such as UV-induced cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts (6-4PP) or adducts produced by chemical carcinogens such as polycyclic aromatic hydrocarbons. NER is a complex process involving the concerted action of about 20 proteins or complexes in human cells [9–11]. There are two sub-pathways in NER (Figure 1), global genome repair (GGR) and transcription-coupled repair (TCR). GGR primarily responds to damage in non-transcribed DNA and the damage is initially recognized by the XPC-HR23B complex. For some lesions, predominantly CPDs, the DNA damage-binding complex (DDB1 and DDB2) is required to further distort the helix and allow for recognition by XPC- HR23B. TCR responds to damage in DNA undergoing transcription, triggered by the stalling of RNA polymerase II at the sites of DNA damage. The stalled polymerase is recognized by CSB and CSA proteins. Following the recognition step, both subpathways closely resemble each other and employ the same set of proteins to complete the repair process. This involves the recruitment of the transcription factor IIH (TFIIH) complex; localized unwinding of the DNA by the helicases XPB and XPD, which are subunits of the TFIIH complex; stabilization of the exposed DNA by XPA and replication protein A; excision of the damaged DNA by XPG and XPF; synthesis of replacement DNA; and ligation by DNA ligase I or III. TCR generally occurs more rapidly than GGR [10,11].

3 Inhibition of NER by arsenic

The first evidence of NER inhibition by arsenic was documented by Okui and Fujiwara [19]. They showed that micromolar concentrations of arsenite and arsenate increased the sensitivity of normal human fibroblasts to UV light. But they did not observe the effect in repair-deficient xeroderma pigmentosum complementation group A (XPA) cells. Furthermore, arsenic reduced unscheduled DNA synthesis (UDS) and the excision of CPDs irradiation. The reported studies of NER inhibition by arsenic [19–37] are summarized in Supporting Information Table S1.

Many different methods were used for determining NER capacity, including the comet assay, transfection based host cell reactivation assay, immunoassay, unscheduled DNA synthesis assay, and ^{32}P-postlabeling assay. Although it is beyond the scope of this review to evaluate them in detail, it is relevant to point out that some detection strategies (such as alkaline elution) are more sensitive than others (such as alkaline sucrose sedimentation). Also, the standard comet assay may not be a good choice when assessing the effects of arsenic on NER. Firstly, DNA repair processes have complex effects on the comet assay: on the one hand, DNA repair eliminates DNA lesions; on the other hand, excision repair in itself causes strand breaks. The former results in a decreased DNA migration and the latter may cause additional DNA migration in the comet assay. Secondly, coexposure to benzo[a]pyrene (BaP), a carcinogenic polycyclic hydrocarbon, or UV and arsenic is a very complex system because both BaP (or UV) and arsenic generate alkali labile sites and DNA strand breaks [38–40], which make the interpretation of the comet assay results difficult. Incorporation of T4 endonuclease, which incises DNA at CPDs, to the standard comet assay has been shown to improve its specificity for pyrimidine dimers [25,28,36].

^{32}P-postlabeling is another method that is prone to producing false positives and artifacts. It may underestimate adduct levels because of incomplete DNA digestion, inefficiency of adduct labeling, and/or loss of adducts during enrichment and separation. Labeling efficiency is often unknown and uncontrolled; and results from different laboratories are sometimes not comparable [41,42].

Even with varied methods employed for the detection of NER capacity and different cell types, the inhibitory effect of inorganic arsenic and its pentavalent and trivalent methylated metabolites on NER has been clearly shown in the majority of studies (17 out of 19). Pentavalent arsenicals are less potent than trivalent arsenicals in inhibiting the NER processes. This is probably because the former are less reactive and enter cells less readily than the latter. Once inside the cell, pentavalent arsenicals are immediately reduced to trivalent arsenicals so the biological effects incurred are attributed to the trivalent arsenicals and their metabolites. In agreement with a previous report [31], our study [32,33] showed that the extent of inhibition of NER by trivalent arsenicals in human cells followed a descending order: MMA^{III}>DMA^{III}>As^{III} (Figure 2).

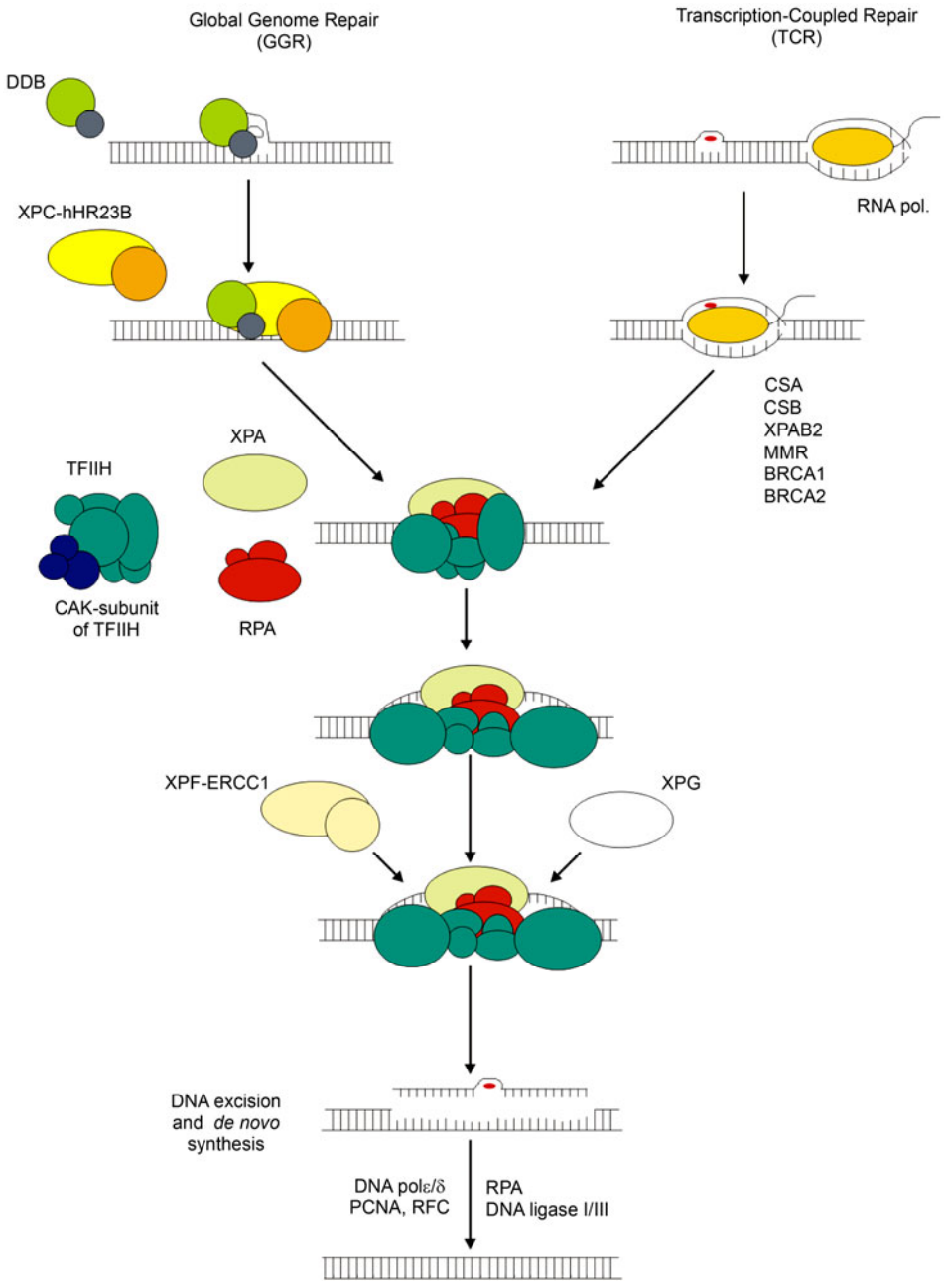

Figure 1 (Color online) Mammalian nucleotide excision repair (NER) pathways (modified from [18]).

4 Possible mechanisms of NER inhibition by arsenic

4.1 Arsenic and NER proteins

(1) NER protein expression. Excision repair cross-complementing protein 1 (ERCC1), which interacts with XPF and performs the 5′-incision step during NER, was one of the first NER proteins found to be modulated by arsenic and is also the most studied. Its gene expression was enhanced 2-fold in liver tissue after treatment of mice with inorganic arsenicals for 3 h, along with induction of some other repair genes including DNA ligases I and III [43] although the mRNA and protein levels of both DNA ligases I and III were found to be significantly reduced in mammalian cells in response to arsenite [44]. Importantly, individuals chronically exposed to higher levels of arsenic in drinking water (>10 μg/L) were found to have decreased DNA repair gene expression of ERCC1, XPF and XPB (but not of XPG and XPA) in their lymphocytes [45]. A follow-up study [46] further demonstrated that expression of ERCC1 was decreased at both the mRNA and protein levels. A dose-dependent decrease in the mRNA expression of ERCC1 was also found in human cardiomyocytes exposed to arsenite for 72 h [47]. However, elevated ERCC1 gene expression has

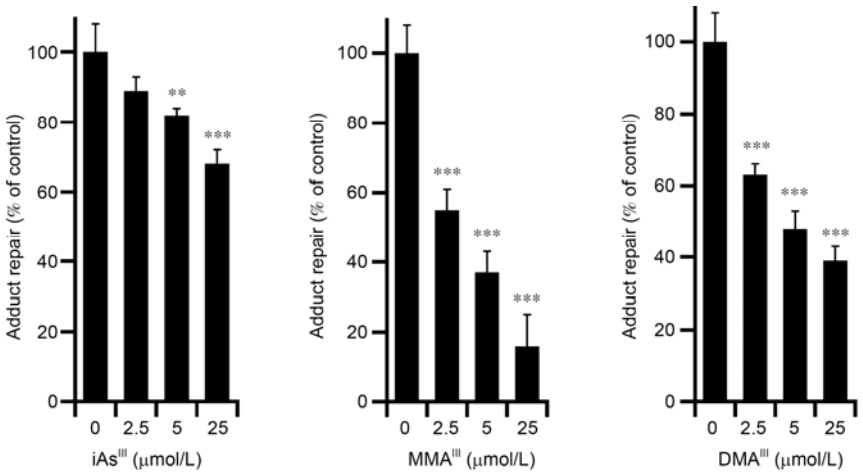

Figure 2 *i*As^{III}, MMA^{III}, and DMA^{III} inhibit the repair of BPDE-DNA adducts. CRL2522 cells were incubated with BPDE (1 μmol/L) for 30 min and then allowed to repair for 24 h in the presence of *i*As^{III}, MMA^{III}, DMA^{III} at the indicated concentrations. The cells were lysed and DNA extracted for analysis of the BPDE-DNA adducts. ** and *** denote statistically significant differences from the controls with $P<0.05$ and $P<0.01$, respectively, using one-way Student's *t*-test. Error bars represent the standard deviation from three independent experiments (adapted from [32]).

been reported in blood cells from individuals chronically exposed to arsenic in drinking water in Inner Mongolia [48].

One early large-scale microarray analysis [49] revealed that expression of four NER proteins (XPC, Damage specific DNA binding protein 2 (DDB2 or p48), DNA polymerase δ, DNA polymerase ε) and p53, along with numerous other repair proteins, was significantly down-regulated by arsenite at submicromolar concentrations in normal human epidermal keratinocytes (NHEK). In another study using human lung cells [50], the gene expression of DNA ligase I, XPD, XPC, and RFA was found to decrease by at least 2-fold after treatment with 5 μmol/L arsenite for 4 h. Interestingly, in SV40-immortalized human keratinocytes (RHEK-1), multiple DNA repair proteins were overexpressed when treated with arsenic alone but suppression of DNA repair protein expression was observed when the cells were treated with an arsenic-containing metal mixture [51]. DMA^{V}, the only methylated metabolite of inorganic arsenic that has been studied in this respect did not change the expression of DNA repair genes, including XPB, of bladder transitional epithelium in F344 rats [52]. Most recently, Nollen et al. [53] found that a 24-h treatment with arsenite or MMA^{III} strongly decreased XPC at both the mRNA and protein levels in normal human skin fibroblasts immortalized by telomerase transfection (VH10hTert). The reduced level of XPC expression led to a diminished localization of XPC to UV-damaged spots in the nucleus. The gene expression of XPE (p48, DDB2) was also reduced. MMA^{III} was shown to have a stronger impact on their expression than arsenite, which may explain the more potent NER inhibition by MMA^{III} compared to arsenite observed previously [31–33]. However, p53, as the transcription factor of both XPC and XPE, was observed to be up-regulated at the total cellular protein level by arsenic, which could not account for the decreased expression of XPC and XPE. Examination of the nuclear p53 level and nuclear p53 transactivating ability may be helpful to understand this discrepancy.

To study the effect of arsenic on the NER protein expression in a more relevant context where co-exposure to arsenic and a primary DNA damaging agent that induces the NER process (NER inducer) occurs, we incubated human cells with benzo[a]pyrene dihydrodiol epoxide (BPDE) to induce DNA adducts reparable by NER and then allowed them to repair with or without the presence of arsenicals. The expression of a panel of NER proteins was examined by Western blotting: XPA, XPC, p48 (DDB2), p62-TFIIH, and p53. We [32] did not observe a significant modulation by arsenic of any of the NER repair proteins except the NER-related protein, p53. Consistent with our observations, Liu [36] did not see an altered expression of critical NER proteins, including ERCC1, XPF, and XPB after co-treatment with UV and arsenic. However, co-treatment with arsenite was found to prevent the induction of p53 and XPC by cisplatin but modestly induce ERCC1 in murine metastatic ovarian cancer xenograft [54].

In summary, data on the effects of arsenic on the expression of NER proteins remain confusing. It is possible that repair protein expression may be lowered following chronic exposure to arsenic [45,55]; however, this mode of action cannot explain the NER repair inhibition by arsenic observed in short-term studies mentioned above.

(2) NER protein function. Early studies showed that both DNA excision repair pathways (BER and NER) were inhibited by arsenite, suggesting that a later step shared by both pathways, the DNA ligation step, might be a major target of arsenic inhibition [4,56]. Subsequent studies confirmed that arsenic retarded DNA ligation and found that arsenite inhibited the cellular activity of DNA ligase III more specifically and DNA ligase I to a lesser extent [57]. However, direct inhibition of ligase I and III enzymatic

activity by arsenic seemed to be less biologically relevant since 1000-fold higher concentrations of arsenite were required to inhibit the purified enzymes [57]. The finding [29] that the damage incision step of the NER process for UV damage was inhibited by arsenite at a concentration as low as 2.5 μmol/L also brought damage recognition/incision into attention. XPA, a zinc finger protein, as a biochemically plausible binding target of trivalent arsenicals, has since been under intensive study [31,58,59]. However, arsenite, MMA^{III} and DMA^{III} steadily induced zinc release from the zinc finger domain of the human XPA (XPAzf) only at concentrations greater than 10 μmol/L [31] and the binding of XPA to an UV-irradiated oligonucleotide was not diminished by arsenite even when its concentration reached 1 mmol/L [58].

The above summary suggests that NER inhibition by arsenic is not caused by direct inhibition of repair enzymes. Indirect effects from arsenic compounds such as generation of reactive oxygen species (ROS) may play an important role in enzymatic inhibition. Zinc finger repair proteins remain the potential targets of arsenic inhibition. Among them is poly(ADP-ribose) polymerase-1 (PARP-1) and its involvement in NER is being investigated [60,61] . The activity of PARP-1 was shown to be inhibited by arsenite, MMA^{III} and DMA^{III} at extremely low (nanomolar) concentrations in HeLa S3 cells after H_2O_2 treatment [62,63]. Besides XPA and PARP, TFIIH, RPA, BRCA1, and ligase III are all zinc finger DNA repair proteins in NER which should be very sensitive to arsenic treatment partly through redox control.

4.2 Arsenic and p53

p53 is also a zinc finger protein and is a very important transcription factor in cell cycle control, apoptosis and control of DNA repair. There is accumulating evidence for a role of p53 in NER [64]. However, the precise molecular mechanism for the involvement of p53 in NER is not completely understood. p53 may regulate NER through transcriptional activation of downstream NER genes [65,66], through modulating chromatin accessibility of damaged DNA [67], through protein-protein interactions to alter the activity of NER gene products [68], or through recruitment of DDB2, XPC, or TFIIH to DNA damaged sites [69–71].

Arsenic has been reported to decrease p53 expression, induce p53 phosphorylation and accumulation, or have no effect on p53 [72]. Therefore, the role of p53 in arsenic-elicited cellular effects is still elusive. The functional status of p53 appears to complicate this issue. Most recently, Yan et al. [73] demonstrated that As_2O_3 induced wild-type p53 but degraded mutant p53 protein.

In a context where co-exposure to arsenic and a primary NER inducer occurs, Tang et al. [74] treated mouse epidermal JB6 Cl41 cells with arsenite for 24 h prior to UV irradiation and found that arsenite inhibited p53 activation, leading to a decreased p21 expression. This inhibition was concordant with the inhibition of UV-induced p53 phosphorylation at serines 15 and 392 and of p53 DNA binding activity. We [32] found similar inhibition of p53 phosphorylation and p53 DNA binding activity by an arsenite metabolite, MMA^{III} in human skin fibroblast CRL2522 cells with an assay system involving BPDE in place of UV. Following treatment of arsenic up to 24 h post-BPDE incubation, we found a striking temporal relationship between the suppression of BPDE-induced p53 expression and DNA repair inhibition. Further investigation revealed that p53 was targeted for NER inhibition by MMA^{III}. We also observed a decrease in p53-regulated p21 levels. Because of the role of p21 in blocking cell cycle progression after DNA damage, the depletion of p21 may imply that overriding the cell cycle arrest at G1, which normally allows sufficient time for DNA repair to take place prior to DNA replication, contributes to the co-mutagenic effect of arsenic. Several studies [75–78] have shown that arsenic could interfere with cell cycle control. However, in synchronized human cells, both we [33] and Liu [36] did not observe any inactivation of cell cycle checkpoints after treatment with BPDE or UV, suggesting that the function of arsenic as co-mutagen/co-carcinogen most likely does not occur via cell cycle checkpoint suppression.

4.3 Arsenic and nitric oxide

Jan and coworkers [25] were the first to propose that nitric oxide (NO) was involved in NER inhibition by arsenite. They found that arsenite increased NO production in Chinese hamster ovary cells and nitric oxide generators inhibited pyrimidine dimer excision. The inhibition of pyrimidine dimer excision by arsenite was suppressible by nitric oxide synthase (NOS) inhibitors. Phenylarsine oxide, an arsenic compound that readily binds to thiols, did not inhibit the excision and did not produce NO, implying that binding of arsenic to thiol groups of DNA repair proteins (such as ligase III) may not be a direct mechanism for arsenite-mediated DNA repair inhibition. They further demonstrated that like nitric oxide generators, arsenite inhibited the DNA-adduct excision in NER induced by UVC, 4-nitroquinoline 1-oxide, BPDE, cisplatin, or mitomycin C, but not that in BER induced by methyl methane sulfonate, H_2O_2, sodium nitrosoprusside, or 3-morpholinosydnonimine [79]. Their finding was confirmed in human keratinocytes by Ding et al. [24] who used different methods for both NO and pyrimidine dimer determinations. It is relevant to point out that although reactive nitrogen oxide species (RNOS) derived from NO can result in strand breaks and mutations, NO itself is probably insufficiently reactive to attack DNA directly [80], which makes this proposal a plausible mechanism for NER inhibition by arsenic, possibly through NO-induced nitrosylation of DNA repair proteins (Figure 3).

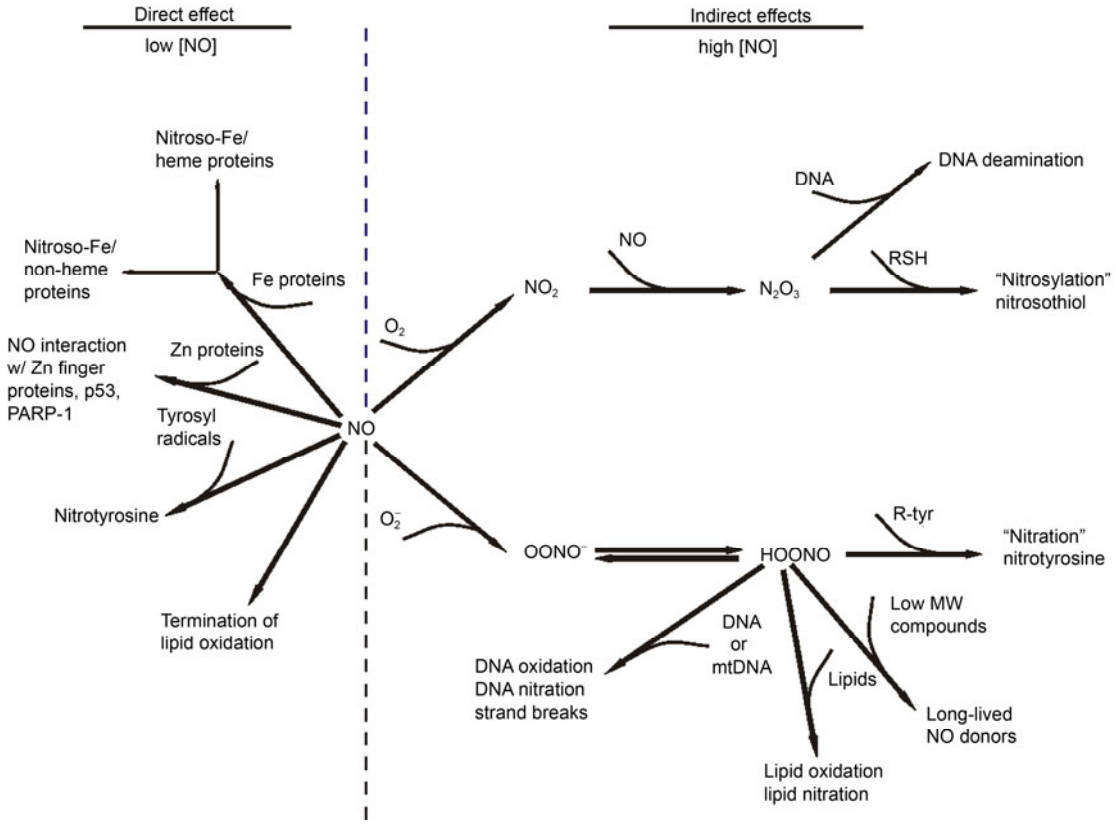

Figure 3 The chemistry of NO interaction with other biomolecules (modified from [80]).

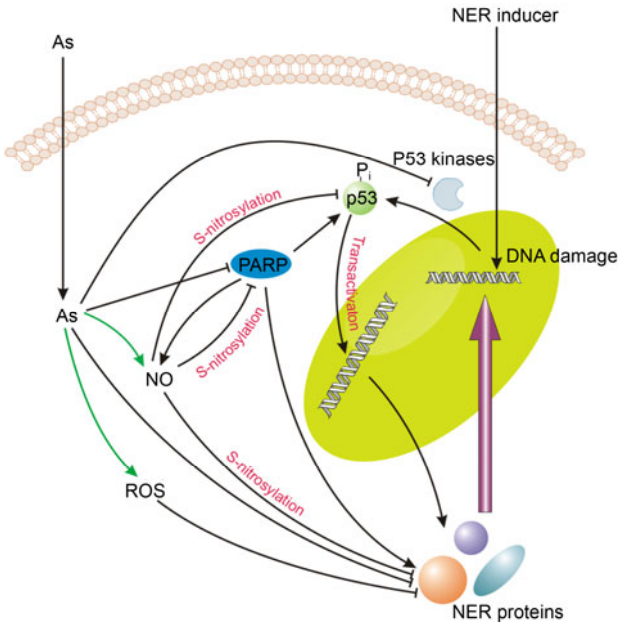

Figure 4 (Color online) The proposed mechanisms of NER inhibition by arsenic.

5 Perspectives

NER inhibition by arsenic has been well documented and it has important implications in the co-mutagenicity/co-carcinogenicity of arsenic. However, mechanisms for this inhibition remain elusive and the mechanisms proposed in this review are shown in Figure 4. Arsenic compounds have capricious effects on modulating the expression of NER related proteins, including p53. It remains unclear as to whether direct inactivation of DNA repair proteins by arsenic binding is a mode of action. However, arsenic-mediated generation of ROS and NO (or reactive nitrogen species derived from NO after reacting with ROS when the local NO concentration is high) in functional impairment of NER repair-related proteins and p53 upstream kinases, especially zinc finger proteins and proteins having thiol residues critical to their function, can play an important role in NER inhibition by arsenic. PARP-1, as a zinc finger protein, is implicated in both DNA repair and apoptosis. Its inhibition by arsenite has been shown to promote cell survival after UV radiation with unrepaired DNA lesions [37], a reasonable model for explaining arsenic co-carcinogenicity. PARP-1 is also involved in NO production by transactivating inducible NOS, a process that can be feedback regulated by the inhibition of PARP-1 by NO via S-nitrosylation [81]. The PARP superfamily has been shown to interact with many proteins, including DNA methyltransferase 1, p53, p21, XPA, BRCA1, ATM, DNA ligase I/III, and DNA polymerase ε [82].

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Supporting Information

Table S1 Effect of arsenic compounds on NER (numbers in parentheses indicate referenced papers)

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