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DNA Helix Destabilization by Alkylating Agents: From Covalent Bonding to DNA Repair

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1. Introduction

Preservation of the integrity of the DNA, carrier of heritage information, is crucial for cell survival. Altered genetic information could lead to major perturbations in cell organization, function and proliferation of cancer cells. Because cancer cells are highly proliferative with high number of replication, DNA was the first clinically used anti-cancer therapeutic target with the drugs directly (intercalators/alkylating drugs) or indirectly (micro-tubules, topoisomerases inhibitors, modifiers of histone acetylation...) targeting DNA. Despite the actual development of targeted chemotherapies (against membrane receptors, kinases, the proteasome,…), direct DNA targeting drugs still represent a major part of the actual anti-cancer pharmacopeia in terms of total prescriptions and efficacy. Compounds mainly bind DNA in three different ways: non-covalent (fitting in major or minor grooves), intercalation between two successive base pairs, or covalent bonding to a base, and generally lead to a stabilization of the DNA double helix. Only a few number from intercalating and alkylating families destabilizes the DNA helix. Cytotoxic effects of alkylating agents (used/developed for chemotherapy or from carcinogens) are strongly attenuated by the cellular DNA repair processes. Optimal use of DNA alkylating drugs in therapy requires a clear understanding of their DNA repair processes. Similarly, knowing how cells cope with the carcinogens-induced DNA damages is of major interest regarding health in our actual society, so prompt to use chemical compounds insufficiently studied for long term toxicities and sometimes eventually identified as carcinogens (food and industries). DNA repair processes infer with both those Yin and Yang aspects of alkylating compounds using different machineries: base excision repair (BER); nucleotide excision repair (NER: long/short-patch, transcription-coupled/global genome); mismatch repair (MMR); homologous recombination (HR) or non-homologous end-joining (NHEJ). Fanconi anemia (FA) repair acts as a coordinator of those repair pathways (Moldovan & D'Andrea, 2009). Since there are yet various complete reviews on DNA repair processes in the literature, the present review will focus on the repair process of DNA destabilizing compounds.

2. DNA destabilizing compounds

Stability of DNA double helix is mainly due to reversible non-covalent hydrogen bonds between Watson-Crick base-pairs. Local or global denaturation (melting or breathing) of the double-stranded DNA (dsDNA) helix is dispensable for different cellular processes: DNA replication, transcription and repair (Choi et al., 2004; Schneider et al., 2001). DNA melting is affected by sequence (AT- or GC-rich portions, some successive base pairs arrangements) and their specific tilt, roll, twist effects (Benham, 1996; Dornberger et al., 1999; Krueger et al., 2006), the formation of local hairpins, 3D structures at terminal regions of the DNA helix (Putnam et al., 1981) or internal portions of B- to Z-DNA transition (Harvey, 1983). Such locally opened sites are good substrates for, or are generated by, some cellular proteins: DNA helicases (Betterton & Julicher, 2005), single strand binding proteins (SSBP) such as replication protein A (RPA) (Wold, 1997), UP1 and myeloma helix-destabilizing protein (Herrick & Alberts, 1976; Planck & Wilson, 1980), GAPDH-related protein P8 (Karpel & Burchard, 1981), High Mobility Group (HMG) proteins (Butler et al., 1985), c-Abl kinase (David-Cordonnier et al., 1998, 1999), HIV-1 nucleocapsid protein (Narayanan et al., 2006), prion protein (Bera et al., 2007), NF-κB transcription factor (Mura & McCammon, 2008) and UHRF-1 protein (Arita et al., 2008). Besides large DNA opening, small modifications such as base flipping locally perturb DNA stability (Hornby & Ford, 1998) during mismatches or repair proteins interaction from NER (Cao et al., 2004), BER (Bellamy et al., 2007; Tubbs et al., 2007) or DNA methylases/demethylases (Sundheim et al., 2008).
Besides naturally occurring DNA breathing, unzipping is induced by clinically used or potential anti-tumor compounds. The vast majority of DNA-interacting compounds stabilize the DNA double helix; only a very few of them displays the pecular ability to destabilize DNA helix. In this latter group, most belong to DNA intercalating or alkylating families.

2.1 DNA intercalators as helix destabilizing agents

2.1.1 Mono-intercalators

Historically, the first DNA intercalating compound evidencing DNA destabilization properties was acridine orange (Figure 1), a well-known dsDNA intercalating compound and a strong single-stranded DNA (ssDNA) binder. It emitted green fluorescence emission from dsDNA binding and red luminescence from ssDNA interaction. Acridine orange enhances the global helix stability but exerts local denaturation of DNA (Kapuscinski & Darzynkiewicz, 1983; 1984; Darzynkiewicz et al, 1983). Ellipticine and adriamycin (Figure 1) also induce local unzipping of the DNA and bind ssDNA (Zunino et al., 1972), in contrast with ethidium bromide (BET), highly specific to dsDNA and stabilizing DNA. Intercalation of acridine orange, ellipticine and adriamycin progressively unzip the DNA helix preferentially in heterochromatin, ribosomes and polysomes (Darzynkiewicz et al., 1983).

2.1.2 Bis-intercalators

Bisacridine A (BisA) (Figure 1) is a DNA unwinding bis-intercalator deriving from acridine orange by cyclization of two acridine planar chromophores using polyammonium bridges. Initially designed to interact with ss- rather than ds-DNA (Teulade-Fichou et al., 1995), BisA shifts duplexes DNA toward hairpins and destabilizes dsDNA (Slama-Schwok et al., 1997).

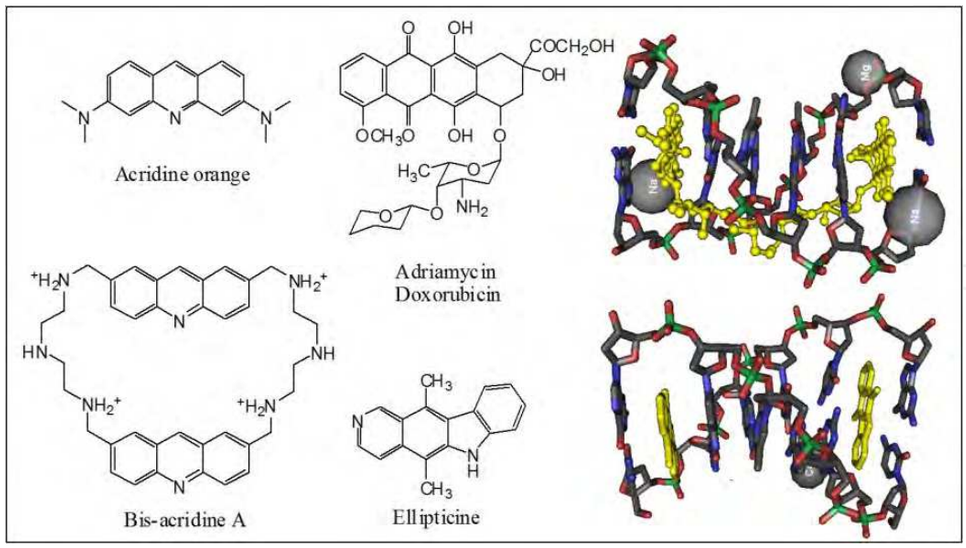

Fig. 1. DNA intercalators that destabilize the DNA helix: structures and 3D orientation of morpholino-doxorubicin (Top, [mmdbId:52942]) or ellipticine (Bottom, [mmdbId:52189]).

2.2 DNA alkylators as helix destabilizing agents

Some DNA alkylating drugs could also locally destabilize DNA double helix. Some of those are used/developed as anticancer drugs such as cisplatin and metal-derivatives, or more recently the benzoacronycine derivative S23906-1. They contrast with most DNA alkylating agents used or not in chemotherapy that stabilize DNA helix (for instance mitomycin C, dinuclear platinum, nitrogen mustards or ecteinascidine 743) (Basu et al., 1993; David-Cordonnier et al., 2005; Fridman et al., 2003; Kasparkova et al., 1999). Electrophilic alkylating drugs react at nucleophilic positions of G-C or A-T bp with preferential targets: N^7 position of dG or dA and O^6 position of dG in the major groove, N^3 positions of dG or dA and exocyclic NH_2 group on C^2 of dG (also called N^2) in the minor groove (Figure 2).

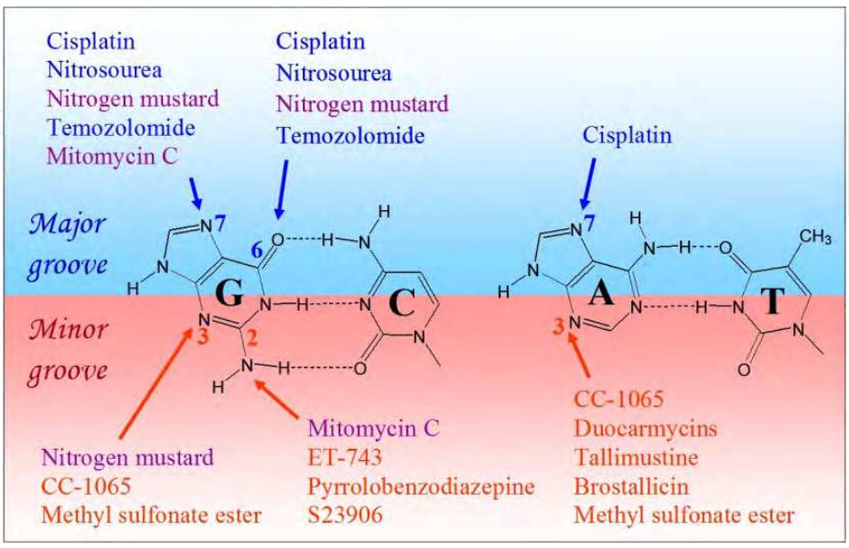

Fig. 2. Position of the reactive sites of some DNA alkylators on G-C or A-T base pairs.

2.2.1 Cisplatin and other transition-metal antitumor agents as DNA destabilizing drugs

Fortuitously discovered in 1965, cisplatin (or *cis*-diaminedichloridoplatinum(II) is used in clinic since 1978 and is still frequently administrated in combinatory chemotherapies as one of the most effective anticancer drugs against solid tumors (Figure 3). Cisplatin forms inter- and intra-strand crosslinks as well as monovalent adducts. Those lesions occur primarily though covalent bonding to the N^7 atom of guanines. The most common lesions are intra-strand crosslink at the 5′-GG (65%) or 5′-AG (25%) dinucleotides and inter-strand crosslinks (5-8%). This latter lesion is more frequent using transplatin (12%), *trans*-$PtCl_2(NH_3)$(quinoline) and *trans*-$PtCl_2(NH_3)$(thiazole) derivatives (up to 30%) (Figure 3). Cisplatin-induced intra-strand crosslinks at GpG base-pairs result in a strong DNA helix bending toward the major groove with an angle of 55-78° associated with DNA distortion, resulting in a destabilization of the Watson-Crick base pairing and local denaturation of the DNA helix (bending at 45° and unwinding by 79+/-4°) (Bellon, 1991; Malinge et al., 1994; Todd & Lippard, 2010). In platinated-GpG intra-strand crosslinks, the distortion varies and depends on the sequence context, with up to a 7 bp distortion for 1,3-intrastrand crosslinks within a TGTGT sequence (Kasparkova et al., 2008a). Such destabilization was found to be enthalpic, but not entropic, in origin. Similarly, when occurring at 5′-TGGT site, cisplatin adducts decrease the melting temperature of the DNA by more than 10°C which is much higher than that induced on 5′-CGGT and 5′-AGGC sequences (~6°C) (Malina et al., 2007).
Such effects are not observed with transplatin which does not change the transition entropy or enthalpy and, consequently, does not destabilize the DNA helix (Kasparkova et al., 2008a). Third-generation platinum antitumor derivative oxaliplatin (Figure 3) induces greater DNA bending, unwinding and helix destabilization than cisplatin, whereas JM118 (Figure 3) induces DNA destabilization profiles similar to that of cisplatin (Kostrhunova et al., 2010). JM118 is the major metabolite of satraplatin (JM216), the first orally administered platinum drug that also evidenced promising therapeutic activities in prostate cancer. JM118 induces a DNA bending with an angle of 28° toward the major groove, an angle smaller than that obtained with cisplatin for the same sequence (34°) (Kostrhunova et al., 2010).
Besides the nature of the platinated drug, the surrounding DNA sequence is also of major importance for helix stability. Indeed, monofunctional platinum adducts at 5′-TGC triplet induces major DNA destabilization (Brabec et al., 1992) but none at 5′-AGT or 5′-TGA triplet (Schwartz et al., 1989). DNA is not the unique nucleic acid destabilized by platinated derivatives as evidenced using *cis*-$[PtCl(NH_3)_2(OH_2)]^+$, *cis*-$[PtCl(NH_3)(c\text{-}C_6H_{11}NH_2)(OH_2)]^+$ and *trans*-$[PtCl(NH_3)(quinoline)(OH_2)]^+$ (Figure 3) which not only destabilize ds-DNA but also ds-RNA (ΔTm of -11°C and -5°C, respectively) (Hägerlöf et al., 2006).
Besides platinum derivatives, ruthenium compounds were developed as anti-cancer drugs. NAMI-A was the first ruthenium derivative that entered phase I clinical trials in 1999 as an anti-metastatic drug (Bergamo et al., 2002), followed by KP1019 (FFC14A) in 2003 (Hartinger et al., 2008). Two gallium compounds, gallium maltolate and KP46 (FFC11), also entered phase I clinical trials in 2003 (Lum et al., 2003). As for cisplatin, ruthenium derivatives evidenced DNA destabilization properties. This is particularly well described for Ru-CYM ($[(\eta6\text{-}\pi\text{-cymene})Ru(II)(en)\text{-}(Cl)]^+$ and Ru-BIP, Ru-DHA or Ru-THA as biphenyl, dihydroanthracene or tetrahydroanthracene derivatives, respectively (Figure 3). Such organometallic ruthenium(II) arene complexes were rationally designed for chemotherapy with the idea that changing platinum for ruthenium would provide additional coordination sites in the octahedral complexes to modify the oxidation rate and change ligand affinity

and binding kinetics (C.X. Zhang & Lippard, 2003). From this series, Ru-CYM presents the highest DNA helix destabilization activity, together with the smaller unwinding angle in supercoiled plasmid DNA (7° *vs.* 14° for Ru-BIP, Ru-DHA and Ru-THA), in correlation with its lack of intercalation and the formation of monoadducts at N^7-dG (Nováková et al., 2009). New Ru-derivatives monodentate-Ru(II) and $[Ru(terpy)(4,4'\text{-}(COLysCONH_2)_2bpy)Cl]^{3+}$ also destabilize DNA (Nováková et al., 2010; Triantafillidi et al., 2011). For gallium-complexed compounds, interaction of trivalent Ga-cations with calf-thymus DNA resulted in major helix destabilization with perturbations at A-T base pairs sites (R. Ahmad et al. 1996).

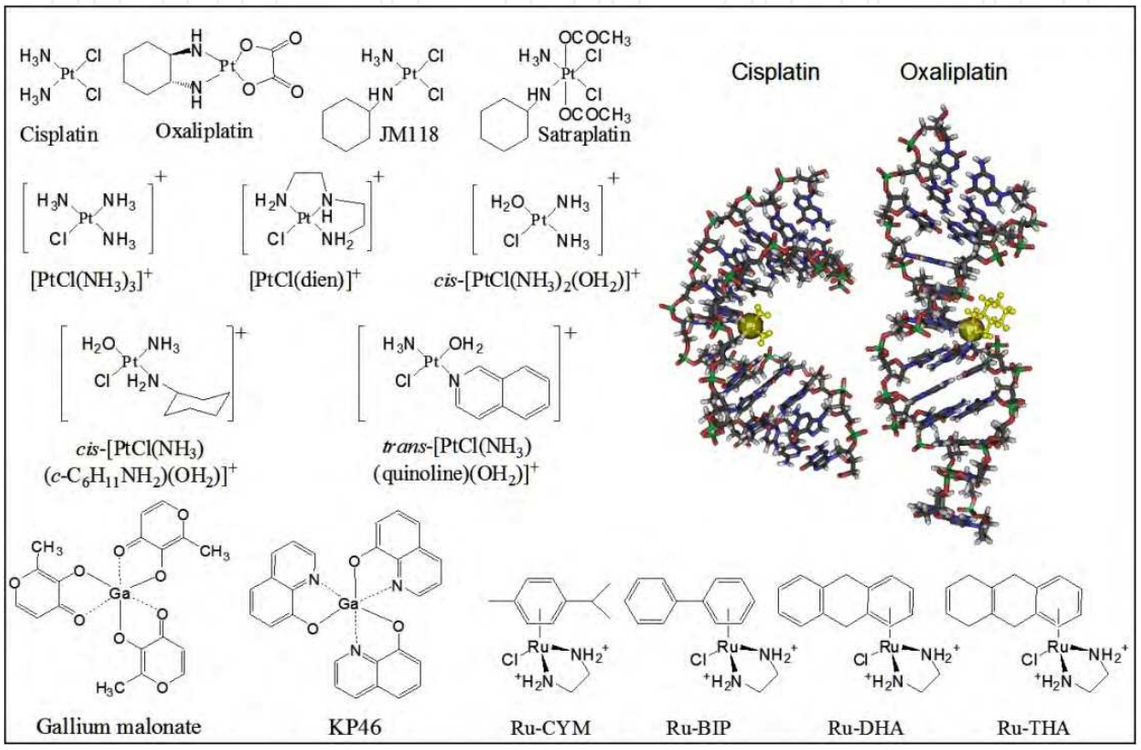

Fig. 3. Structure of cisplatin and other transition-metal agents as DNA destabilizing drugs and 3D orientation [mmdbId:47796] (cisplatin) and [mmdbId:69361] (oxaliplatin).

2.2.2 Carcinogens as DNA destabilizing agents

DNA interaction of carcinogen, adduct formation and their repair processes are widely studied using carcinogens from environmental and tobacco smoke. Some of them have the ability to destabilize the DNA helix: BPDE ((+/-)-*anti*-benzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxide) and 4-OHEN (4-hydroxyequilenin-O-quinone) (Figure 4).

The smoke carcinogen benzo[*a*]pyrene (BaP) is metabolized into several enantiomers of BPDE that covalently bond the exocyclic NH_2 group of guanines to form a bulky adduct in the minor groove of the DNA helix, resulting in its destabilization (Zou & Van Houten, 1999). Due to the orientation of the reactive epoxide group on asymmetric carbons, several enantiomers are produced. The most carcinogenic is 10S(+)-*trans*-*anti*-BPDE N^2-dG adduct followed by the stereo-isomeric 10R(+)-*cis*-*anti*-BPDE-N^2-dG adducts. Covalent bonding to DNA is associated with base-displaced intercalation where the bulky adduct prevents the hydrogen bonding of the amino group of guanine with the opposite cytosine. This results in

a base-flipping where the (+)-*anti*-B[*a*]P-N²-dG bulky adduct is located in the minor groove and the opposite cytosine is positioned in the major groove (Cosman et al., 1993). The precise orientation of this highly carcinogenic 10S(+)-*trans-anti*-B[*a*]P-N²-dG adduct depends on the sequence surrounding the target guanine (Cai et al., 2010). DNA is untwisted at 5′-CGG*C sites where a large bend is induced in the DNA helix, but not at 5′-CG*GC sequences where, conversely, DNA helix is destabilized in its portion orientated 5′ to the lesion (Rodríguez et al., 2007). Such differences result in different protein/DNA recognition and repair activities (see 3.4). Thermal destabilization was also observed using 14R(+)-*trans-anti*-DB[*a,l*]P-N²-dG adduct (Zheng et al., 2010) or *14S*(-)-*trans-anti*-DB[*a,l*]P-N⁶-dA adducts whereas *14R*(+) isomer stabilizes the ds-DNA (Cai et al., 2011).

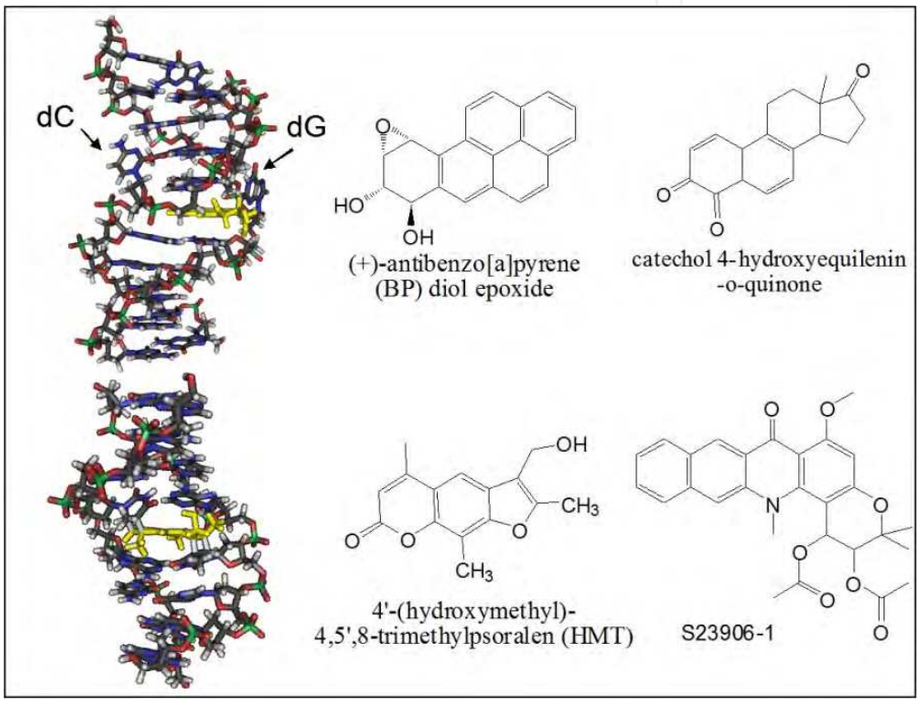

Fig. 4. 3D orientation of (+)-*anti*-BPDE [mmdbId:52106] and the psoralen derivative HMT [mmdbId:52343] and structure of some DNA alkylators that destabilize the DNA helix.

The hormone-derived genotoxic compound, 4-OHEN, derives from equilin and equilenin, two equine oestrogens present in hormone substitution therapies used to prevent the uncomfortable effects of menopauses but are also thought to increase breast cancer incidence in the population of hormonally-treated women (Rossouw et al., 2002). Its ortho-quinone form is cytotoxic and genotoxic (Pisha et al., 2001) through the formation of bulky DNA lesions at dA, dC and dG (but not at T residues) (Kolbanovskiy et al., 2005) which were detected in both cell culture and breast cancer biopsies from patients treated with hormone substitution therapies (Embrechts et al., 2003). 4-OHEN derived from the intermediate catechol 4-hydroxyequilenin which was generated from a rapid conversion of both equilin and equilenin in the organism to four stereo-isomers differently affecting the 3D-structure of the DNA helix (Ding et al., 2007). For adducts on cytosine, the *syn*- or *anti*-conformations of the bulky rings of 4-OHEN point along the major or the minor groove (Ding et al., 2005). Interestingly, alkylation at dA or dC residues is associated with a strong

decrease in the melting temperature (Tm) of a 11-bp oligonucleotide, with the magnitude of the negative ΔTm values being lower when the adduct is located at 1 or 2-bp from the end of the 11-bp DNA (-6 to -9°C) then when it is located in its medium part (positions 4 to 8) with up to a -21 to -27°C decrease of Tm. Similarly, the stereoisomeric orientation of the 4-OHEN adduct affects the base-stacking, groove sizes and subsequent distortions and is also crucial for the extent of DNA destabilization (Kolbanovskiy et al., 2005).

2.2.3 Psoralen derivatives

Psoralen is a chemotherapeutic agent known to cause DNA inter-strand crosslinks (ICLs) upon absorption of two photons from UVA irradiation at 365 nm, preferentially at 5′-TA and to a lesser extend at 5′-AT dinucleotides. This activity was the basis for use of psoralen and UVA exposure (PUVA therapy) to treat cutaneous diseases like psoriasis, vitiligo, atopic dermatitis or cutaneous T cell lymphomas. However, such treatment increased the risk of squamous and basal cell carcinomas (Teicher, 1996). Psoralen-induced ICLs are classically used models for DNA repair of ICLs. The psoralen derivative 4'-(hydroxymethyl)-4,5',8-trimethylpsoralen (HMT) (Figure 4) evidenced DNA destabilization by mono-addition of a psoralen residue to both thymines (one on each strand) of 5′-GGGTACCC sequence.

2.2.4 Benzo-acronycine derivatives

Acronycine is a natural alkaloid extracted from the bark of an Australian ash scrub that presented interesting antitumor activities but was poorly soluble and, consequently, too toxic in first clinical trials. The discovery of an unstable acronycine epoxide opened the way to the rational drug design of S23906-1 (Figure 4), that appeared to be a highly active compound (Guilbaud et al., 2001) with an original mode of action (David-Cordonnier 2002; 2005; Depauw et al., 2009) and consequently entered phase I clinical trials in 2006. As for the clinically used drug Ecteinascidine 743 (ET-743, Trabectedin, Yondelis ™ from Pharmamar), S23906-1 alkylates the exocyclic NH_2 group of guanines in the minor groove. But, in contrast with ET-743, S23906-1 does not reinforce the stability of the ds-DNA helix but destabilizes it, generating portions of ss-DNA (David-Cordonnier et al., 2005; Depauw et al., 2009). Various spectral and biochemical approaches convinced with this conclusion. Indeed, classical DNA melting temperature studies evidenced a strong decrease of the Tm values upon alkylation with S23906-1 or other biologically active benzo-acronycine derivatives. Similarly, spectral analysis of the ratio of fluorescence properties of picogreen (a ds- and ss-DNA interacting dye) and BET (a ds-DNA specific dye) evidenced an increase of picogreen *vs*. BET fluorescence which enlightens the generation of single-stranded portions of the DNA upon S23906-1 alkylation. Biochemical approaches like digestion of the alkylated DNA by single-strand specific nuclease S1 and electrophoretic mobility shift assays (EMSAs) confirmed the opening of the DNA. The destabilization was relatively wide since mapping with nuclease S1 evidenced locally opened DNA portions within a 117 bp DNA fragment alkylated by S23906-1 whereas EMSAs, performed with oligonucleotides as long as 24 bp, evidenced fully single-stranded alkylated oligonucleotides in the presence of S23906-1 or derivatives (David-Cordonnier et al., 2005; Depauw et al., 2009).

3. Repair processes for DNA destabilizing lesions

DNA adducts are critical lesions for cell proliferation and survival. Single or multiple DNA repair machineries could be implicated in the removal of these damages, as for example

BER, GG-NER (global genome) or TC-NER (transcription-coupled), MMR, HR or NHEJ. Only few data are published about the consequences of non-covalent DNA destabilizing agents on protein/DNA binding from the repair machineries. These data on BisA function reported that insertion of BisA could flip the mispaired thymine to an extrahelical base subsequently inducing a sterical blockage of DNA glycosylases binding (David, 2003). The present section will therefore focus on alkylating compounds. As examples, we will shortly present the repair processes for the well-studied temolozomide-induced lesions in the major groove and for the DNA stabilizing drug ET-743, as an original minor groove alkylating agents that "poison" the NER machinery to exert its anti-tumor properties, before presenting the current knowledge on DNA repair of DNA destabilizing lesions.

3.1 Repair of temolozomide-induced DNA lesions

Temolozomide (TMZ, Temodar®, Figure 5) is a monofunctional alkylating agent chemically related to dacarbazine. It is active in vitro and in vivo against a wide variety of tumor type and particularly efficient in malignant glioma (Newlands et al., 1997). Contrasting with dacarbazine, TMZ does not require to be activated by enzymatic oxidation, but spontaneously hydrolyses to 5-(3-methyltriazen-l-yl)-imidazole-4-carboximide (MITC) at pH above 7. MITC is then broken down to (*i*) the reactive methyldiazonium cation which next loses the methyl group in the presence of DNA or proteins and (*ii*) the inactive 5-aminoimidazole-4-carboxyamide moiety (AIC) (**1**). TMZ treatment leads to different adducts on the double helix DNA: N^3-methyladenine, N^7-methylguanine and O^6-methylguanine

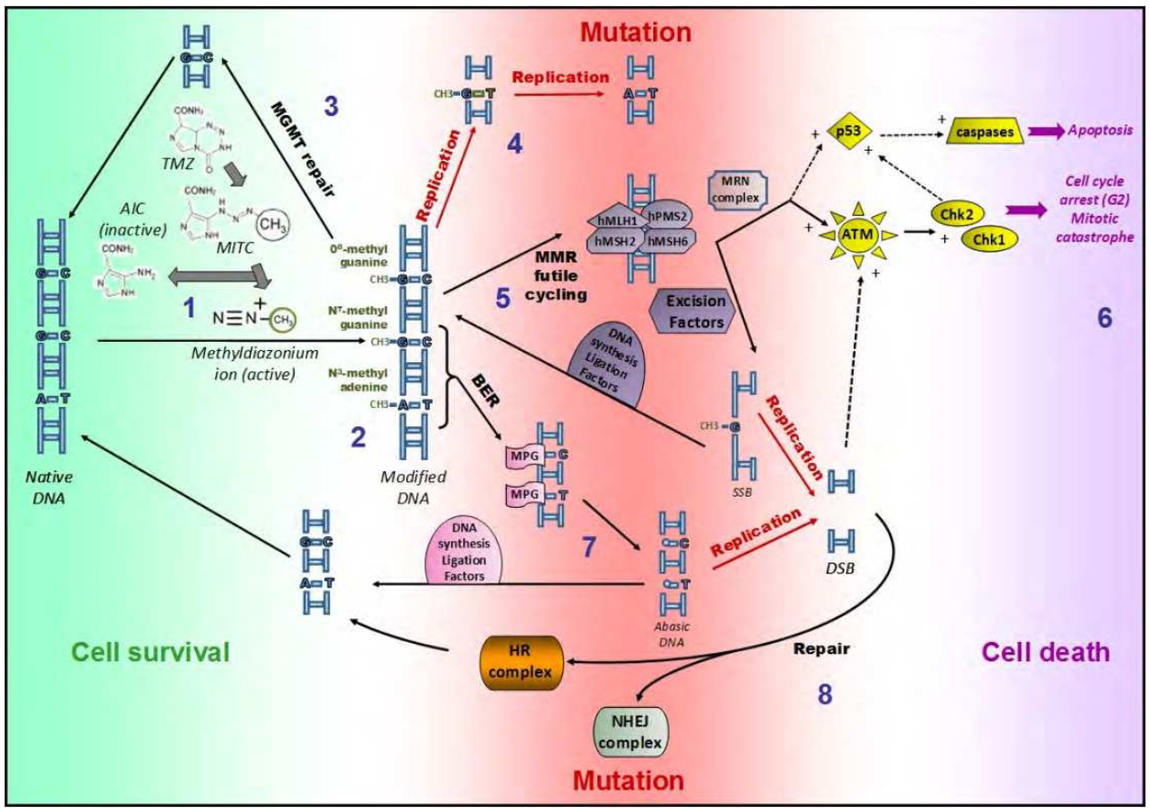

Fig. 5. DNA repair pathways for TMZ-induced damage.

(Newlands et al., 1997) and cell sensitivity to TMZ treatment depends on multiple DNA repair mechanisms (**2**). The major one is the recognition of methyl lesions from O^6 position of guanines by the O^6-methylguanine DNA methyltransferase (MGMT) protein which directly converts the methylated DNA to its normal, undamaged state (**3**). MGMT enzymatic activity is crucial for TMZ resistance in vivo suggesting that MGMT expression may predict the response of patients to TMZ treatment (Everhard et al., 2006; McCormack et al., 2009). However, other repair mechanisms are also implicated since some cell lines with low MGMT expression still evidence significant resistance to TMZ (Fukushima et al., 2009).
When O^6-methyguanine is not repaired by MGMT, it may lead to an O^6-methylguanine:thymine mismatch during DNA replication. The following DNA replication cycle can then pair thymine with adenine in place of the original guanine, thus leading to transition mutations (**4**). However, the cytotoxic property of TMZ is mostly linked to MMR pathway through O^6-methylguanine:thymine mismatch recognition and repair by this system **(5**). MMR is not involved in TMZ chemo-resistance but in TMZ cytotoxicity, associated with cell cycle blockade at G2 checkpoint (Caporali et al., 2004), activation of p53 and ATM, leading to cell death (**6**). The MRN (Mre11/Rad50/Nbs1) complex was evidenced as the earliest sensor of TMZ-induced damage (Mirzoeva et al., 2006). It undergoes a series of conformational changes that activates the protein sensor ATM (ataxia telangiectasia mutated) which, subsequently, activates Chk1 and Chk2 to block cell cycle. TMZ induces p53-mediated apoptosis in MMR-proficient but not in MMR-deficient cells (D'Atri et al., 1998). Thus, deficient MMR is another mechanism for resistance to TMZ (Cahill et al., 2007).
Besides MGMT and MMR, BER is also implicated in TMZ lesion repair. More than 80% of N^7-methylated purines are recognized and excised by the BER enzyme N-methylpurine DNA glycosylase (MPG) (Trivedi et al., 2008; J. Zhang et al., 2010) (**7**). As a consequence, disruption of BER system sensitizes MMR-deficient and proficient cells (Liu et al., 1999). The major MPG-dependent repair occurs via short-patch BER, a mechanism whereby only the damaged nucleotide is excised. So, BER pathway is another contributor of cell resistance to TMZ and its efficacy depends on specific BER gene expression and activity (Fishel et al., 2008). DNApol β or MPG-deficient cells are more sensitive than wild-type cells to TMZ-induced cell death, whereas MPG over-expression increases TMZ-induced cytotoxicity (Tang et al., 2011; Trivedi et al., 2008). Similarly, inhibition of poly(ADP-ribose) polymerase-1 partially restored sensitivity to TMZ (J. Zhang et al., 2010).
Both methylated DNA lesions can lead to SSBs in a DNA repair-dependent manner (BER, MMR). If unrepaired before replication, SSBs convert in DSBs, a more mutagenic and lethal lesion (Newlands et al., 1997). However, DSBs could be processed by the conservative HR pathway to give back undamaged double stand DNA or by NHEJ repair machinery potentially resulting in chromosomal rearrangements between chromatide or deleterious genomic rearrangements as other toxic lesions (**8**). Other inter-crossings between repair pathways are not presented in this scheme: a role of some MMR proteins in the NHEJ pathway to repair DSB during G1 phase of the cell cycle or in HR pathway through the regulation of the early G2 checkpoint and inhibition of DSB repair (Y. Zhang et al., 2009) as well as the implication of Fanconi anemia FANC-D1 (Kondo et al., 2011).

3.2 DNA repair process and implication in ET-743 expressing cytotoxicity

ET-743 is a tetrahydroisoquinoline alkaloid isolated from the tunicate *Ecteinascidia turbinata* which is approved as an orphan drug against advanced soft tissue sarcoma and, in

association with doxorubicine, in refractory cisplatin-sensitive ovarian cancers. This DNA minor groove binder (Pommier et al., 1996) bends DNA toward the major groove (Hurley & Zewail-Foote, 2001). ET-743 (Figure 6) is composed of three subunits: A and B are involved in DNA binding at specific sites (David-Cordonnier et al. 2005; García-Nieto et al., 2000; Pommier et al., 1996) and C protrudes out of the double helix thus facilitating the interaction of ET-743 with nuclear proteins such as transcription factors or DNA repair proteins (**1**). The formation of such protein/ET-743-DNA complex prevents the transcription of different genes (Friedman et al., 2002; Jin et al., 2000) and induces a rapid degradation of transcribing RNA polymerase II in TC-NER proficient, but not deficient, cells (Aune et al., 2008).

By contrast with other DNA damaging agents, NER-deficient cell lines are resistant to ET-743, and restoration of NER functions sensitizes cells to the drug. Indeed, the TC-NER complex is trapped during the repair process of ET-743-DNA damage (Damia et al., 2001; Takebayashi et al., 2001) through the formation of a stable XPG/DNA 'cytotoxic complex' (Herrero et al., 2006)(**2**). In a replication-independent manner, the MRN complex is recruited (**3**) and induces DSBs subsequently recognized by DNA-PK from the HR machinery. DNA-PK then phosphorylates H2AX and activates ATM (Damia et al., 2001) and Chk1 to bypass G2/M and S phases checkpoints and promote cell death (Herrero et al., 2006).

Protein recognition of ET-743-DNA adducts also induces the formation of DSBs through replication fork collapse (Soares et al., 2007; Takebayashi et al., 2001)(**4**), as well known for topoisomerase/drug/DNA poisoning complexes. Such DSBs are repaired by HR (acting mainly in G2-M phases) but not by NHEJ (Soares et al., 2007; Tavecchio et al., 2008)(**5**).

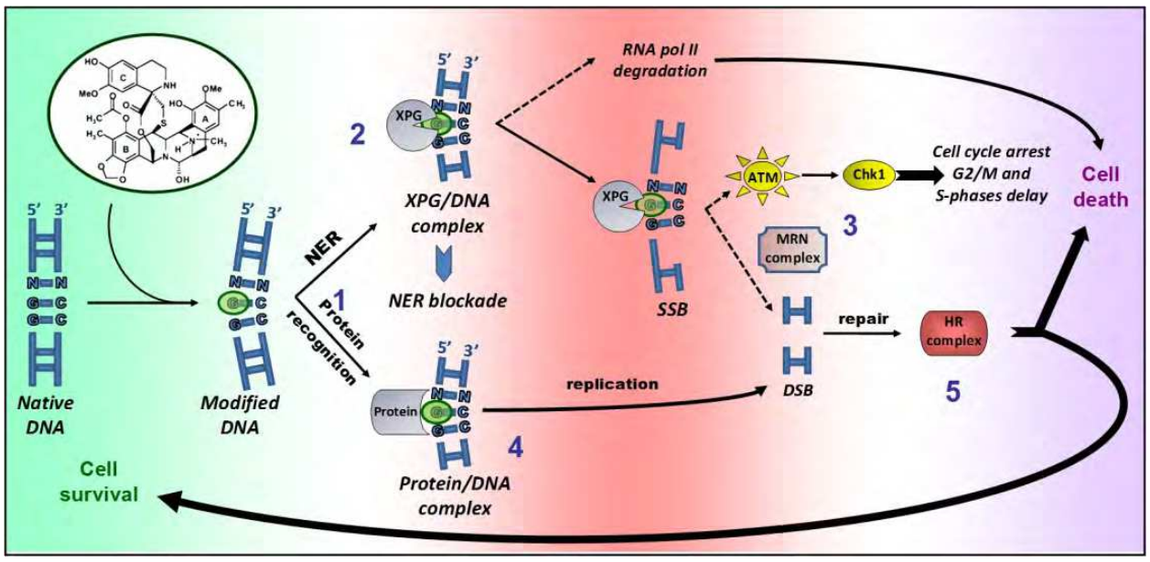

Fig. 6. DNA repair pathways for ET-743-induced DNA damage.

3.3 DNA repair for cisplatin and other transition-metal antitumor agents

Regarding DNA repair, local destabilization of the double helix, base-flipping, DNA bending and poor base-stacking following cisplatin alkylation are determinant for recognition of DNA lesions by repair proteins (C.G. Yang et al., 2009; W. Yang, 2006). Several repair machineries are implicated in metal-drug-induced DNA adduct recognition, removal and cytotoxicity (Basu & Krishnamurthy, 2010; S. Ahmad, 2010). First, NER is an important actor for the

removal of both 5′-GG, 5′-AG and 5′-GNG cisplatin intra-strand crosslinks, with a preference for the latter site. The induced-kink, being greater for 5′-GNG than 5′-GG or 5′-AG alkylated sites, seems to be of major relevance for NER recognition (**1**, in Figure 7). Particularly, platinum adducts are recognized by the global genome-NER XPC/hHR23B "sensor complex" (Neher et al., 2010) and XPC expression or polymorphism predicts the response to cisplatin treatment in lung cancers (Lai et al., 2011; L.B. Zhu et al., 2010). Lesions induced by cisplatin, oxaliplatin and JM216 are similarly repaired whereas transplatin-induced lesions, which poorly affect 3D structure of DNA, are poorly repaired by NER.

MMR is also important to remove platinated lesions (**2**). Facilitated by cisplatin-induced kink, MSH2 binding is associated with a 60° angle generated through intercalation of its Phe39 at the lesion site. MSH2/MSH6 complex (Mut-Sα) recognizes cisplatin crosslinks (Castellano-Castillo et al., 2008; Fourrier et al., 2003) but not transplatin mono-adducts from $[Pt(dien)Cl]^+$. Translesion bypass is also implicated in cisplatin toxicity. Interestingly, oxaliplatin lesions are more bypassed by DNA polymerases than cisplatin, in relation with their difference in DNA bending/destabilization potencies. Mutants FANC-C and –D of Fanconi anemia pathway also sensitize cells to Pt-drug (Kachnic et al., 2010).

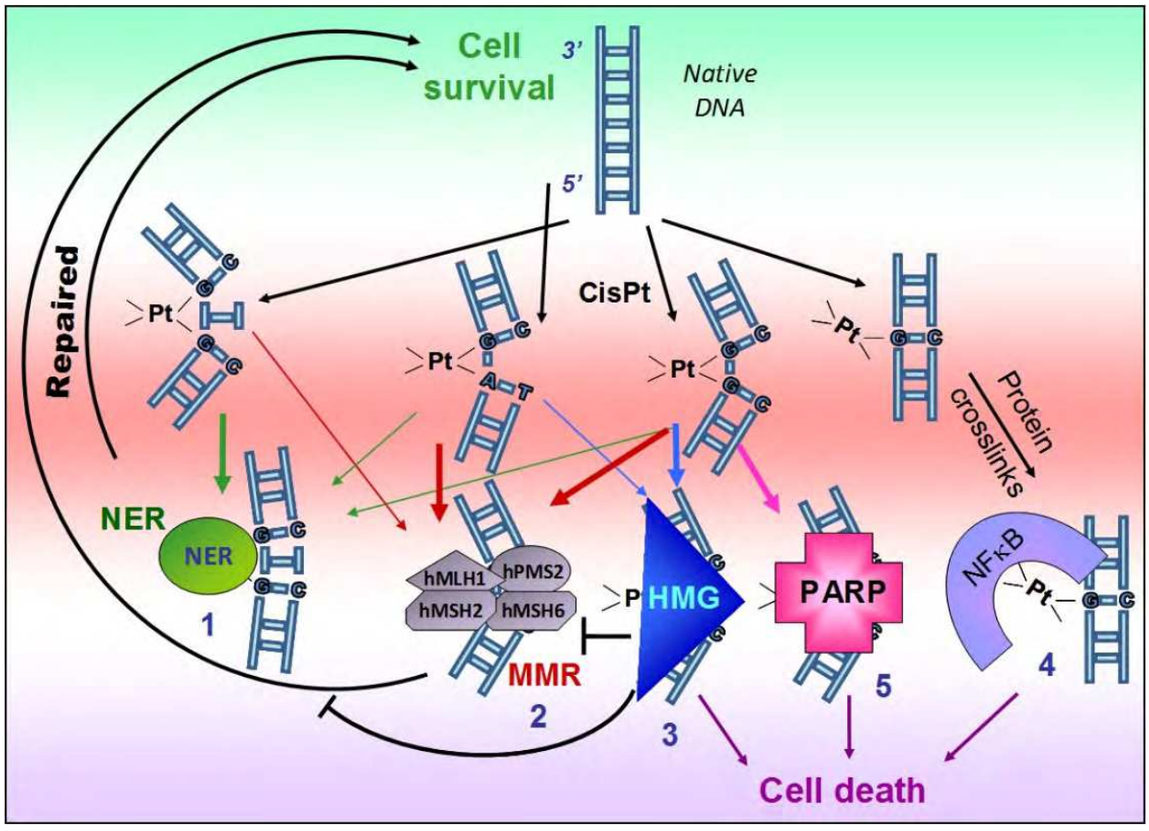

Fig. 7. DNA repair pathways for platinated DNA.

Of major concern, cisplatin adducts are also recognized by HMG proteins (**3**). Similarly to MutS complex recognition, the large induced bend is crucial for this recognition and fits perfectly with the L-shaped structure of HMG DNA binding domain (HMG-box) to reduce the "cost" of DNA bending for HMG-box (Privalov et al., 2009). Insertion of Phe37 between

the two platinated guanines in 5'GG dinucleotide stabilizes the binding but is regulated in a redox manner. Indeed, the formation of a disulfure bond between the thiol groups of Cys22 and Cys44 on helix II and III, respectively, of HMG-box infers with the correct planar insertion of Phe37 between the two guanines at crosslink site (Park & Lippard, 2011). Binding of HMG-B1 (and HMG-B2) stabilizes the cisplatin-induced bent and supercoiling of the DNA helix, increases the sensitivity of the cells to cisplatin and shields the platinated adducts from repair by the human DNA excision machinery (J.C. Huang et al., 1994). As a consequence of the degree of kink of the DNA, HMG proteins poorly bind to oxaliplatin adducts which induce relatively small DNA-bending and DNA destabilization (Figure 3), and so poorly protects them from DNA repair (Kasparkova et al., 2008b). This difference correlates with the lower level of DNA lesions in oxaliplatin- versus cisplatin-treated cells. If HMG-B1 and –B2 binding participates in platinated-agent-induced cytotoxicity (Sharma et al., 2009), bent platinated-DNA is also a good substrate for transcription factors from HMG-box family such as SRY, LEF-1 and UBF-1, resulting in the transcriptional changes observed in treated cells (Chvalova et al., 2008; Treiber et al., 1994; Trimmer et al., 1998). For the repair of other platinum derivative-induced DNA damages, JM108 evidenced higher level of protein/DNA cross-links such as DNA-Pt_{II}-NF-κB cross-linked complexes (**4**). Those lesions are less efficiently removed from DNA by the cell repair system (Kostrhunova et al., 2010). Other studies described the binding of PARP-1 protein to cisplatin adduct at 5'-GG and 5'-GNG intra-strand crosslinks on duplex DNA with a preference for 5'-GG platinated site to protect it from DNA repair and thus to increase cytotoxicity (G.Y. Zhu et al., 2010), particularly in MSH3-deficient cells (Takahashi et al., 2011) (**5**). Such side effect of PARP-1 orientates current phase I/II clinical trials using PARP inhibitors (CEP-6800, AZD2281 or ABT-888) as sensitizing agents in combination with cisplatin and carboplatin. A recent paper suggests that PARP is a pharmacological target of platinum- and other metal-based drugs showing PARP inhibition using Pt- (cisplatin), Ru- (RAPTA-T, NAMI-A) or Au- (Auphen, Aubipy) derived drugs (Mendes et al., 2011).

In a general manner, NER process of DNA lesions induced by ruthenium-drug appears to be less efficient than for platinum adducts. Ru-CYM and Ru-THA destabilize the DNA helix via different enthalpic effects and differ in terms of their DNA base-pair intercalation propensities. Comparison of their DNA repair processes has been used as a model for understanding the link between DNA destabilization and repair. Interestingly, Ru-CYM adducts (that destabilize the DNA helix much more than Ru-THA adducts) are excised more efficiently than Ru-THA complex adducts. Such observation is in good agreement with lower binding of RPA helicase to Ru-THA- than to Ru-CYM- adducts (Nováková et al., 2005). Ru-THA is also more cytotoxic than Ru-CYM, suggesting that DNA destabilization plays a major role in the cytotoxicity of these series of compounds.

3.4 DNA repair for the carcinogen BaP (BPDE) and 4-OHEN adducts

In prokaryote, the NER sensor protein UvrB recognizes BPDE/DNA adduct (**1** in Figure 8). Lesion-induced local thermodynamic destabilization and associated nucleotide flipping facilitate this recognition (Jia et al., 2009) with excision efficiencies changing up to a factor of 3 with stereoisomery (i.e. (+) *vs*. (-), *cis*- *vs*. *trans*-orientation)(Zou & Van Houten, 1999).

By contrast, the BaP-induced lesions are recognized in eukaryotic higher cells by the NER machinery's "sensor" protein XPC, associated with HR23B to initiate DNA repair (**2**). Weaker recognition by XPC/HR23B complex of the (+)-*trans*-B[*a*]P-N^2-dG adduct, relatively

to that of the other conformers, contributes to its higher mutagenic potential (Mocquet et al., 2007). Lesion recognition by XPC requires DNA bending facilitated by local conformational flexibility (Clement et al., 2010) and destabilization of the base-pairing (Brown et al., 2010). Such recognition is driven by Trp690 and Thp733 amino-acids identified as "aromatic sensors" (Maillard et al., 2007). Upon treatment with BaP, human bronchial epithelial 16HBE cells expressed higher levels of the heat shock protein 70 and the NER proteins XPA and XPG, both three proteins co-localizing in the nucleus, suggesting that Hsp70 is also implicated in the DNA repair response to BPDE-DNA adducts (J. Yang et al., 2009). The highly mutagenic (+)-(7R,8S,9S,10R)-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-benzo[*a*]pyrene-DNA lesion leads to different repair processes depending on sequence context, associated with the destabilization potency. Indeed, for an identical BaP-DNA lesion leading to differently orientated bulky lesions, sequence-dependent effect was observed: DNA destabilized at 5′-CG*GC site is more rapidly excised in cell-free human HeLa extracts than DNA bent at 5′-CGG*C site (Rodríguez et al., 2007). As the DNA helix is readily opened upon alkylation, recognition of the lesion by repair protein (including induction of base flipping) is less energetic and, thus, is quicker for DNA already destabilized at 5′-CG*GC site than for duplex DNA bent at 5′-CGG*C site, clearly evidencing the importance of DNA sequence/global structure context for an efficient repair of BPDE-DNA adducts (Yuqin et al., 2009). Moreover, interesting data arise from comparison of the 3D conformation and the NER excision efficiencies for dA adducts formed using the bay region BPDE and the fjord region benzo[*c*]phenanthrene diol epoxide (B[*c*]PhDE) (M. Wu et al., 2002). The bay region of B[*a*]P is more extended, planar and rigid than the B[c]Ph fjord region, being twisted and curved. Consequently, B[*a*]P-dA adducts are associated with greater backbone distortion, unwinding, intercalation potency and

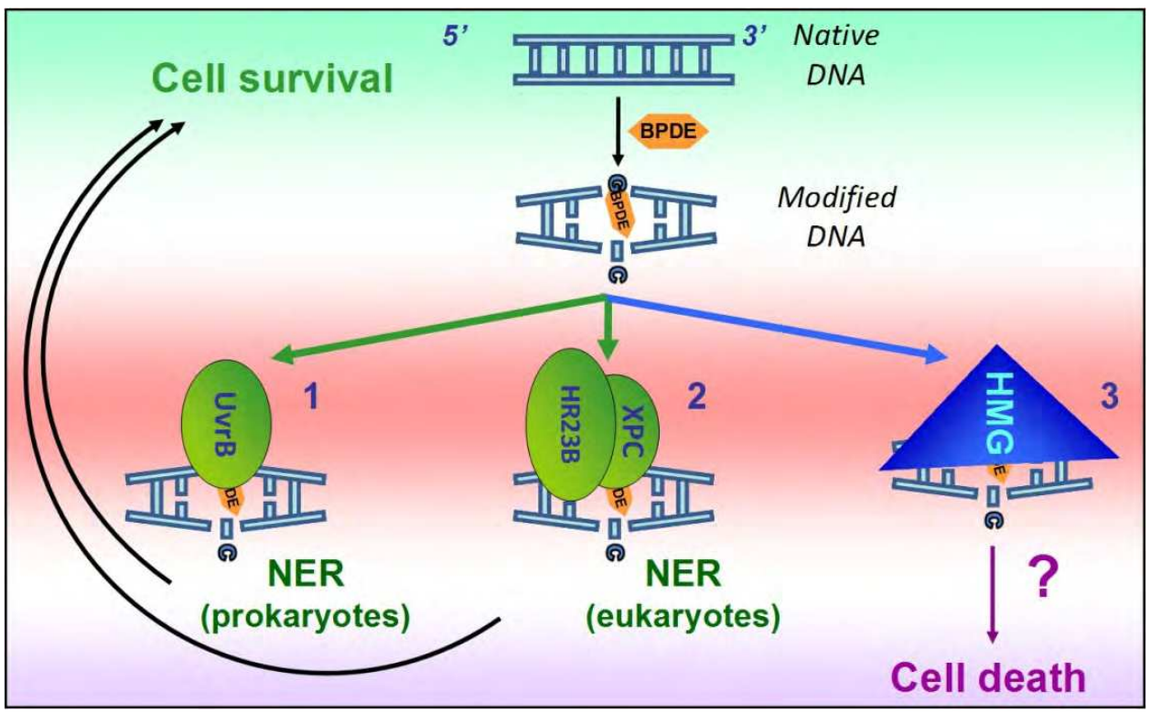

Fig. 8. DNA repair pathways for BPDE-induced DNA damage.

disturbed Watson-Crick hydrogen bonding than B[*c*]Ph-dA adducts, in correlation with stronger excision efficiency by NER machinery. The fjord region B[*c*]Ph-dA adducts being poorly excised lead to more tumorigenic activities. HMG-1 and -2 proteins are also implicated in bulky BPDE-adducts recognition (Lanuszewska & Widlak, 2000) but the consequences on repair or cell death are unknown (**3**). HMG binding might protects adduct recognition by repair proteins as for platinated DNA, but this needs further evaluation.
Excision of bulky 4-OHEN-DNA adducts by NER proteins also depends on both the nature of the alkylated base, its stereo-isomery and the sequence context. For instance, 4-OHEN-dC adducts are more efficiently excised from the DNA than the 4-OHEN-dA adducts (D. Chen et al., 2006). It was reported in male zebrafish that 17a-ethinylestradiol, as a source of 4-OHEN, induces a decrease in NER activity as part of a decrease of the expression level of some NER genes such as XPC, XPA, XPD and XPF, but not of HR23B (Notch et al., 2007).

3.5 DNA repair for psoralen-DNA adducts

DNA alkylation by psoralen can lead to inter-strand crosslinks (ICL) or mono-adducts (MA). Psoralen-ICLs (Figure 9) are eliminated during the replication process, associated with HR (**1**), MMR (**2**) and error-prone translesion DNA polymerases (Dronkert & Kanaar, 2001). NER proteins such as XPC/hHR23B complex and XPA/RPA complexes are also implicated in the repair of psoralen-ICL (Thoma et al., 2005) and could cooperate with MMR to excise the lesions (Zhao et al., 2009). By contrast, thymine-psoralen mono-adducts (**3**) are moderately excised from the DNA by the NER system (Vasquez et al., 2002), because of adduct recognition by HMG-B1 which recruits RPA helicase (**4**) (Lange et al., 2009) or by MMR

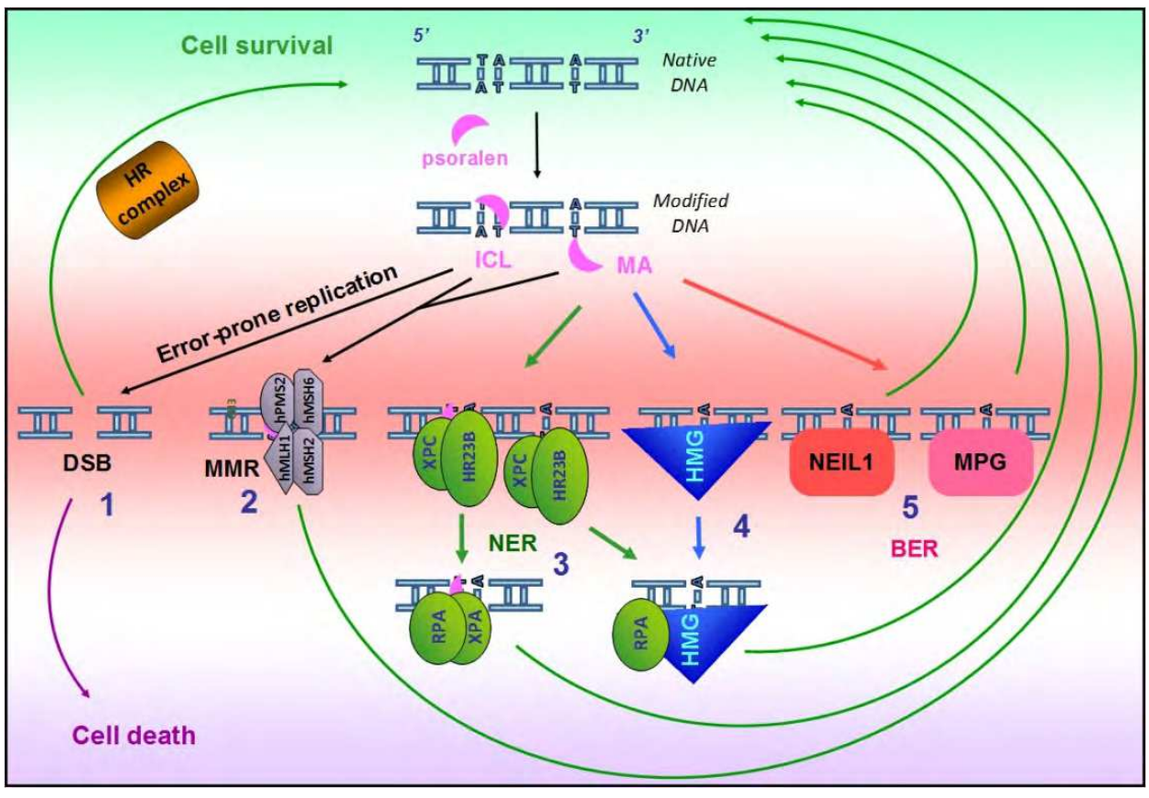

Fig. 9. DNA repair pathways for psoralen-induced DNA damage.

(Q. Wu et al., 2005; 2008). Psoralen monoadducts are good substrates for 3-Methyladenine DNA glycosylase (MPG) (Maor-Shoshani et al., 2008) and the human oxidative DNA glycosylase, NEIL1, which catalyses the β,δ-elimination at AP site, leaving a 3'-P termini at the resulting SSB (**5**) (Couvé-Privat et al., 2007). Fanconi anemia pathway was also implicated in the repair process, in link with NEIL1 stability and NER efficiency (Macé-Aimé et al., 2010).

3.6 DNA repair for benzoacronycine-DNA adducts

S23906-1 alkylates the DNA in the minor groove and induces a strong destabilization of the DNA helix. Two reactive acetate groups are positioned on asymmetric carbons leading to four pure enantiomers: 2 *cis* (1R;2R and 1S;2S) (the *cis*-racemate being S23906-1) and two *trans* (1R;2S and 1S;2R) isomers. Both pure enantiomers react with DNA and destabilize the DNA helix but at different extends. The most potent DNA destabilizing ones (1S;2S and 1S;2R) being those presenting the most active anti-tumour activities in animal models (Depauw et al., 2009). Therefore, the rate of DNA destabilization is different depending on the orientation of the core of the adducts regarding the opened drug/DNA structure, and correlates with different cellular and anti-tumour effects. Such strong destabilisation could affect single-stranded endonuclease and DNA repair activities. There is currently only partial knowledge on the repair of S23906-1 DNA adducts. The NER proteins XPC and CSB are involved in cell sensitivity to S23906-1, associated with both global genome repair and transcription-coupled NER (Rocca et al., 2010). ATR coordination, RPA recognition and Chk1 activation were also implicated in responses to S23906-1 DNA damages (Soares et al., 2011). Process of the lesions is associated with DSB as secondary DNA lesions important for cytotoxicity of S23906-1, associated with histone H2AX phosphorylation (Léonce et al., 2006). Of major interest, the most potent destabilizing isomer of S23906-1 was evidenced to be also the most cytotoxic on cellular models and the most efficient on xenografted animal models (Depauw et al., 2009). Current ongoing research is identifying proteins implicated in S23906-1/DNA adduct recognition and evaluating their impact on S23906-1 cytotoxic activity (personal communication). Locally destabilized DNA could favour the recognition of DNA lesion by "DNA repair sensors" thus increasing the efficiency/kinetic of the removal of the DNA lesion.

4. Conclusion

Destabilization of the DNA helix that is induced by drugs is an important aspect of the antitumor mechanism of action of this series of compounds besides they represent just few droplets in an ocean of DNA-interacting compounds that mainly stabilize the double helix. As evidenced here, stabilizing *vs.* destabilizing compounds differs in terms of molecular and cellular processes: DNA repair, transcription or replication. From the different series (platinum, ruthenium, BPDE, benzoacronycines), the level of DNA destabilization correlates with the efficiency of protein recognition and anti-tumor/cytotoxic activities. Therefore, we believe that it is important not to consider DNA destabilization as a unique process but in relation with potential associated bending of the DNA helix (as evidenced using oxaliplatin- and cisplatin-induced distortions or the different isomers of BPDE) and with the size of the locally destabilized DNA (for instance, portions of DNA opened by benzoacronycines are strongly sensitive to single-strand-specific nucleases). The most recent and ongoing studies

on the importance of DNA destabilization on DNA repair processes and induced-cytotoxic activities illustrate the need for an accurate examination of precise mode of binding /bonding to DNA of potential anti-cancer drugs in terms of 3D structure/activity relationships and to clearly evaluate the cellular consequences (cytotoxicity, DNA repair processes).

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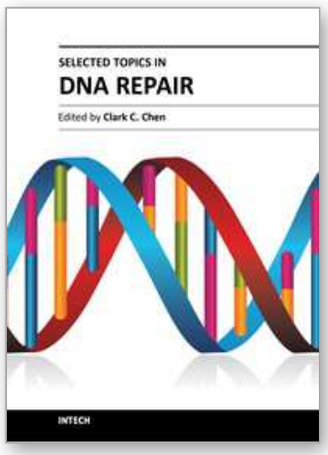

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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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