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Targeting BER enzymes in cancer therapy

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Abstract

Base excision repair (BER) repairs mutagenic or genotoxic DNA base lesions, thought to be important for both the etiology and treatment of cancer. Cancer phenotypic stress induces oxidative lesions, and deamination products are responsible for one of the most prevalent mutational signatures in cancer. Chemotherapeutic agents induce genotoxic DNA base damage that are substrates for BER, while synthetic lethal approaches targeting BER-related factors are making their way into the clinic. Thus, there are three strategies by which BER is envisioned to be relevant in cancer chemotherapy: (i) to maintain cellular growth in the presence of endogenous DNA damage in stressed cancer cells, (ii) to maintain viability after exogenous DNA damage is introduced by therapeutic intervention, or (iii) to confer synthetic lethality in cancer cells that have lost one or more additional DNA repair pathways. Here, we discuss the potential treatment strategies, and briefly summarize the progress that has been made in developing inhibitors to core BER-proteins and related factors.

Keywords
Cancer, base excision repair, chemical biology, cancer therapy, DNA repair, synthetic lethality.

Abbreviations

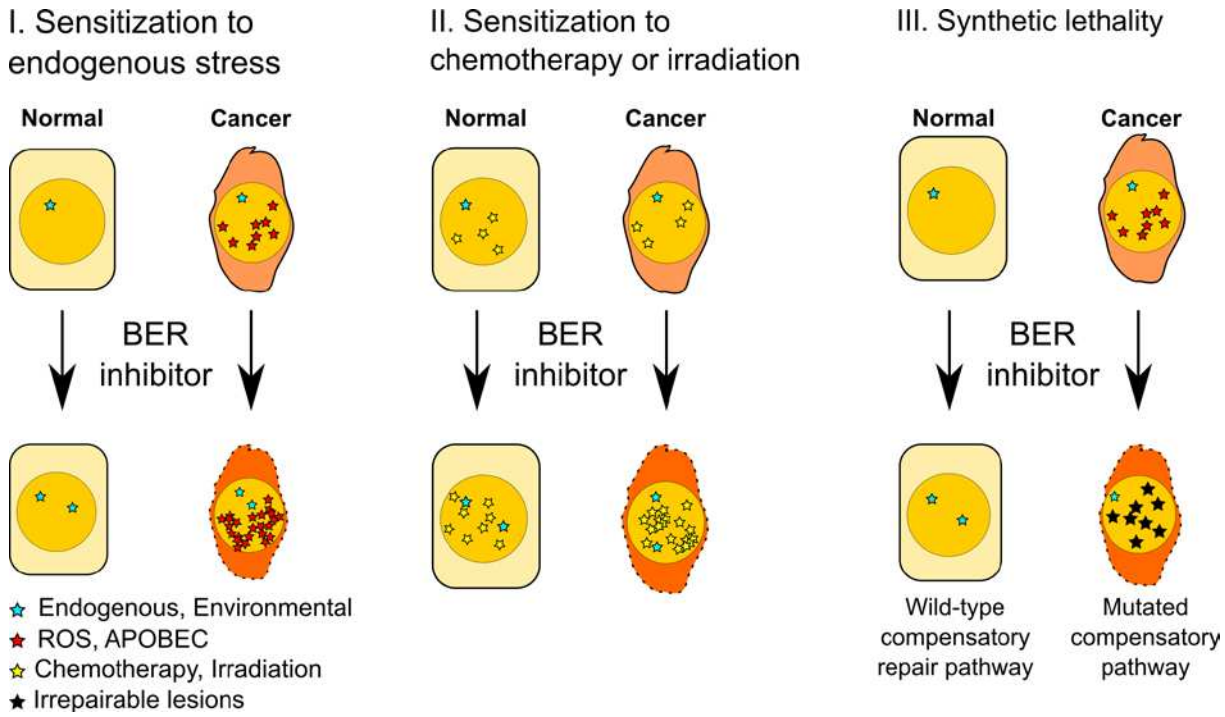
5-FU, 5-fluorouracil; 5-FdU, 5-Fluoro-2'-deoxyuridine; 8-oxoG, 8-oxoguanine; 8-oxodG, 7,8-dihydro-8-oxo-2´-deoxyguanosine; ADME, absorption, distribution, metabolism, and excretion; APE1, apurinic/apyrimidinic endodeoxyribonuclease 1; BCNU, 1,3-bis(2-chloroethyl)-l-nitrosourea (BCNU); BER, Base excision repair; BRCA1/2, BRCA1/2 DNA repair associated; FaPyG, 2,6-diamino-4-hydroxy-5-formamidopyrimidine; FEN1, flap structure-specific endonuclease 1; Gh, 5-guanidinohydantoin; LIG, DNA ligase; MBD4, methyl-CpG binding domain 4, DNA glycosylase; MEF, mouse embryonic fibroblast; MMC, mitomycin C; MPG, N-methylpurine DNA glycosylase; MTH1, MutT homolog 1; MUTYH, mutY DNA glycosylase; NEIL, nei-like DNA glycosylase; NTHL1, nth like DNA glycosylase 1; OGG1, 8-oxoguanine-DNA glycosylase 1; PARP1, poly(ADP-ribosyl) polymerase 1; POL, DNA polymerase; ROS, reactive oxygen species; SMUG1, single-strand selective monofunctional uracil-DNA glycosylase 1; Sp, spiroiminodihydantoin; TDG, thymine-DNA glycosylase; TMZ, temozolomide; UNG, uracil-DNA glycosylase; XRCC1**,** X-ray repair cross complementing 1.

1. Introduction

Damage to nucleobases and backbone of DNA is one of the root causes of mutations, which enables tumors to acquire the hallmarks of cancer [1]. The quantitatively dominant repair pathway for these kinds of lesions is the base excision repair pathway (BER) [2–5]. Aggressive cancer cells contain higher levels of lesions such as uracil [6] or 8-oxoguanine (8-oxoG) [5,7], and may therefore be expected to specifically rely on efficient repair pathways to maintain viability. Moreover, many (if not most) classical chemotherapeutic treatments exert their anti-cancer effect through damage to DNA [8,9]. Irradiation [10–15], fluoropyrimidines [16–18], antifolates [19–21], platinum drugs [22–28], demethylating agents [29], anthracyclines and monofunctional alkylating agents such as temozolomide [30–32] have been shown to directly or indirectly cause the DNA damage that is typically repaired by BER. Despite progress in immuno- and targeted therapies, these classical cancer treatment agents are likely to also be extensively used in the future. Therefore, the cellular pathways that protect against these lesions are promising targets for cancer adjuvant therapy.

2. Base excision repair

To cope with the large number of small base lesions that arise in the genome, human cells are equipped with DNA repair mechanisms which recognize and repair aberrant DNA structures. BER is the main pathway for the repair of small base lesions and is arguably the quantitatively most important DNA repair pathway in mammalian cells [8]. Given the importance of DNA damage in the evolution of cancer cells and the induction of BER substrates by cancer chemotherapy agents, there is a tremendous potential for targeting BER pharmaceutically. To this end at least three different treatment strategies may be envisioned (Figure 1).

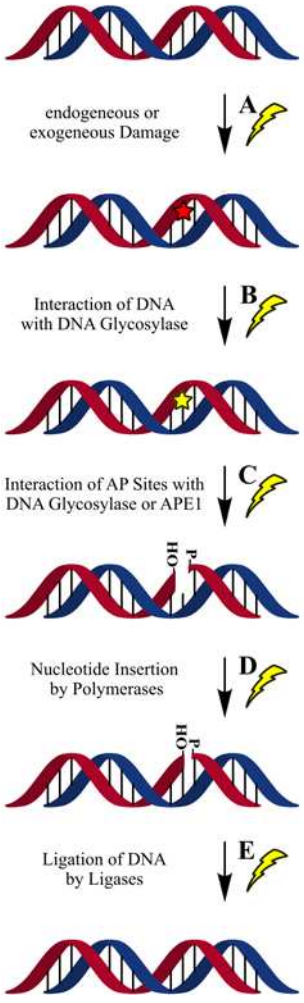


[FIGURE1 is a 2-column figure]

Figure 1: Three therapeutic strategies for BER inhibitors. I. Sensitization to endogenous cancer-specific stress. Cancer cells harbor high levels of genomic instability in the form of ROS or APOBEC-induced lesions. By targeting the dominant repair pathway with BER inhibitors, it should be possible to increase the DNA damage level beyond what a replicating cell can handle. Normal cells do not have cancer-specific genomic instability and may cope with somewhat higher levels of damage of endogenous or environmental origin. **II.** Sensitization to chemotherapy or irradiation. BER inhibitors may potentiate the effect of chemotherapy or irradiation in both normal and cancer cells. Selectivity of current chemo- and radiotherapy regimens arises from targeting the high proliferation rate of cancer cells, but may also increase the DNA damage levels in normal cells causing dose-

limiting toxicity. **III.** Synthetic lethality. Using BER inhibitors in cells deficient in compensatory repair pathways. leads to irreparable DNA damage and cell death. Normal cells are spared because they have lower levels of BER substrates in the first place and are proficient in the compensatory repair pathway.

Briefly, BER is initiated by one of eleven known human DNA glycosylases that recognize and excise the aberrant base by cleaving the N-glycosidic bond between base and deoxyribose. AP endonuclease 1 (APE1) recognizes these abasic sites and incises the DNA backbone to generate a 3' hydroxyl group. This structure is a substrate for DNA polymerases, which insert one or more nucleotides (short patch and long patch pathway, respectively). Following end-polishing by flap endonuclease 1 or deoxyribophosphate lyase activity of DNA polymerase β, DNA ligases reconstitute the integrity of the DNA backbone (Figure 2). For a detailed and comprehensive description of the mechanisms in BER and function of individual BER enzymes we recommend the following literature list to interested readers [2,33–39].



[FIGURE2 is a one-column figure]
Figure 2: Simplified summary of potential strategic therapeutic targeting of the BER pathway: A) High levels of ROS in cancer cells can be complemented by Fenton reaction inducing nanoparticles, crosslinkers, radiotherapy and/or DNA intercalators; B) Recognition, binding and excision of nucleobase lesions can be targeted by, even covalently, inhibiting allosteric, metal-binding and active sites of DNA glycosylases, DNA-protein interactions or by DNA intercalation; C) Bifunctional DNA glycosylases and APE1 can be unspecifically inhibited by reaction of nucleophiles with the AP site and specifically by inhibitors for allosteric, metal-binding and catalytic sites. Additionally downstream factors which release the modified BER enzymes from substrates might be targeted for reduced enzyme recycling; D) Inhibition of polymerases by traditional small molecules or DNA mimicking nucleotide analogues; E) Targeting of DNA substrate or DNA ligase enzymes can be performed by inhibitors or interaction with active, allosteric and metal-binding sites.

In principle, the BER pathway may be drugged at any point of this process (Figure 1). However, knockout mice for the core enzymes of the pathway, i.e. *Ape1*, *Polb*, *Xrcc1*, *Lig3* and *Fen1* are all embryonic lethal, with the exception of *Parp1*$^{-/-}$, which appear to be viable and fertile. On the other hand, knockout mice for DNA glycosylases are all viable and fertile, with the exception of *Tdg*$^{-/-}$. These observations indicate that inhibitors to the core enzymes may have unforeseen on-target toxicities in normal tissues, but inhibitors to DNA glycosylases and PARP1 may be tolerated.

3. Known BER inhibitors

The substrate specificity and reaction mechanism during BER repair may be exploited by using small molecules targeting the different intermediate stages of both long and short patch repair pathways (Figure 2).

To this date, targeting the initial repair steps performed by the DNA glycosylases has resulted in only moderate success of developing small molecules against UNG, NEIL1 and OGG1 [40–46]. The underlying reasons for this might be due to the challenging nature of drugging carbohydrate or DNA-binding proteins, often regarded as close to undruggable, and glycosylases in DNA-bound and apo-states in general [47–49].

Only recently these obstacles have been overcome for OGG1 by the development of a potent first in class compound series by Tahara *et al* [50]. However, it remains to be seen how these unusual nonpolar molecules behave in different cell lines and ADME studies.

Like APE1, some DNA glycosylases with bifunctional mode of action can be inhibited from binding the intermediate abasic site. Methoxyamine, which is already used in the clinic in combination therapies, or small molecules with similar nucleophilic properties are examples of this interesting approach of mimicking the active DNA glycosylase site [51–53]. Additionally, a number of other substances are reported in the literature [54–63].

Development of inhibitors against DNA Polymerase β has been attempted in a number of studies [64–68]. However, most of the identified small molecules either lack potency or specificity. Recently, a DNA mimicking compound was shown to increase cytotoxicity in combination therapy with methyl methanesulfonate in HeLa cells [69]. DNA Ligases can also be targeted by several mechanisms. Consequently, an impressive amount of work has been invested into different approaches, but only yielding inhibitors with moderate potency and specificity [70]. A benzocumarine-stilbene hybrid molecule was recently reported to reduce the growth of breast cancer in a mouse model and is the most advanced DNA ligase-inhibitor known so far [71].

The only approved drugs targeting the BER pathway are for the treatment of BRCA-mutated breast and high grade serious ovarian cancer. Olaparib, Niraparib and Rucaparib target PARP1 during single-strand break repair and in contrast to simple catalytic inhibition by covalent substances cause toxicity due to the formation of double-strand breaks. All three drugs are currently in clinical trials for combination therapies with classical DNA damaging agents [72–76].

4. BER as an anti-cancer target

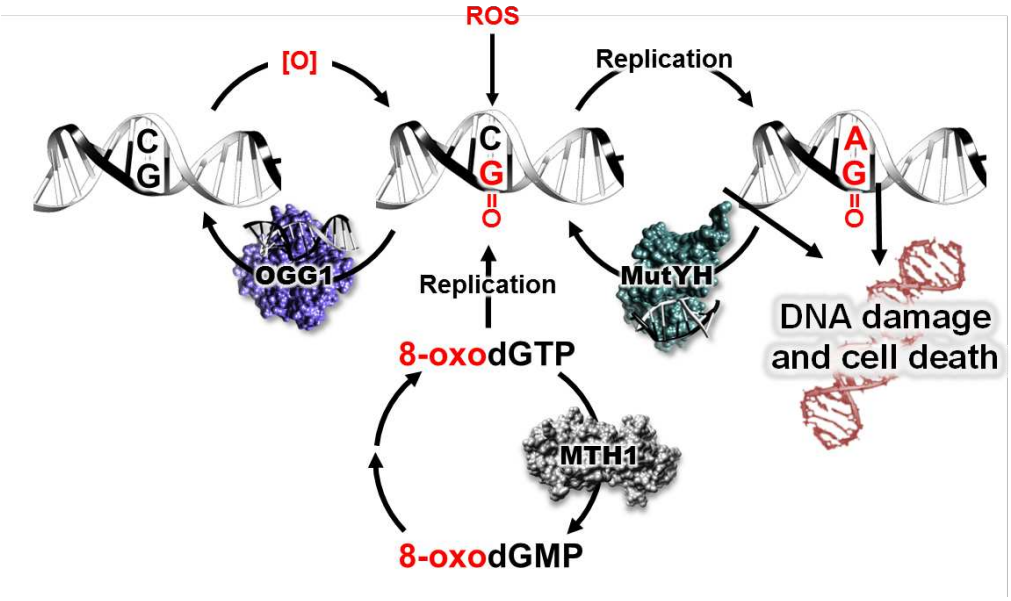
4.1 Sensitization to endogenous cancer-specific DNA damage

The high mutation load in cancer cells is to a large degree driven by endogenous DNA damage caused by metabolic imbalances. Activation of oncogenes contributes to genomic instability through replication stress at an early step in carcinogenesis [77,78]. While the mechanistic details underlying the replication stress are far from clear, at least a subset of oncogenes such as c-Myc and Ras confer an increase in reactive oxygen species (ROS) and oxidative DNA damage [79–81], causing higher levels of oxidized bases in cancer cells [82,83]. While the absolute quantification of oxidized bases in the genome has proven to be

technically challenging [84,85], oxidized bases in the genome of cancer cells or free oxidized bases and nucleotides in serum and urine are robust biomarkers for cancer [7,86], also reviewed in [5,34,87]. It is thought that a high load of ROS drives cancer cell proliferation and metastasis at the cost of causing oxidative damage to macromolecules [88].

The high level of ROS in cancer could in principle be handled in two ways: by quenching the pro-survival, growth stimulatory ROS signaling using antioxidants or by increasing the amount of ROS to allow its damaging effects to incapacitate cancerous cells. While pro-oxidant conditions such as inflammation and exposure to ionizing radiation promote tumor development, agents that directly or indirectly increase intracellular ROS are used extensively and with great efficacy in cancer therapy [89]. On the other hand, while increased intake of foods rich in antioxidants are recommended to the general population for being protective against cancer, it has been shown that excessive antioxidant treatment stimulates, rather than inhibits, the generation and spread of cancer in mice [90,91] and humans [92,93]. Taken together, this suggests that high ROS in cancer cells with its associated inevitable damage to DNA and macromolecules forms a barrier to carcinogenesis and metastasis. Pathways for preventing the accumulation of oxidative DNA lesions may therefore raise the threshold of how much oxidative stress a replicating cell can handle. Thus, these pathways are promising targets for cancer therapy. The best evidence for this concept was recently provided by us and others, by establishing MTH1 inhibition as a strategy to sensitize cancer cells to endogenous stress [94–96].

Guanine has the lowest redox potential among nucleobases and is therefore highly prone to oxidation [4,36,97], resulting in oxidation products 8-oxoG and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FaPyG) in DNA or in the deoxynucleotide pool (8-oxodGTP). Mammalian cells are equipped with three enzymes which act in concert to prevent the mutagenic potential of 8-oxoG: MutT homolog 1 (MTH1), MUTYH and OGG1 (Figure 3). MTH1 sanitizes the nucleotide pool from 8-oxodGTP, thereby preventing its incorporation into DNA, and MUTYH excises adenines misincorporated opposite genomic 8-oxoG. However, the main enzyme to remove genomic 8-oxoG is OGG1, which specifically recognizes and excises 8-oxoG paired with cytosine in double-stranded DNA. Deficiencies in this repair system may lead to increased mutagenesis or cell death through different mechanisms [98–100]. Moreover, 8-oxoG is prone to further oxidation, resulting in the generation of 5-guanidinohydantoin (Gh) or spiroiminodihydantoin (Sp), which in turn are substrates for the NEIL DNA glycosylases [36,101,101–104].



[FIGURE3 is a 1.5-column figure]

Figure 3: Cellular defense mechanisms against oxidized guanines. Cancer cells contain high levels of 8-oxodGTP, which may be incorporated into DNA unless hydrolyzed by MTH1. Once into DNA, 8-oxoguanine is recognized and repaired by OGG1, and downstream BER reconstitutes the original DNA sequence. However, replicative DNA polymerases may frequently insert adenine opposite 8-oxoguanine, causing an A:8-oxoG mispair. The adenine is a substrate for MUTYH, providing downstream BER the chance to insert a cytosine opposite 8-oxoguanine, and generate a substrate for OGG1 to remove the offending 8-oxoguanine from DNA. When MTH1 is inhibited or lowly expressed, inhibition of either OGG1 or MUTYH may be expected to be toxic to cancer cells, triggering toxic futile repair cycles and/or cell death.

MTH1 facilitates cell survival and proliferation after oncogene-induced oxidative stress [105–109], and inhibitors to MTH1 are promising candidates for anti-cancer therapy [94–96]. While the underlying biology behind MTH1's involvement in tolerance to oncogene-induced oxidative stress is emerging [87,105–111], the biology of small molecule MTH1 inhibitors remains unresolved in the literature. Several MTH1 inhibitor series fail to kill cancer cells, despite apparent successful target engagement in cells [112–115]. A key observation is that the anti-cancer effect seems to be coupled to accumulation of oxidized bases in the genome, as the MTH1 inhibitors that fail to accumulate oxidized bases also fail to kill cancer cells [96,115]. Since these oxidized bases are substrates for BER, it follows that inhibitors to BER could be used to either potentiate the effect of MTH1 inhibitors, or to kill subsets of cancers where the cancer cell relies more on downstream BER than MTH1 to maintain viability. This implies that the downstream repair enzymes OGG1 and MUTYH may be promising candidates to inhibit proliferation of high ROS cancers, either alone or in combination with MTH1 inhibitors. Consistently, MUTYH knockdown reduces cell proliferation and tumor growth and increases apoptosis in pancreatic cancer cells [116]. In a T-cell ALL cell line, proliferation is inhibited and apoptosis is induced by knockdown of MTH1 and MUTYH, both alone and synergistically [100]. Furthermore, OGG1 overexpression protects against Ras-induced senescence [117]. These observations point to a role of OGG1 and MUTYH in protecting against endogenous oxidative cancer-related stress, and suggest that these DNA glycosylases may be promising targets for the development of DNA glycosylase inhibitors.

4.2 Sensitizing cells to cancer therapy-induced DNA damage

Targeting the BER pathway is a promising strategy to sensitize cancer cells to chemo-and radiotherapy since many of the current therapies aim to induce genotoxic DNA lesions.

These therapies are however not specific for cancer, but introduce genotoxic damage in all proliferating cells. Their efficacy is thus limited by the toxic side effects resulting from targeting the non-cancerous proliferating cells. Efficient sensitization to chemotherapy and radiotherapy has been observed in several biological systems where one or more BER enzymes were depleted. It is thought that BER inhibitors will recapitulate these phenotypes. Interestingly, in some instances overexpressing some BER components, rather than their depletion, conferred a higher sensitivity. This can be explained in light of their role in BER and the nature of DNA intermediates that arise when such BER components are manipulated. Examples of these effects are briefly summarized below and in Table 1.

A number of inhibitors of the folate pathway results in the accumulation of dUMP in the nucleotide pool and misincorporation of uracil into DNA leading to thymine-less death [118–120]. The resulting genomic U:A base pairs are predominantly recognized and excised by UNG in mammals [121–123]. Notably, UNG expression was found to positively correlate with pemetrexed resistance in human lung cancer cell lines and UNG depletion resulted in enhancing its cytotoxic effect [20,21]. Moreover, Bulgar and colleagues [19] were able to re-sensitize $UNG^{+/+}$ cells with acquired pemetrexed resistance by co-treating the cells with methoxyamine, highlighting the importance of BER in mediating the cellular response to pemetrexed treatment.

BER is also implicated in the cytotoxicity of 5-fluorouracil (5-FU), a widely used anticancer drug whose metabolites are incorporated into both DNA and RNA in addition to inhibiting thymidylate synthase [124]. Of the five different repair pathways shown to process genomic 5-FU, UNG is the main repair pathway in cancer cells, with only a modest contribution of SMUG1, TDG, MBD4 or mismatch repair in repairing 5-FU containing DNA [16]. Interestingly, knocking down uracil-DNA glycosylases or employing BER inhibitors did not significantly enhance the fluoropyrimidine cytotoxicity. Instead, 5-FU cytotoxicity under the conditions employed was found to be mainly due to its incorporation into RNA rather than the DNA-mediated effects [16]. However, Yan *et al*. [18] pointed out that p53 status together with UNG plays a role in determining the cytotoxicity of 5-Fluoro-2'-deoxyuridine (5-FdU, floxuridine), another fluoropyrimidine that is efficiently incorporated into DNA rather than RNA. In absence of UNG, genomic 5-FU was found to block replication and induce double-strand breaks [125]. Consequently, targeting or depleting core BER factors such as XRCC1 and PARP1 sensitizes cancer cells to 5-FdU [126–128]. This strongly suggests that BER is an important modulator of the DNA-mediated effects of 5-FU.

Targeting BER also enhances the sensitivity to temozolomide (TMZ), a DNA alkylating agent used in the treatment of glioblastoma. Besides O6-methylguanine adducts, TMZ- induced DNA lesions include N3-methyladenine and N7-methylguanine base lesions, which are recognized by methyl purine DNA glycosylase (MPG) [32]. It is reported that depleting POLβ sensitizes murine embryonic fibroblasts to TMZ. This sensitivity is further enhanced by overexpressing MPG, suggesting that the accumulation of BER intermediates is likely the cause behind such hypersensitivity [31]. Another study by Tang and colleagues [30] shows that MPG overexpression significantly enhances TMZ cytotoxicity when combined with methoxyamine. Such a potentiation effect is abolished by overexpressing POLβ highlighting that both MPG and POLβ contribute to TMZ efficacy and influence methoxyamine potentiation of TMZ [30]. Interestingly, MPG depletion in murine cells is reported to confer increased sensitivity to two bifunctional alkylating agents; namely 1,3-bis(2-chloroethyl)-l-nitrosourea (BCNU) and mitomycin C (MMC) suggesting that MPG initiated BER plays an important role in counteracting those agents [129].

The BER pathway also influences the cytotoxicity of DNA crosslinking agents such as psoralen and cisplatin. Psoralen- induced monoadducts function as substrates for NEIL1 where HeLa cells deficient in NEIL1 and/or APE1 exhibit hypersensitivity to psoralen upon UVA photoactivation [130]. Furthermore, NEIL1 and NEIL3 have been shown to be involved

in the repair of bulky psoralen- induced interstrand cross-links [131–133]. On the other hand, cisplatin cytotoxicity is attributed to inducing different types of DNA lesions including mono-adducts, intrastrand and interstrand cross-links [134] in addition to resulting in an increased generation of ROS and oxidative DNA damage [28]. Importantly, UNG, POLβ and APE1 have been shown to be involved in modulating cisplatin resistance [135]. Indeed, depleting POLβ, UNG or using methoxyamine conferred cisplatin resistance in MDA-MB-231, HeLaS3, A2780 human cell lines and MEFs by affecting the processing of cisplatin DNA interstrand crosslinks [23]. APE1 expression level in tumor specimens from patients with non-small cell lung cancer was found to positively correlate with cisplatin resistance and high APE1 expression was associated with poor prognosis. This was further supported by showing that APE1 depletion sensitises A549 cells to cisplatin [136]. NTHL1 is another BER glycosylase that can serve as a target to potentiate cisplatin cytotoxic effects. Knocking down NTH1 was found to re-sensitise the otherwise cisplatin resistant Y-box-binding protein-1 overexpressing tumor cells [22].

Finally, the BER status affects the cellular response to ionizing radiation. Irradiation results in a broad range of DNA lesions including single strand breaks, double strand breaks and oxidized DNA lesions. The latter are recognized and repaired by the BER pathway. Accordingly, a number of BER aberrations are reported to influence the response to radiotherapy and thus offer a potential strategy for radiosensitization [10]. For instance, the status of OGG1 activity in human leukemia cell lines is regarded as a key player in determining cell survival following irradiation [12]. In addition, NTHL1 overexpression sensitizes human lymphoblastoid cells to gamma-irradiation [137]. Furthermore, SMUG depletion in UNG deficient cells results in radiosensitization [138].

4.3 Synthetic Lethality approaches

The dependence on compensatory repair pathways in cancer cells may be exploited as a therapeutic strategy in cancer therapy. Cancer cells deficient in a certain repair pathway can be specifically targeted via the inhibition or down-regulation of a compensatory repair pathway. Normal cells are protected by the activity of the same repair pathways mutated in the tumor (Figure 1). A well described example of such synthetic lethality is provided by inhibition of PARP1 in cells deficient in homologous recombination [139,140]. While PARP1 does not participate in BER per se [141–143], it is activated by the single-strand break intermediates. Three inhibitors, Olaparib, Niraparib and Rucaparib, are already approved for the treatment of hereditary breast and ovarian cancer and clinical trials of these compounds in combination therapies with DNA damaging agents are in progress [144,145]. However, the success of PARP1-inhibitors hides a very complex biology, where inhibition of catalytic activity can be well tolerated. Instead, compounds that trap PARP1 covalently at single-strand break repair intermediates cause toxicity because these structures are converted into double-strand breaks in BRCA1/2-deficient cells, whereas poor PARP1-trappers do not cause toxicity [146,147]. Thus, the pre-clinical efficacy of PARP-inhibitors correlate well with their ability to trap PARP1, at least in a monotherapy setting [144,148]. Combination regimens, while highly efficient *in vitro*, are hard to administer clinically, because of dose-limiting toxicity in normal tissues [144]. This stems from the lack of cancer selectivity of the classical chemotherapeutic drugs, which are toxic to all proliferating cells.

Other recent examples of synthetic lethality involving BER proteins include the inhibition of APE1, which sensitizes cells deficient in DSB repair [149]. The combination of inhibitors of double-strand break repair [150] or PARP-1 [143] sensitize cells deficient in XRCC1. Cells lacking functional mismatch repair often display enhanced tolerance to cytotoxic drugs, but may be sensitized to methotrexate by downregulation of POLβ or OGG1 [151].

5. Summary and perspectives

Not many high quality small molecule inhibitors of the BER pathway exist today, although the underlying role of BER in the repair of DNA damage and the success of the PARP1-inhibitors justify developing new compounds. Targeting the DNA glycosylases would be of special significance, since knockout mice for these enzymes are viable, fertile and for the most part healthy [152].

One issue that has stopped researchers from creating small molecule inhibitors of various BER factors is the concept of redundancy and “backup” repair pathways that are postulated to account for the absence of clear phenotypes following experimental treatments. Yet, truly redundant pathways are not favored through evolution, because inactivating mutations in “backup” genes would not be selected against. Even though BER enzymes have somewhat overlapping substrate specificities, they are all very well conserved in higher eukaryotes, indicating there is a selective pressure maintaining them and implying that all BER factors have separate, specialized functions. Although apparently inseparable *in vitro* or in a lysate, in cells these functions are separated in time during the cell cycle [153] or embryonal development [154], in space in subnuclear compartments such as telomeres, replication forks, eu- or heterochromatin, nucleolus or by binding to different interaction partners. Thus, if one BER factor is deficient or inhibited, repair by a suboptimal pathway will be triggered and the DNA damage will be repaired at a suboptimal time, place or by the wrong downstream repair factors. An example of this is that despite there being at least 5 different pathways that are biochemically capable of removing 5-FU from DNA [16], depletion of only one factor has proven sufficient to sensitize cells to fluoropyrimidines in various contexts [125,138,155]. Therefore, despite the presence of apparent redundancy, targeting of only a single BER protein may still be sufficient to achieve pharmaceutical efficacy.

That being mentioned, the biology of the BER pathway is very complex. While the idea that proteins overexpressed in cancer are promising therapeutic targets is a common assumption, this may not hold true for the BER pathway since the intermediates of the BER pathway, AP-sites and strand breaks in various configurations, are themselves genotoxic [143,156–163]. Thus, overexpression of DNA glycosylases may sensitize rather than rescue cells from treatment with genotoxic agents [137,160,162,164–167], or cells deficient in the same DNA glycosylases may be resistant against genotoxic treatments [98,160,162,164]. Second, overexpression of BER proteins may interfere with other repair pathways. Expression of DNA polymerase β is mutagenic since it interferes with high fidelity polymerases [168] and overexpression of proteins such as NTHL1 is sufficient to cause replication stress and genomic instability, even when a catalytically dead mutant is expressed [169]. This implies that the expression levels of BER proteins must be tightly regulated in order not to impede cancer cell proliferation, which is under a strong selective pressure to divide fast.

Moreover, if potent and pharmacologically acceptable BER inhibitors are to be generated, we have so far only vague ideas on how to implement them in therapy since our understanding of DNA damage in cancer in general is lacking. While we know cancer is genomically unstable and BER substrates are prevalent in cancer genomes, we only have a rudimentary understanding of how the different lesions contribute to the cancer phenotype, and how this might be exploited to kill cancer cells. Likewise, a quantitative understanding is lacking. The levels of uracil and 8-oxoG in normal cells seem to be no more than 1 lesion per 10^6 bp [6,34,85,170], but the absolute level that can be tolerated by cancer and normal cells is unknown. This understanding would be vital to avoid damage to normal cells, especially in combination treatments, as seen for the PARP1-inhibitors [144]. Avoiding on-target toxicity in normal tissues would be of particular importance if the core enzymes of the pathway are targeted, where knockout mice are embryonic lethal.

Table 1: Targeting the BER pathway to sensitize cancer cells to chemo- and radiotherapy induced DNA damage. DLD1 and HT29, colorectal adenocarcinoma cell lines; H460 and A549, non-small-cell lung cancer cell lines; OVCAR-8 and A2780, ovarian cancer cell lines; MEF, mouse embryonic fibroblasts; LN428; glioma cell line; Ab1, mouse embryonic stem cells; HeLa and HeLa S3, cervical adenocarcinoma cell lines; MCF7 and MDA-MB-231, breast cancer cell lines; TK6, human lymphoblastoid cells.

Cell line	BER manipulation or inhibition	Chemo- or radiotherapy	Treatment Outcome	Reference
DLD1	UNG depletion	Pemetrexed	Sensitization	[20]
DLD1, H460 & A549 Xenografts	Methoxyamine treatment			[19]
OVCAR-8	XRCC1 depletion	Floxuridine	Sensitization	[126]
	PARP1 depletion			
	PARP inhibition			
HT29	XRCC1 depletion			[128]
	APE1 depletion			
MEF	POLβ depletion	Temozolomide	Sensitization	[31]
LN428	MPG overexpression with Methoxyamine co-treatment			[30]
Ab1	MPG depletion	Mitomycin C or BCNU	Sensitization	[129]
HeLa	NEIL1 depletion	Psoralen	Sensitization	[130]
	APE1 depletion			
A549	APE1 depletion	Cisplatin	Sensitization	[136]
MCF7	NTHL1 depletion			[22]
MEF, A2780, HeLa S3, MDA-MB-231	POLβ depletion, UNG depletion, Methoxyamine treatment		Resistance	[23]
TK6	NTHL1 overexpression	γ-radiation	Sensitization	[137]
MEF	SMUG1 depletion in UNG $^{-/-}$ cells			[171]

Conflict of interest

T.H. is named an inventor on patents for the use of MTH1 inhibitors for treatments of cancer and inflammation and a patent on the use of PARP1 inhibitors for the treatment of cancer. T.V., A.C.K. and T.H. are named as inventors on a provisional patent application for the use of OGG1 inhibitors in treatments of proliferative conditions. The authors declare that there are no other conflicts of interest.

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References

[1] D. Hanahan, R.A. Weinberg, Hallmarks of Cancer: The Next Generation, Cell. 144 (2011) 646–674. doi:10.1016/j.cell.2011.02.013.

[2] H.E. Krokan, M. Bjørås, Base Excision Repair, Cold Spring Harb. Perspect. Biol. 5 (2013). doi:10.1101/cshperspect.a012583.

[3] E.C. Friedberg, DNA repair and mutagenesis, 2nd ed., ASM Press, Washington, D.C., 2006.

[4] T. Lindahl, Instability and decay of the primary structure of DNA, Nature. 362 (1993) 709–15.

[5] B. van Loon, E. Markkanen, U. Hübscher, Oxygen as a friend and enemy: How to combat the mutational potential of 8-oxo-guanine, DNA Repair. 9 (2010) 604–616. doi:10.1016/j.dnarep.2010.03.004.

[6] H.S. Pettersen, A. Galashevskaya, B. Doseth, M.M.L. Sousa, A. Sarno, T. Visnes, P.A. Aas, N.-B. Liabakk, G. Slupphaug, P. Sætrom, B. Kavli, H.E. Krokan, AID expression in B-cell lymphomas causes accumulation of genomic uracil and a distinct AID mutational signature, DNA Repair. 25 (2015) 60–71. doi:10.1016/j.dnarep.2014.11.006.

[7] L. Xia, W. Huang, M. Bellani, M.M. Seidman, K. Wu, D. Fan, Y. Nie, Y. Cai, Y.W. Zhang, L.-R. Yu, H. Li, C.A. Zahnow, W. Xie, R.-W.C. Yen, F.V. Rassool, S.B. Baylin, CHD4 Has Oncogenic Functions in Initiating and Maintaining Epigenetic Suppression of Multiple Tumor Suppressor Genes, Cancer Cell. 31 (2017) 653-668.e7. doi:10.1016/j.ccell.2017.04.005.

[8] N.J. Curtin, DNA repair dysregulation from cancer driver to therapeutic target, Nat. Rev. Cancer. 12 (2012) 801–817. doi:10.1038/nrc3399.

[9] T. Helleday, E. Petermann, C. Lundin, B. Hodgson, R.A. Sharma, DNA repair pathways as targets for cancer therapy, Nat. Rev. Cancer. 8 (2008) 193–204. doi:10.1038/nrc2342.

[10] C. Vens, A.C. Begg, Targeting Base Excision Repair as a Sensitization Strategy in Radiotherapy, Semin. Radiat. Oncol. 20 (2010) 241–249. doi:10.1016/j.semradonc.2010.05.005.

[11] T.A. Rosenquist, E. Zaika, A.S. Fernandes, D.O. Zharkov, H. Miller, A.P. Grollman, The novel DNA glycosylase, NEIL1, protects mammalian cells from radiation-mediated cell death, DNA Repair. 2 (2003) 581–591. doi:10.1016/S1568-7864(03)00025-9.

[12] J.-W. Hyun, G.-J. Cheon, H.-S. Kim, Y.-S. Lee, E.-Y. Choi, B.-H. Yoon, J.-S. Kim, M.-H. Chung, Radiation sensitivity depends on OGG1 activity status in human leukemia cell lines, Free Radic. Biol. Med. 32 (2002) 212–220.

[13] N. Yang, H. Galick, S.S. Wallace, Attempted base excision repair of ionizing radiation damage in human lymphoblastoid cells produces lethal and mutagenic double strand breaks, DNA Repair Amst. 3 (2004) 1323–34. doi:10.1016/j.dnarep.2004.04.014.

[14] H. Kasai, H. Tanooka, S. Nishimura, Formation of 8-hydroxyguanine residues in DNA by X-irradiation, Gan. 75 (1984) 1037–1039.

[15] J. Cadet, T. Douki, J.-L. Ravanat, Oxidatively Generated Damage to Isolated and Cellular DNA, in: N.E. Geacintov, S. Broyde (Eds.), Chem. Biol. DNA Damage, Wiley-VCH Verlag GmbH & Co. KGaA, 2010: pp. 53–80. http://onlinelibrary.wiley.com/doi/10.1002/9783527630110.ch3/summary (accessed May 26, 2016).

[16] H.S. Pettersen, T. Visnes, C.B. V\aagbø, E.K. Svaasand, B. Doseth, G. Slupphaug, B. Kavli, H.E. Krokan, UNG-initiated base excision repair is the major repair route for 5-fluorouracil in DNA, but 5-fluorouracil cytotoxicity depends mainly on RNA incorporation, Nucleic Acids Res. 39 (2011) 8430–8444.

[17] D.B. Longley, D.P. Harkin, P.G. Johnston, 5-fluorouracil: mechanisms of action and clinical strategies, Nat Rev Cancer. 3 (2003) 330–8.

[18] Y. Yan, Y. Qing, J.J. Pink, S.L. Gerson, Loss of Uracil DNA Glycosylase Selectively Resensitizes p53-Mutant and -Deficient Cells to 5-FdU, Mol. Cancer Res. MCR. (2017). doi:10.1158/1541-7786.MCR-17-0215.

[19] A.D. Bulgar, L.D. Weeks, Y. Miao, S. Yang, Y. Xu, C. Guo, S. Markowitz, N. Oleinick, S.L. Gerson, L. Liu, Removal of uracil by uracil DNA glycosylase limits pemetrexed cytotoxicity: overriding the limit with methoxyamine to inhibit base excision repair, Cell Death Dis. 3 (2012) e252. doi:10.1038/cddis.2011.135.

[20] L.D. Weeks, G.E. Zentner, P.C. Scacheri, S.L. Gerson, Uracil DNA glycosylase (UNG) loss enhances DNA double strand break formation in human cancer cells exposed to pemetrexed, Cell Death Dis. 5 (2014) e1045. doi:10.1038/cddis.2013.477.

[21] L.D. Weeks, P. Fu, S.L. Gerson, Uracil DNA glycosylase expression determines human lung cancer cell sensitivity to pemetrexed, Mol. Cancer Ther. (2013). doi:10.1158/1535-7163.MCT-13-0172.

[22] D. Guay, C. Garand, S. Reddy, C. Schmutte, M. Lebel, The human endonuclease III enzyme is a relevant target to potentiate cisplatin cytotoxicity in Y-box-binding protein-1 overexpressing tumor cells, Cancer Sci. 99 (2008) 762–769. doi:10.1111/j.1349-7006.2008.00739.x.

[23] A. Kothandapani, V.S.M.N. Dangeti, A.R. Brown, L.A. Banze, X.-H. Wang, R.W. Sobol, S.M. Patrick, Novel Role of Base Excision Repair in Mediating Cisplatin Cytotoxicity, J. Biol. Chem. 286 (2011) 14564–14574. doi:10.1074/jbc.M111.225375.

[24] E. Caiola, D. Salles, R. Frapolli, M. Lupi, G. Rotella, A. Ronchi, M.C. Garassino, N. Mattschas, S. Colavecchio, M. Broggini, L. Wiesmüller, M. Marabese, Base excision repair-mediated resistance to cisplatin in KRAS(G12C) mutant NSCLC cells, Oncotarget. 6 (2015) 30072–30087.

[25] M. Berndtsson, M. Hägg, T. Panaretakis, A.M. Havelka, M.C. Shoshan, S. Linder, Acute apoptosis by cisplatin requires induction of reactive oxygen species but is not associated with damage to nuclear DNA, Int. J. Cancer J. Int. Cancer. 120 (2007) 175–180. doi:10.1002/ijc.22132.

[26] D. Gao, J. Hu, X. Zhang, C. Gao, J. Hong, Effect of hOGG1 Over-Expression on Cisplatin Resistance in Esophageal Squamous Carcinoma Cells, Cancer Biother. Radiopharm. 28 (2013) 433–440. doi:10.1089/cbr.2012.1287.

[27] T.J. Preston, J.T. Henderson, G.P. McCallum, P.G. Wells, Base excision repair of reactive oxygen species–initiated 7,8-dihydro-8-oxo-2′-deoxyguanosine inhibits the cytotoxicity of platinum anticancer drugs, Mol. Cancer Ther. 8 (2009) 2015–2026. doi:10.1158/1535-7163.MCT-08-0929.

[28] A. Siomek, J. Tujakowski, D. Gackowski, R. Rozalski, M. Foksinski, T. Dziaman, K. Roszkowski, R. Olinski, Severe oxidatively damaged DNA after cisplatin treatment of cancer patients, Int. J. Cancer. 119 (2006) 2228–2230. doi:10.1002/ijc.22088.

[29] M.L. Orta, A. Höglund, J.M. Calderón-Montaño, I. Domínguez, E. Burgos-Morón, T. Visnes, N. Pastor, C. Ström, M. López-lázaro, T. Helleday, The PARP inhibitor Olaparib disrupts base excision repair of 5-aza-2′-deoxycytidine lesions, Nucleic Acids Res. (2014) gku638. doi:10.1093/nar/gku638.

[30] J. Tang, D. Svilar, R.N. Trivedi, X. Wang, E.M. Goellner, B. Moore, R.L. Hamilton, L.A. Banze, A.R. Brown, R.W. Sobol, N-methylpurine DNA glycosylase and DNA polymerase β modulate BER inhibitor potentiation of glioma cells to temozolomide, Neuro-Oncol. 13 (2011) 471–486.
[31] R.N. Trivedi, K.H. Almeida, J.L. Fornsaglio, S. Schamus, R.W. Sobol, The role of base excision repair in the sensitivity and resistance to temozolomide-mediated cell death, Cancer Res. 65 (2005) 6394–400. doi:10.1158/0008-5472.CAN-05-0715.
[32] E.S. Newlands, M.F. Stevens, S.R. Wedge, R.T. Wheelhouse, C. Brock, Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials, Cancer Treat Rev. 23 (1997) 35–61.
[33] A.L. Jacobs, P. Schär, DNA glycosylases: in DNA repair and beyond, Chromosoma. 121 (2012) 1–20. doi:10.1007/s00412-011-0347-4.
[34] M. Dizdaroglu, Oxidatively induced DNA damage and its repair in cancer, Mutat. Res. Mutat. Res. 763 (2015) 212–245. doi:10.1016/j.mrrev.2014.11.002.
[35] S.S. Wallace, Base excision repair: A critical player in many games, DNA Repair. 19 (2014) 14–26. doi:10.1016/j.dnarep.2014.03.030.
[36] A.M. Fleming, C.J. Burrows, Formation and processing of DNA damage substrates for the hNEIL enzymes, Free Radic. Biol. Med. 107 (2017) 35–52. doi:10.1016/j.freeradbiomed.2016.11.030.
[37] R.J. Carter, J.L. Parsons, Base Excision Repair, a Pathway Regulated by Posttranslational Modifications, Mol. Cell. Biol. 36 (2016) 1426–1437. doi:10.1128/MCB.00030-16.
[38] N.C. Bauer, A.H. Corbett, P.W. Doetsch, The current state of eukaryotic DNA base damage and repair, Nucleic Acids Res. 43 (2015) 10083–10101. doi:10.1093/nar/gkv1136.
[39] K.L. Limpose, A.H. Corbett, P.W. Doetsch, BERing the burden of damage: Pathway crosstalk and posttranslational modification of base excision repair proteins regulate DNA damage management, DNA Repair. 56 (2017) 51–64. doi:10.1016/j.dnarep.2017.06.007.
[40] Y.L. Jiang, D.J. Krosky, L. Seiple, J.T. Stivers, Uracil-Directed Ligand Tethering: An Efficient Strategy for Uracil DNA Glycosylase (UNG) Inhibitor Development, J. Am. Chem. Soc. 127 (2005) 17412–17420. doi:10.1021/ja055846n.
[41] S. Chung, J.B. Parker, M. Bianchet, L.M. Amzel, J.T. Stivers, Impact of linker strain and flexibility in the design of a fragment-based inhibitor, Nat. Chem. Biol. 5 (2009) 407–413. doi:10.1038/nchembio.163.
[42] D.J. Krosky, M.A. Bianchet, L. Seiple, S. Chung, L.M. Amzel, J.T. Stivers, Mimicking damaged DNA with a small molecule inhibitor of human UNG2, Nucleic Acids Res. 34 (2006) 5872–5879. doi:10.1093/nar/gkl747.
[43] H. Huang, J.T. Stivers, M.M. Greenberg, Competitive Inhibition of Uracil DNA Glycosylase by a Modified Nucleotide Whose Triphosphate is a Substrate for DNA Polymerase, J. Am. Chem. Soc. 131 (2009) 1344–1345. doi:10.1021/ja807705z.
[44] N. Donley, P. Jaruga, E. Coskun, M. Dizdaroglu, A.K. McCullough, R.S. Lloyd, Small Molecule Inhibitors of 8-Oxoguanine DNA Glycosylase-1 (OGG1), ACS Chem. Biol. 10 (2015) 2334–2343. doi:10.1021/acschembio.5b00452.
[45] Dai Ran, Wilson Daniel J., Geders Todd W., Aldrich Courtney C., Finzel Barry C., Inhibition of Mycobacterium tuberculosis Transaminase BioA by Aryl Hydrazines and Hydrazides, ChemBioChem. 15 (2014) 575–586. doi:10.1002/cbic.201300748.
[46] A.C. Jacobs, M.J. Calkins, A. Jadhav, D. Dorjsuren, D. Maloney, A. Simeonov, P. Jaruga, M. Dizdaroglu, A.K. McCullough, R.S. Lloyd, Inhibition of DNA Glycosylases via Small Molecule Purine Analogs, PLOS ONE. 8 (2013) e81667. doi:10.1371/journal.pone.0081667.
[47] P.J. Hajduk, J.R. Huth, C. Tse, Predicting protein druggability, Drug Discov. Today. 10 (2005) 1675–1682. doi:10.1016/S1359-6446(05)03624-X.
[48] P.J. Hajduk, J.R. Huth, S.W. Fesik, Druggability Indices for Protein Targets Derived from NMR-Based Screening Data, J. Med. Chem. 48 (2005) 2518–2525. doi:10.1021/jm049131r.

[49] J. Aretz, E.-C. Wamhoff, J. Hanske, D. Heymann, C. Rademacher, Computational and Experimental Prediction of Human C-Type Lectin Receptor Druggability, Front. Immunol. 5 (2014). doi:10.3389/fimmu.2014.00323.
[50] Y. Tahara, D. Auld, D. Ji, A.A. Beharry, A.M. Kietrys, D.L. Wilson, M. Jimenez, D. King, Z. Nguyen, E.T. Kool, Potent and Selective Inhibitors of 8-Oxoguanine DNA Glycosylase, J. Am. Chem. Soc. 140 (2018) 2105–2114. doi:10.1021/jacs.7b09316.
[51] S. Khoei, R. Poorabdollahi, A. Mostaar, F. Faeghi, Methoxyamine Enhances 5-Fluorouracil-Induced Radiosensitization in Colon Cancer Cell Line HT29, Cell J Yakhteh. (2016). / (accessed March 23, 2018).
[52] L. Liu, Y. Nakatsuru, S.L. Gerson, Base Excision Repair as a Therapeutic Target in Colon Cancer, Clin. Cancer Res. 8 (2002) 2985–2991.
[53] S. Madhusudan, F. Smart, P. Shrimpton, J.L. Parsons, L. Gardiner, S. Houlbrook, D.C. Talbot, T. Hammonds, P.A. Freemont, M.J.E. Sternberg, G.L. Dianov, I.D. Hickson, Isolation of a small molecule inhibitor of DNA base excision repair, Nucleic Acids Res. 33 (2005) 4711–4724. doi:10.1093/nar/gki781.
[54] C. Zhong, M. Xu, Y. Wang, J. Xu, Y. Yuan, An APE1 inhibitor reveals critical roles of the redox function of APE1 in KSHV replication and pathogenic phenotypes, PLOS Pathog. 13 (2017) e1006289. doi:10.1371/journal.ppat.1006289.
[55] A. Bapat, L.S. Glass, M. Luo, M.L. Fishel, E.C. Long, M.M. Georgiadis, M.R. Kelley, Novel Small-Molecule Inhibitor of Apurinic/Apyrimidinic Endonuclease 1 Blocks Proliferation and Reduces Viability of Glioblastoma Cells, J. Pharmacol. Exp. Ther. 334 (2010) 988–998. doi:10.1124/jpet.110.169128.
[56] T. Ren, J. Shan, M. Li, Y. Qing, C. Qian, G. Wang, Q. Li, G. Liu, C. Li, Y. Peng, H. Luo, S. Zhang, Y. Yang, Y. Cheng, D. Wang, S.-F. Zhou, Small-molecule BH3 mimetic and pan-Bcl-2 inhibitor AT-101 enhances the antitumor efficacy of cisplatin through inhibition of APE1 repair and redox activity in non-small-cell lung cancer, Drug Des. Devel. Ther. (2015). doi:10.2147/DDDT.S82724.
[57] J. Zhang, M. Luo, D. Marasco, D. Logsdon, K.A. LaFavers, Q. Chen, A. Reed, M.R. Kelley, M.L. Gross, M.M. Georgiadis, Inhibition of Apurinic/Apyrimidinic Endonuclease I's Redox Activity Revisited, Biochemistry (Mosc.). 52 (2013) 2955–2966. doi:10.1021/bi400179m.
[58] G.-M. Zou, A. Maitra, Small-molecule inhibitor of the AP endonuclease 1/REF-1 E3330 inhibits pancreatic cancer cell growth and migration, Mol. Cancer Ther. 7 (2008) 2012–2021. doi:10.1158/1535-7163.MCT-08-0113.
[59] A. Simeonov, A. Kulkarni, D. Dorjsuren, A. Jadhav, M. Shen, D.R. McNeill, C.P. Austin, D.M.W. Iii, Identification and Characterization of Inhibitors of Human Apurinic/apyrimidinic Endonuclease APE1, PLOS ONE. 4 (2009) e5740. doi:10.1371/journal.pone.0005740.
[60] Guerreiro Patrícia S., Corvacho Eduardo, Costa João G., Saraiva Nuno, Fernandes Ana S., Castro Matilde, Miranda Joana P., Oliveira Nuno G., The APE1 redox inhibitor E3330 reduces collective cell migration of human breast cancer cells and decreases chemoinvasion and colony formation when combined with docetaxel, Chem. Biol. Drug Des. 90 (2017) 561–571. doi:10.1111/cbdd.12979.
[61] R.L. Nyland, M. Luo, M.R. Kelley, R.F. Borch, Design and Synthesis of Novel Quinone Inhibitors Targeted to the Redox Function of Apurinic/Apyrimidinic Endonuclease 1/Redox Enhancing Factor-1 (Ape1/Ref-1), J. Med. Chem. 53 (2010) 1200–1210. doi:10.1021/jm9014857.
[62] B.A. Manvilla, O. Wauchope, K.L. Seley-Radtke, A.C. Drohat, NMR Studies Reveal an Unexpected Binding Site for a Redox Inhibitor of AP Endonuclease 1, Biochemistry (Mosc.). 50 (2011) 10540–10549. doi:10.1021/bi201071g.
[63] D. Su, S. Delaplane, M. Luo, D.L. Rempel, B. Vu, M.R. Kelley, M.L. Gross, M.M. Georgiadis, Interactions of Apurinic/Apyrimidinic Endonuclease with a Redox Inhibitor: Evidence for an Alternate Conformation of the Enzyme, Biochemistry (Mosc.). 50 (2011) 82–92. doi:10.1021/bi101248s.

[64] R.A.O. Bennett, D.M. Wilson, D. Wong, B. Demple, Interaction of human apurinic endonuclease and DNA polymerase β in the base excision repair pathway, Proc. Natl. Acad. Sci. 94 (1997) 7166–7169.
[65] Y. Matsumoto, K. Kim, D.S. Katz, J. Feng, Catalytic Center of DNA Polymerase β for Excision of Deoxyribose Phosphate Groups, Biochemistry (Mosc.). 37 (1998) 6456–6464. doi:10.1021/bi9727545.
[66] M.S. DeMott, E. Beyret, D. Wong, B.C. Bales, J.-T. Hwang, M.M. Greenberg, B. Demple, Covalent Trapping of Human DNA Polymerase β by the Oxidative DNA Lesion 2-Deoxyribonolactone, J. Biol. Chem. 277 (2002) 7637–7640. doi:10.1074/jbc.C100577200.
[67] J.L. Parsons, I.I. Dianova, S.V. Khoronenkova, M.J. Edelmann, B.M. Kessler, G.L. Dianov, USP47 Is a Deubiquitylating Enzyme that Regulates Base Excision Repair by Controlling Steady-State Levels of DNA Polymerase β, Mol. Cell. 41 (2011) 609–615. doi:10.1016/j.molcel.2011.02.016.
[68] K.H. Barakat, M.M. Gajewski, J.A. Tuszynski, DNA polymerase beta (pol β) inhibitors: A comprehensive overview, Drug Discov. Today. 17 (2012) 913–920. doi:10.1016/j.drudis.2012.04.008.
[69] R. Paul, S. Banerjee, M.M. Greenberg, Synergistic Effects of an Irreversible DNA Polymerase Inhibitor and DNA Damaging Agents on HeLa Cells, ACS Chem. Biol. 12 (2017) 1576–1583. doi:10.1021/acschembio.7b00259.
[70] Singh Deependra Kumar, Krishna Shagun, Chandra Sharat, Shameem Mohammad, Deshmukh Amit Laxmikant, Banerjee Dibyendu, Human DNA Ligases: A Comprehensive New Look for Cancer Therapy, Med. Res. Rev. 34 (2014) 567–595. doi:10.1002/med.21298.
[71] M.K. Hussain, D.K. Singh, A. Singh, M. Asad, M.I. Ansari, M. Shameem, S. Krishna, G.R. Valicherla, V. Makadia, S. Meena, A.L. Deshmukh, J.R. Gayen, M. Imran Siddiqi, D. Datta, K. Hajela, D. Banerjee, A Novel Benzocoumarin-Stilbene Hybrid as a DNA ligase I inhibitor with in vitro and in vivo anti-tumor activity in breast cancer models, Sci. Rep. 7 (2017) 10715. doi:10.1038/s41598-017-10864-3.
[72] C.J. Lord, A. Ashworth, PARP inhibitors: Synthetic lethality in the clinic, Science. 355 (2017) 1152–1158. doi:10.1126/science.aam7344.
[73] M. Rouleau, A. Patel, M.J. Hendzel, S.H. Kaufmann, G.G. Poirier, PARP inhibition: PARP1 and beyond, Nat. Rev. Cancer. 10 (2010) 293–301. doi:10.1038/nrc2812.
[74] J. Murai, S.N. Huang, B.B. Das, A. Renaud, Y. Zhang, J.H. Doroshow, J. Ji, S. Takeda, Y. Pommier, Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors, Cancer Res. 72 (2012) 5588–5599. doi:10.1158/0008-5472.CAN-12-2753.
[75] Helleday Thomas, The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings, Mol. Oncol. 5 (2011) 387–393. doi:10.1016/j.molonc.2011.07.001.
[76] Y. Shen, M. Aoyagi-Scharber, B. Wang, Trapping Poly(ADP-Ribose) Polymerase, J. Pharmacol. Exp. Ther. 353 (2015) 446–457. doi:10.1124/jpet.114.222448.
[77] T.D. Halazonetis, V.G. Gorgoulis, J. Bartek, An Oncogene-Induced DNA Damage Model for Cancer Development, Science. 319 (2008) 1352–1355. doi:10.1126/science.1140735.
[78] G.-Y. Liou, P. Storz, Reactive oxygen species in cancer, Free Radic. Res. 44 (2010) 479–496. doi:10.3109/10715761003667554.
[79] O. Vafa, M. Wade, S. Kern, M. Beeche, T.K. Pandita, G.M. Hampton, G.M. Wahl, c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability, Mol. Cell. 9 (2002) 1031–1044.
[80] A.C. Lee, B.E. Fenster, H. Ito, K. Takeda, N.S. Bae, T. Hirai, Z.-X. Yu, V.J. Ferrans, B.H. Howard, T. Finkel, Ras Proteins Induce Senescence by Altering the Intracellular Levels of Reactive Oxygen Species, J. Biol. Chem. 274 (1999) 7936–7940. doi:10.1074/jbc.274.12.7936.
[81] A. Maya-Mendoza, J. Ostrakova, M. Kosar, A. Hall, P. Duskova, M. Mistrik, J.M. Merchut-Maya, Z. Hodny, J. Bartkova, C. Christensen, J. Bartek, Myc and Ras oncogenes engage different energy metabolism programs and evoke distinct patterns of oxidative and DNA replication stress, Mol. Oncol. 9 (2015) 601–616. doi:10.1016/j.molonc.2014.11.001.

[82] A. Matsui, T. Ikeda, K. Enomoto, K. Hosoda, H. Nakashima, K. Omae, M. Watanabe, T. Hibi, M. Kitajima, Increased formation of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, in human breast cancer tissue and its relationship to GSTP1 and COMT genotypes, Cancer Lett. 151 (2000) 87–95. doi:10.1016/S0304-3835(99)00424-3.

[83] S. Toyokuni, K. Okamoto, J. Yodoi, H. Hiai, Persistent oxidative stress in cancer, FEBS Lett. 358 (1995) 1–3. doi:10.1016/0014-5793(94)01368-B.

[84] ESCODD (European Standards Committee on Oxidative DNA Damage), Comparative analysis of baseline 8-oxo-7,8-dihydroguanine in mammalian cell DNA, by different methods in different laboratories: an approach to consensus, Carcinogenesis. 23 (2002) 2129–2133.

[85] E. (European S.C. on O.D. Damage), C.M. Gedik, A. Collins, Establishing the background level of base oxidation in human lymphocyte DNA: results of an interlaboratory validation study, FASEB J. (2004). doi:10.1096/fj.04-1767fje.

[86] C. Ma-on, A. Sanpavat, P. Whongsiri, S. Suwannasin, N. Hirankarn, P. Tangkijvanich, C. Boonla, Oxidative stress indicated by elevated expression of Nrf2 and 8-OHdG promotes hepatocellular carcinoma progression, Med. Oncol. 34 (2017) 57. doi:10.1007/s12032-017-0914-5.

[87] Y. Nakabeppu, Cellular Levels of 8-Oxoguanine in either DNA or the Nucleotide Pool Play Pivotal Roles in Carcinogenesis and Survival of Cancer Cells, Int. J. Mol. Sci. 15 (2014) 12543–12557. doi:10.3390/ijms150712543.

[88] Y. Zhang, Y. Du, W. Le, K. Wang, N. Kieffer, J. Zhang, Redox Control of the Survival of Healthy and Diseased Cells, Antioxid. Redox Signal. 15 (2011) 2867–2908. doi:10.1089/ars.2010.3685.

[89] C. Gorrini, I.S. Harris, T.W. Mak, Modulation of oxidative stress as an anticancer strategy, Nat. Rev. Drug Discov. 12 (2013) 931–947. doi:10.1038/nrd4002.

[90] V.I. Sayin, M.X. Ibrahim, E. Larsson, J.A. Nilsson, P. Lindahl, M.O. Bergo, Antioxidants Accelerate Lung Cancer Progression in Mice, Sci. Transl. Med. 6 (2014) 221ra15-221ra15. doi:10.1126/scitranslmed.3007653.

[91] E. Piskounova, M. Agathocleous, M.M. Murphy, Z. Hu, S.E. Huddlestun, Z. Zhao, A.M. Leitch, T.M. Johnson, R.J. DeBerardinis, S.J. Morrison, Oxidative stress inhibits distant metastasis by human melanoma cells, Nature. 527 (2015) 186–191. doi:10.1038/nature15726.

[92] T.A.-T.B.C.C.P.S. Group, The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers, N. Engl. J. Med. 330 (1994) 1029–1035. doi:10.1056/NEJM199404143301501.

[93] E.A. Klein, I.M. Thompson, C.M. Tangen, J.J. Crowley, M.S. Lucia, P.J. Goodman, L.M. Minasian, L.G. Ford, H.L. Parnes, J.M. Gaziano, D.D. Karp, M.M. Lieber, P.J. Walther, L. Klotz, J.K. Parsons, J.L. Chin, A.K. Darke, S.M. Lippman, G.E. Goodman, F.L. Meyskens, L.H. Baker, Vitamin E and the Risk of Prostate Cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT), JAMA. 306 (2011) 1549–1556. doi:10.1001/jama.2011.1437.

[94] H. Gad, T. Koolmeister, A.-S. Jemth, S. Eshtad, S.A. Jacques, C.E. Ström, L.M. Svensson, N. Schultz, T. Lundbäck, B.O. Einarsdottir, A. Saleh, C. Göktürk, P. Baranczewski, R. Svensson, R.P.-A. Berntsson, R. Gustafsson, K. Strömberg, K. Sanjiv, M.-C. Jacques-Cordonnier, M. Desroses, A.-L. Gustavsson, R. Olofsson, F. Johansson, E.J. Homan, O. Loseva, L. Bräutigam, L. Johansson, A. Höglund, A. Hagenkort, T. Pham, M. Altun, F.Z. Gaugaz, S. Vikingsson, B. Evers, M. Henriksson, K.S.A. Vallin, O.A. Wallner, L.G.J. Hammarström, E. Wiita, I. Almlöf, C. Kalderén, H. Axelsson, T. Djureinovic, J.C. Puigvert, M. Häggblad, F. Jeppsson, U. Martens, C. Lundin, B. Lundgren, I. Granelli, A.J. Jensen, P. Artursson, J.A. Nilsson, P. Stenmark, M. Scobie, U.W. Berglund, T. Helleday, MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool, Nature. advance online publication (2014). doi:10.1038/nature13181.

[95] K.V.M. Huber, E. Salah, B. Radic, M. Gridling, J.M. Elkins, A. Stukalov, A.-S. Jemth, C. Göktürk, K. Sanjiv, K. Strömberg, T. Pham, U.W. Berglund, J. Colinge, K.L. Bennett, J.I. Loizou, T. Helleday, S. Knapp, G. Superti-Furga, Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy, Nature. 508 (n.d.) 222–227. doi:10.1038/nature13194.

[96] U.W. Berglund, K. Sanjiv, H. Gad, C. Kalderén, T. Koolmeister, T. Pham, C. Gokturk, R. Jafari, G. Maddalo, B. Seashore-Ludlow, A. Chernobrovkin, A. Manoilov, I.S. Pateras, A. Rasti, A.-S. Jemth, I. Almlöf, O. Loseva, T. Visnes, B.O. Einarsdottir, F.Z. Gaugaz, A. Saleh, B. Platzack, O.A. Wallner, K.S.A. Vallin, M. Henriksson, P. Wakchaure, S. Borhade, P. Herr, Y. Kallberg, P. Baranczewski, E.J. Homan, E. Wiita, V. Nagpal, T. Meijer, N. Schipper, S.G. Rudd, L. Bräutigam, A. Lindqvist, A. Filppula, T.-C. Lee, P. Artursson, J.A. Nilsson, V.G. Gorgoulis, J. Lehtiö, R.A. Zubarev, M. Scobie, T. Helleday, Validation and development of MTH1 inhibitors for treatment of cancer, Ann. Oncol. (2016) mdw429. doi:10.1093/annonc/mdw429.

[97] S. Steenken, S.V. Jovanovic, How Easily Oxidizable Is DNA? One-Electron Reduction Potentials of Adenosine and Guanosine Radicals in Aqueous Solution, J. Am. Chem. Soc. 119 (1997) 617–618. doi:10.1021/ja962255b.

[98] S. Oka, M. Ohno, D. Tsuchimoto, K. Sakumi, M. Furuichi, Y. Nakabeppu, Two distinct pathways of cell death triggered by oxidative damage to nuclear and mitochondrial DNAs, EMBO J. 27 (2008) 421–432. doi:10.1038/sj.emboj.7601975.

[99] M. Ohno, K. Sakumi, R. Fukumura, M. Furuichi, Y. Iwasaki, M. Hokama, T. Ikemura, T. Tsuzuki, Y. Gondo, Y. Nakabeppu, 8-oxoguanine causes spontaneous de novo germline mutations in mice, Sci. Rep. 4 (2014). doi:10.1038/srep04689.

[100] S. Eshtad, Z. Mavajian, S.G. Rudd, T. Visnes, J. Boström, M. Altun, T. Helleday, hMYH and hMTH1 cooperate for survival in mismatch repair defective T-cell acute lymphoblastic leukemia, Oncogenesis. 5 (2016) e275. doi:10.1038/oncsis.2016.72.

[101] H. Dou, S. Mitra, T.K. Hazra, Repair of oxidized bases in DNA bubble structures by human DNA glycosylases NEIL1 and NEIL2, J Biol Chem. 278 (2003) 49679–84. doi:10.1074/jbc.M308658200.

[102] S.Z. Krokeide, J.K. Laerdahl, M. Salah, L. Luna, F.H. Cederkvist, A.M. Fleming, C.J. Burrows, B. Dalhus, M. Bjørås, Human NEIL3 is mainly a monofunctional DNA glycosylase removing spiroimindiohydantoin and guanidinohydantoin, DNA Repair. 12 (2013) 1159–1164. doi:10.1016/j.dnarep.2013.04.026.

[103] M. Liu, V. Bandaru, J.P. Bond, P. Jaruga, X. Zhao, P.P. Christov, C.J. Burrows, C.J. Rizzo, M. Dizdaroglu, S.S. Wallace, The mouse ortholog of NEIL3 is a functional DNA glycosylase in vitro and in vivo, Proc. Natl. Acad. Sci. 107 (2010) 4925–4930. doi:10.1073/pnas.0908307107.

[104] J. Hu, N.C. de Souza-Pinto, K. Haraguchi, B.A. Hogue, P. Jaruga, M.M. Greenberg, M. Dizdaroglu, V.A. Bohr, Repair of formamidopyrimidines in DNA involves different glycosylases: role of the OGG1, NTH1, and NEIL1 enzymes, J Biol Chem. 280 (2005) 40544–51. doi:10.1074/jbc.M508772200.

[105] P. Rai, T.T. Onder, J.J. Young, J.L. McFaline, B. Pang, P.C. Dedon, R.A. Weinberg, Continuous elimination of oxidized nucleotides is necessary to prevent rapid onset of cellular senescence, Proc. Natl. Acad. Sci. 106 (2009) 169–174. doi:10.1073/pnas.0809834106.

[106] A. Patel, D.G.A. Burton, K. Halvorsen, W. Balkan, T. Reiner, C. Perez-Stable, A. Cohen, A. Munoz, M.G. Giribaldi, S. Singh, D.J. Robbins, D.M. Nguyen, P. Rai, MutT Homolog 1 (MTH1) maintains multiple KRAS-driven pro-malignant pathways, Oncogene. 34 (2015) 2586. doi:10.1038/onc.2014.195.

[107] M.G. Giribaldi, A. Munoz, K. Halvorsen, A. Patel, P. Rai, MTH1 expression is required for effective transformation by oncogenic HRAS, Oncotarget. 6 (2015) 11519–11529.

[108] L. Li, L. Song, X. Liu, X. Yang, X. Li, T. He, N. Wang, S. Yang, C. Yu, T. Yin, Y. Wen, Z. He, X. Wei, W. Su, Q. Wu, S. Yao, C. Gong, Y. Wei, Artificial Virus Delivers CRISPR-Cas9 System for Genome Editing of Cells in Mice, ACS Nano. 11 (2017) 95–111. doi:10.1021/acsnano.6b04261.

[109] Y. Tu, Z. Wang, X. Wang, H. Yang, P. Zhang, M. Johnson, N. Liu, H. Liu, W. Jin, Y. Zhang, D. Cui, Birth of MTH1 as a therapeutic target for glioblastoma: MTH1 is indispensable for gliomatumorigenesis, Am. J. Transl. Res. 8 (2016) 2803–2811.

[110] K. Sakumi, Y. Tominaga, M. Furuichi, P. Xu, T. Tsuzuki, M. Sekiguchi, Y. Nakabeppu, Ogg1 knockout-associated lung tumorigenesis and its suppression by Mth1 gene disruption, Cancer Res. 63 (2003) 902–5.

[111] P. Rai, Oxidation in the nucleotide pool, the DNA damage response and cellular senescence: Defective bricks build a defective house, Mutat. Res. Toxicol. Environ. Mutagen. 703 (2010) 71–81. doi:10.1016/j.mrgentox.2010.07.010.
[112] T. Kawamura, M. Kawatani, M. Muroi, Y. Kondoh, Y. Futamura, H. Aono, M. Tanaka, K. Honda, H. Osada, Proteomic profiling of small-molecule inhibitors reveals dispensability of MTH1 for cancer cell survival, Sci. Rep. 6 (2016). doi:10.1038/srep26521.
[113] J.G. Kettle, H. Alwan, M. Bista, J. Breed, N.L. Davies, K. Eckersley, S. Fillery, K.M. Foote, L. Goodwin, D.R. Jones, H. Käck, A. Lau, J.W.M. Nissink, J. Read, J.S. Scott, B. Taylor, G. Walker, L. Wissler, M. Wylot, Potent and Selective Inhibitors of MTH1 Probe Its Role in Cancer Cell Survival, J. Med. Chem. 59 (2016) 2346–2361. doi:10.1021/acs.jmedchem.5b01760.
[114] A. Petrocchi, E. Leo, N.J. Reyna, M.M. Hamilton, X. Shi, C.A. Parker, F. Mseeh, J.P. Bardenhagen, P. Leonard, J.B. Cross, S. Huang, Y. Jiang, M. Cardozo, G. Draetta, J.R. Marszalek, C. Toniatti, P. Jones, R.T. Lewis, Identification of potent and selective MTH1 inhibitors, Bioorg. Med. Chem. Lett. 26 (2016) 1503–1507. doi:10.1016/j.bmcl.2016.02.026.
[115] M. Ellermann, A. Eheim, F. Rahm, J. Viklund, J. Guenther, M. Andersson, U. Ericsson, R. Forsblom, T. Ginman, J. Lindström, C. Silvander, L. Trésaugues, A. Giese, S. Bunse, R. Neuhaus, J. Weiske, M. Quanz, A. Glasauer, K. Nowak-Reppel, B. Bader, H. Irlbacher, H. Meyer, N. Queisser, M. Bauser, A. Haegebarth, M. Gorjánácz, Novel Class of Potent and Cellularly Active Inhibitors Devalidates MTH1 as Broad-Spectrum Cancer Target, ACS Chem. Biol. 12 (2017) 1986–1992. doi:10.1021/acschembio.7b00370.
[116] G. Sharbeen, J. Youkhana, A. Mawson, J. McCarroll, A. Nunez, A. Biankin, A. Johns, D. Goldstein, P. Phillips, MutY-Homolog (MYH) inhibition reduces pancreatic cancer cell growth and increases chemosensitivity, Oncotarget. 8 (2016) 9216–9229. doi:10.18632/oncotarget.13985.
[117] Z.M. Ramdzan, C. Vadnais, R. Pal, G. Vandal, C. Cadieux, L. Leduy, S. Davoudi, L. Hulea, L. Yao, A.N. Karnezis, M. Paquet, D. Dankort, A. Nepveu, RAS Transformation Requires CUX1-Dependent Repair of Oxidative DNA Damage, PLoS Biol. 12 (2014) e1001807. doi:10.1371/journal.pbio.1001807.
[118] S.H. Berger, D.L. Pittman, M.D. Wyatt, Uracil in DNA: consequences for carcinogenesis and chemotherapy, Biochem. Pharmacol. 76 (2008) 697–706. doi:10.1016/j.bcp.2008.05.019.
[119] N.J. Curtin, A.N. Hughes, Pemetrexed disodium, a novel antifolate with multiple targets, Lancet Oncol. 2 (2001) 298–306.
[120] A. Khodursky, E.C. Guzmán, P.C. Hanawalt, Thymineless Death Lives On: New Insights into a Classic Phenomenon, Annu. Rev. Microbiol. 69 (2015) 247–263. doi:10.1146/annurev-micro-092412-155749.
[121] T. Visnes, M. Akbari, L. Hagen, G. Slupphaug, H.E. Krokan, The rate of base excision repair of uracil is controlled by the initiating glycosylase, DNA Repair. 7 (2008) 1869–1881.
[122] B. Kavli, O. Sundheim, M. Akbari, M. Otterlei, H. Nilsen, F. Skorpen, P.A. Aas, L. Hagen, H.E. Krokan, G. Slupphaug, hUNG2 is the major repair enzyme for removal of uracil from U:A matches, U:G mismatches, and U in single-stranded DNA, with hSMUG1 as a broad specificity backup, J Biol Chem. 277 (2002) 39926–36.
[123] B. Doseth, T. Visnes, A. Wallenius, I. Ericsson, A. Sarno, H.S. Pettersen, A. Flatberg, T. Catterall, G. Slupphaug, H.E. Krokan, Uracil-DNA Glycosylase in Base Excision Repair and Adaptive Immunity SPECIES DIFFERENCES BETWEEN MAN AND MOUSE, J. Biol. Chem. 286 (2011) 16669–16680.
[124] P.M. Wilson, P.V. Danenberg, P.G. Johnston, H.-J. Lenz, R.D. Ladner, Standing the test of time: targeting thymidylate biosynthesis in cancer therapy, Nat. Rev. Clin. Oncol. 11 (2014) 282. doi:10.1038/nrclinonc.2014.51.
[125] A.M. Huehls, C.J. Huntoon, P.M. Joshi, C.A. Baehr, J.M. Wagner, X. Wang, M.Y. Lee, L.M. Karnitz, Genomically Incorporated 5-Fluorouracil that Escapes UNG-Initiated Base Excision Repair Blocks DNA Replication and Activates Homologous Recombination, Mol. Pharmacol. 89 (2016) 53–62. doi:10.1124/mol.115.100164.

[126] A.M. Huehls, J.M. Wagner, C.J. Huntoon, L. Geng, C. Erlichman, A.G. Patel, S.H. Kaufmann, L.M. Karnitz, Poly(ADP-Ribose) polymerase inhibition synergizes with 5-fluorodeoxyuridine but not 5-fluorouracil in ovarian cancer cells, Cancer Res. 71 (2011) 4944–4954. doi:10.1158/0008-5472.CAN-11-0814.
[127] D.R. McNeill, W. Lam, T.L. DeWeese, Y.C. Cheng, D.M. Wilson, Impairment of APE1 function enhances cellular sensitivity to clinically relevant alkylators and antimetabolites, Mol Cancer Res. 7 (2009) 897–906. doi:10.1158/1541-7786.MCR-08-0519.
[128] L. Geng, A.M. Huehls, J.M. Wagner, C.J. Huntoon, L.M. Karnitz, Checkpoint signaling, base excision repair, and PARP promote survival of colon cancer cells treated with 5-fluorodeoxyuridine but not 5-fluorouracil, PloS One. 6 (2011) e28862. doi:10.1371/journal.pone.0028862.
[129] B.P. Engelward, A. Dreslin, J. Christensen, D. Huszar, C. Kurahara, L. Samson, Repair-deficient 3-methyladenine DNA glycosylase homozygous mutant mouse cells have increased sensitivity to alkylation-induced chromosome damage and cell killing, EMBO J. 15 (1996) 945–952.
[130] S. Couvé-Privat, G. Macé, F. Rosselli, M.K. Saparbaev, Psoralen-induced DNA adducts are substrates for the base excision repair pathway in human cells, Nucleic Acids Res. 35 (2007) 5672–5682. doi:10.1093/nar/gkm592.
[131] S. Couvé, G. Macé-Aimé, F. Rosselli, M.K. Saparbaev, The human oxidative DNA glycosylase NEIL1 excises psoralen-induced interstrand DNA cross-links in a three-stranded DNA structure, J. Biol. Chem. 284 (2009) 11963–11970. doi:10.1074/jbc.M900746200.
[132] Z. Yang, M.I. Nejad, J.G. Varela, N.E. Price, Y. Wang, K.S. Gates, A role for the base excision repair enzyme NEIL3 in replication-dependent repair of interstrand DNA cross-links derived from psoralen and abasic sites, DNA Repair. 52 (2017) 1–11. doi:10.1016/j.dnarep.2017.02.011.
[133] D.R. Semlow, J. Zhang, M. Budzowska, A.C. Drohat, J.C. Walter, Replication-Dependent Unhooking of DNA Interstrand Cross-Links by the NEIL3 Glycosylase, Cell. 167 (2016) 498-511.e14. doi:10.1016/j.cell.2016.09.008.
[134] E.R. Jamieson, S.J. Lippard, Structure, Recognition, and Processing of Cisplatin-DNA Adducts, Chem. Rev. 99 (1999) 2467–2498.
[135] A. Sawant, A.M. Floyd, M. Dangeti, W. Lei, R.W. Sobol, S.M. Patrick, Differential role of base excision repair proteins in mediating cisplatin cytotoxicity, DNA Repair. 51 (2017) 46–59. doi:10.1016/j.dnarep.2017.01.002.
[136] D. Wang, D.-B. Xiang, X. Yang, L.-S. Chen, M.-X. Li, Z.-Y. Zhong, Y.-S. Zhang, APE1 overexpression is associated with cisplatin resistance in non-small cell lung cancer and targeted inhibition of APE1 enhances the activity of cisplatin in A549 cells, Lung Cancer. 66 (2009) 298–304. doi:10.1016/j.lungcan.2009.02.019.
[137] N. Yang, M.A. Chaudhry, S.S. Wallace, Base excision repair by hNTH1 and hOGG1: a two edged sword in the processing of DNA damage in gamma-irradiated human cells, DNA Repair Amst. 5 (2006) 43–51. doi:10.1016/j.dnarep.2005.07.003.
[138] Q. An, P. Robins, T. Lindahl, D.E. Barnes, 5-Fluorouracil incorporated into DNA is excised by the Smug1 DNA glycosylase to reduce drug cytotoxicity, Cancer Res. 67 (2007) 940–5. doi:10.1158/0008-5472.CAN-06-2960.
[139] H.E. Bryant, N. Schultz, H.D. Thomas, K.M. Parker, D. Flower, E. Lopez, S. Kyle, M. Meuth, N.J. Curtin, T. Helleday, Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase, Nature. 434 (2005) 913–917. doi:10.1038/nature03443.
[140] H. Farmer, N. McCabe, C.J. Lord, A.N.J. Tutt, D.A. Johnson, T.B. Richardson, M. Santarosa, K.J. Dillon, I. Hickson, C. Knights, N.M.B. Martin, S.P. Jackson, G.C.M. Smith, A. Ashworth, Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy, Nature. 434 (2005) 917. doi:10.1038/nature03445.
[141] Y. Kubota, R.A. Nash, A. Klungland, P. Schar, D.E. Barnes, T. Lindahl, Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein, EMBO J. 15 (1996) 6662–70.

[142] A. Klungland, T. Lindahl, Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1), EMBO J. 16 (1997) 3341–3348. doi:10.1093/emboj/16.11.3341.
[143] C.E. Ström, F. Johansson, M. Uhlén, C.A.-K. Szigyarto, K. Erixon, T. Helleday, Poly (ADP-ribose) polymerase (PARP) is not involved in base excision repair but PARP inhibition traps a single-strand intermediate, Nucleic Acids Res. 39 (2011) 3166–3175. doi:10.1093/nar/gkq1241.
[144] C.J. Lord, A. Ashworth, PARP inhibitors: Synthetic lethality in the clinic, Science. 355 (2017) 1152–1158. doi:10.1126/science.aam7344.
[145] M. Rouleau, A. Patel, M.J. Hendzel, S.H. Kaufmann, G.G. Poirier, PARP inhibition: PARP1 and beyond, Nat Rev Cancer. 10 (2010) 293–301. doi:10.1038/nrc2812.
[146] J. Murai, S.N. Huang, B.B. Das, A. Renaud, Y. Zhang, J.H. Doroshow, J. Ji, S. Takeda, Y. Pommier, Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors, Cancer Res. 72 (2012) 5588–5599. doi:10.1158/0008-5472.CAN-12-2753.
[147] T. Helleday, The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings, Mol. Oncol. 5 (2011) 387–393. doi:10.1016/j.molonc.2011.07.001.
[148] Y. Shen, M. Aoyagi-Scharber, B. Wang, Trapping Poly(ADP-Ribose) Polymerase, J. Pharmacol. Exp. Ther. 353 (2015) 446–457. doi:10.1124/jpet.114.222448.
[149] R. Sultana, D.R. McNeill, R. Abbotts, M.Z. Mohammed, M.Z. Zdzienicka, H. Qutob, C. Seedhouse, C.A. Laughton, P.M. Fischer, P.M. Patel, D.M. Wilson 3rd, S. Madhusudan, Synthetic lethal targeting of DNA double-strand break repair deficient cells by human apurinic/apyrimidinic endonuclease inhibitors, Int. J. Cancer J. Int. Cancer. 131 (2012) 2433–2444. doi:10.1002/ijc.27512.
[150] R. Sultana, T. Abdel-Fatah, R. Abbotts, C. Hawkes, N. Albarakati, C. Seedhouse, G. Ball, S. Chan, E.A. Rakha, I.O. Ellis, S. Madhusudan, Targeting XRCC1 deficiency in breast cancer for personalized therapy, Cancer Res. 73 (2013) 1621–1634. doi:10.1158/0008-5472.CAN-12-2929.
[151] S.A. Martin, N. McCabe, M. Mullarkey, R. Cummins, D.J. Burgess, Y. Nakabeppu, S. Oka, E. Kay, C.J. Lord, A. Ashworth, DNA polymerases as potential therapeutic targets for cancers deficient in the DNA mismatch repair proteins MSH2 or MLH1, Cancer Cell. 17 (2010) 235–248. doi:10.1016/j.ccr.2009.12.046.
[152] H. Sampath, Oxidative DNA damage in disease—Insights gained from base excision repair glycosylase-deficient mouse models, Environ. Mol. Mutagen. 55 (2014) 689–703. doi:10.1002/em.21886.
[153] U. Hardeland, C. Kunz, F. Focke, M. Szadkowski, P. Schar, Cell cycle regulation as a mechanism for functional separation of the apparently redundant uracil DNA glycosylases TDG and UNG2, Nucleic Acids Res. 35 (2007) 3859–67. doi:10.1093/nar/gkm337.
[154] D. Cortázar, C. Kunz, J. Selfridge, T. Lettieri, Y. Saito, E. MacDougall, A. Wirz, D. Schuermann, A.L. Jacobs, F. Siegrist, R. Steinacher, J. Jiricny, A. Bird, P. Schär, Embryonic lethal phenotype reveals a function of TDG in maintaining epigenetic stability, Nature. 470 (2011) 419–423. doi:10.1038/nature09672.
[155] C. Kunz, F. Focke, Y. Saito, D. Schuermann, T. Lettieri, J. Selfridge, P. Schar, Base excision by thymine DNA glycosylase mediates DNA-directed cytotoxicity of 5-fluorouracil, PLoS Biol. 7 (2009) e91. doi:10.1371/journal.pbio.1000091.
[156] S. Boiteux, M. Guillet, Abasic sites in DNA: repair and biological consequences in Saccharomyces cerevisiae, DNA Repair. 3 (2004) 1–12.
[157] A. Collura, P.A.V.D. Kemp, S. Boiteux, Abasic sites linked to dUTP incorporation in DNA are a major cause of spontaneous mutations in absence of base excision repair and Rad17-Mec3-Ddc1 (9-1-1) DNA damage checkpoint clamp in Saccharomyces cerevisiae, DNA Repair. 11 (2012) 294–303. doi:10.1016/j.dnarep.2011.12.004.
[158] J.K. Horton, D.F. Joyce-Gray, B.F. Pachkowski, J.A. Swenberg, S.H. Wilson, Hypersensitivity of DNA polymerase beta null mouse fibroblasts reflects accumulation of cytotoxic repair intermediates from site-specific alkyl DNA lesions, DNA Repair Amst. 2 (2003) 27–48.

[159] R.W. Sobol, M. Kartalou, K.H. Almeida, D.F. Joyce, B.P. Engelward, J.K. Horton, R. Prasad, L.D. Samson, S.H. Wilson, Base excision repair intermediates induce p53-independent cytotoxic and genotoxic responses, J Biol Chem. 278 (2003) 39951–9. doi:10.1074/jbc.M306592200.
[160] J.A. Calvo, C.A. Moroski-Erkul, A. Lake, L.W. Eichinger, D. Shah, I. Jhun, P. Limsirichai, R.T. Bronson, D.C. Christiani, L.B. Meira, L.D. Samson, Aag DNA glycosylase promotes alkylation-induced tissue damage mediated by parp1, PLoS Genet. 9 (2013) e1003413. doi:10.1371/journal.pgen.1003413.
[161] D. Fu, J.A. Calvo, L.D. Samson, Balancing repair and tolerance of DNA damage caused by alkylating agents, Nat. Rev. Cancer. 12 (2012) 104–120. doi:10.1038/nrc3185.
[162] L.B. Meira, C.A. Moroski-Erkul, S.L. Green, J.A. Calvo, R.T. Bronson, D. Shah, L.D. Samson, Aag-initiated base excision repair drives alkylation-induced retinal degeneration in mice, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 888–893. doi:10.1073/pnas.0807030106.
[163] N.M. Leguisamo, H.C. Gloria, A.N. Kalil, T.V. Martins, D.B. Azambuja, L.B.` Meira, J. Saffi, N.M. Leguisamo, H.C. Gloria, A.N. Kalil, T.V. Martins, D.B. Azambuja, L.B.` Meira, J. Saffi, Base excision repair imbalance in colorectal cancer has prognostic value and modulates response to chemotherapy, Oncotarget. 5 (2017). doi:10.18632/oncotarget.14909.
[164] F. Grasso, V. Ruggieri, G. De Luca, P. Leopardi, M.T. Mancuso, I. Casorelli, P. Pichierri, P. Karran, M. Bignami, MUTYH mediates the toxicity of combined DNA 6-thioguanine and UVA radiation, Oncotarget. 6 (2015) 7481–7492. doi:10.18632/oncotarget.3037.
[165] T. Coquerelle, J. Dosch, B. Kaina, Overexpression of N-methylpurine-DNA glycosylase in Chinese hamster ovary cells renders them more sensitive to the production of chromosomal aberrations by methylating agents--a case of imbalanced DNA repair, Mutat Res. 336 (1995) 9–17.
[166] M. Rinne, D. Caldwell, M.R. Kelley, Transient adenoviral N-methylpurine DNA glycosylase overexpression imparts chemotherapeutic sensitivity to human breast cancer cells, Mol Cancer Ther. 3 (2004) 955–67.
[167] Y. Yoshikawa, A. Yamasaki, K. Takatori, M. Suzuki, J. Kobayashi, M. Takao, Q.-M. Zhang-Akiyama, Excess processing of oxidative damaged bases causes hypersensitivity to oxidative stress and low dose rate irradiation, Free Radic. Res. 49 (2015) 1239–1248. doi:10.3109/10715762.2015.1061186.
[168] Y. Canitrot, C. Cazaux, M. Frechet, K. Bouayadi, C. Lesca, B. Salles, J.S. Hoffmann, Overexpression of DNA polymerase beta in cell results in a mutator phenotype and a decreased sensitivity to anticancer drugs, Proc Natl Acad Sci U A. 95 (1998) 12586–90.
[169] K.L. Limpose, K.S. Trego, Z. Li, S.W. Leung, A.H. Sarker, J.A. Shah, S.S. Ramalingam, E.M. Werner, W.S. Dynan, P.K. Cooper, A.H. Corbett, P.W. Doetsch, Overexpression of the base excision repair NTHL1 glycosylase causes genomic instability and early cellular hallmarks of cancer, Nucleic Acids Res. (n.d.). doi:10.1093/nar/gky162.
[170] A. Galashevskaya, A. Sarno, C.B. Vågbø, P.A. Aas, L. Hagen, G. Slupphaug, H.E. Krokan, A robust, sensitive assay for genomic uracil determination by LC/MS/MS reveals lower levels than previously reported, DNA Repair. 12 (2013) 699–706. doi:10.1016/j.dnarep.2013.05.002.
[171] Q. An, P. Robins, T. Lindahl, D.E. Barnes, C --> T mutagenesis and gamma-radiation sensitivity due to deficiency in the Smug1 and Ung DNA glycosylases, EMBO J. 24 (2005) 2205–13. doi:10.1038/sj.emboj.7600689.