Targeting the DNA Damage Response in Cancer

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Contents

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1. Introduction

U.S. general Ulysses S. Grant once said: *"The art of war is simple enough. Find out where your enemy is. Get at him as soon as you can. Strike him as hard as you can."* The decision-makings of military generals are similar to the decision-makings of oncologists weighing different options in the battle against tumors threatening their patients. Early cancer detection is crucial, and the choice of therapy is vitally important to obtain tumor control. If the tumor is not defeated up front, it most likely will come back more aggressive than before. We are at an important crossroad in cancer research and clinical oncology where we should consider bold new strategies for cancer treatment. Great advances have been made mapping out the cellular pathways altered in tumors[1−3] and the pathways that respond to cancer therapeutics.[4−7] The obvious importance of the components of DNA damage response pathways as potential cancer therapeutic targets has stimulated researchers and pharmaceutical companies to develop numerous chemical inhibitors for many of the proteins involved in these pathways[7] (Tables 1−4).

Proteins and pathways involved in the DNA damage response have, in this review, been grouped into four functional groups, namely, DNA repair, DNA repair accessory functions, DNA damage signaling, and cell survival. Furthermore, compounds or drugs known to inhibit these targets are listed in Tables 1−4. Whether inactivation of these targets preferentially sensitizes cancer cells to DNA-damaging therapeutics is not known for most of these agents, and future studies need to be conducted to assess whether these agents actually increase the therapeutic window of a particular treatment. A favorable therapeutic window for a systemic treatment is achieved if a particular tumor is preferentially sensitized to a treatment based on dependence or "addiction" to a particular DNA repair system, DNA damage signaling protein or survival factor. For a targeted treatment, such as radiation, an enhanced therapeutic window may be more successfully achieved because inhibition of the DNA damage response will preferentially sensitize cells in the field of radiation. The development of new drugs for the targeting of the DNA damage response is a very active field of research and one of considerable interest to pharmaceutical companies. Because of the rapid pace of basic science discovery and drug development in this area, the lists of potential therapeutic DDR targets and corresponding inhibitors are by no means fully comprehensive. I apologize in advance for overlooking many important contributions to this field.

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Mats Ljungman was born in Sweden. In 1979 he went to Murray State University in Kentucky on a tennis scholarship and received his undergraduate degree in 1983. He then returned to Sweden where he worked in the lab of Dr. Gunnar Ahnström at Stockholm University and received his Ph.D. degree in 1990. He then got the opportunity to perform postdoctoral studies in the lab of Dr. Phil Hanawalt at Stanford University before accepting a faculty position at the University of Michigan in 1994. He is now an Associate Professor in Radiation Oncology at the University of Michigan. The research in Dr. Ljungman's lab is focused on studying cellular DNA damage responses and how to use this knowledge to develop better therapies for cancer treatment.

2. Targeting DNA Repair Pathways

The anticancer activities of radiation therapy and many chemotherapeutic agents rely on the cytotoxic consequences of DNA damage. The cytotoxicity of DNA damage is primarily a manifestation of its inhibitory action on vital cellular processes such as transcription and replication.[8−10] Some tumor cells may have acquired DNA repair defects during carcinogenesis because loss of DNA damage surveillance contributes to a hypermutable phenotype that drives early tumor development.[11,12] Tumor-specific defects in DDR present a unique opportunity for cancer-specific therapies (see section 6). However, most cancer cells would be expected to have proficient DNA repair pathways, and thus, therapeutic targeting of specific components of DNA repair pathways in cancer cells should enhance the efficacy of anticancer treatments.

2.1. DNA Double-Strand Break Repair

DNA double-strand breaks (DSBs) are considered the most important type of lesion for the biological effect of ionizing radiation.[13] Radiation-induced DSBs are repaired by nonhomologous end joining (NHEJ) or by homologous recombination (HR).[14] The components of these repair pathways as well as factors influencing DSB repair are of considerable interest as potential therapeutic targets for radiosensitization (Figure 1). The DNA-dependent protein kinase (DNA-PK) plays an important role in the NHEJ pathway, and a number of chemical compounds have been developed that specifically target its kinase activity or expression level (Table 1). These inhibitors significantly radiosensitize cells, but whether cancer cells are specifically sensitized is not obvious since normal cells exposed to the radiation treatment rely on this repair pathway as well, so the true therapeutic usefulness of these compounds needs to be further explored. However, because of the focused delivery of radiation to the tumor, targeting of DNA repair proteins would lead to a selective killing of cancer cells in the irradiated field. Other DSB repair factors that could be therapeutically targeted include KU, RAD51, DNA ligase IV, and BRCA2 (Table 1). Current and future clinical trials combining inhibitors of DSB repair with radiotherapy have great potential to impact patient care.

2.2. Base Excision Repair and Methyl Transferase

The base excision repair (BER) pathway is utilized by cells to repair base lesions and single-strand breaks induced in the DNA template by oxidative and alkylating agents from both endogenous and exogenous sources.[13] Inhibition of the enzyme APE1/REF-1 involved in the BER pathway sensitizes cancer cells to alkylating agents[15−17] (Figure 1, Table 1). Another protein important for resistance to alkylating agents is the methyl guanine methyl transferase (MGMT), which removes potentially mutagenic O(6)-methyl groups from guanine bases in DNA via a direct reversal mechanism.[7,18−20] The specific MGMT inhibitors O(6)benzylguanine and lomeguatrib have been shown to efficiently enhance the sensitivity of cancer cells to alkylating agents such as 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)[18] and Temozolomide.[7,19] Furthermore, tamoxifen has been shown to target MGMT via proteasome-mediated degradation.[20] Although it would appear that combining tamoxifen with alkylating agents would be a promising treatment, clinical trials combining these two treatment modalities have shown mixed results.[21,22]

2.3. Nucleotide Excision Repair

The nucleotide excision repair (NER) pathway evolved primarily to deal with DNA-distorting lesions induced by ultraviolet light (UV).[13] However, this repair pathway also repairs lesions induced by many chemotherapeutic agents such as cisplatin. Recently it was shown that the EGFR inhibitor cetuximab sensitizes cancer cells to oxaliplatin by reducing the expression of two key components of NER, namely, XPF[23] and ERCC1.[24] High levels of ERCC1 expression correlate to resistance to cisplatin,[25] and conversely, tumors with low levels of ERCC1 are more sensitive to cisplatin.[26,27] Thus, cetuximab and similar EGFR-targeting drugs may have dual anticancer uses by both inhibiting EGFR-mediated tumor growth and interfering with NER, resulting in sensitization to cisplatin compounds. Another drug that has been shown to sensitize cells to cisplatin by interfering with protein−protein interactions among NER proteins is the CHK1 inhibitor UCN-1.[28]

2.4. Replication and DNA Repair Synthesis

DNA polymerase α, δ, and ε are considered to be the main enzymes synthesizing nuclear DNA during replication, nucleotide excision repair, and mismatch repair, while DNA polymerase β has a specialized function during base excision repair.[29] There are many DNA polymerase inhibitors available (Table 1), and these compounds may have some utility in cancer treatment by selectively targeting proliferating cells. Since these polymerases also play crucial roles during NER and BER, combining these inhibitors with DNA damaging agents may be advantageous. Indeed, inhibitors of DNA polymerase α abrogate nucleotide excision repair[30,31] and increase cell death when combined with cisplatin,[32,33] while inhibitors of DNA polymerase β sensitize cancer cells to alkylating agents such as Temozolomide[34] and, surprisingly, cisplatin.[35]

Table 1. Targeting DNA Repair Proteins

Target	Function	Inhibitor
DNA-PK	DNA-dependent protein kinase; nonhomologous end joining; DNA damage signaling	Vanillin,[474] OK-1035,[475] NU7026[65,476] NU7441,[477,478] IC87361,[479] IC87102,[422] Phenylbutyrate,[480] Cetuximab,[481] SU11752,[422] Salvicine[422]
KU	nonhomologous end joining	LAQ-824,[482] Vorinostat,[149] Flavopiridol[483]
RAD51	homologous recombination repair	Erlotinib,[82] Gefitinib,[484,485] LAQ-824,,[482] Flavopiridol,[486] PCI-2478,[487] Imatineb,[488,489] MG-132[123]
DNA ligase IV	nonhomologous end joining	L189[490]
BRCA2	Fanconi anemia DNA damage response pathway and DSB repair	17-AAG,[491] O(6)benzylguanine[492]
APE1	Endonuclease; base excision repair	Methoxyamine,[15,493] NCA,[15] Lucanthone,[15,494] Resveratrol,[15] E3330,[16,17] CRT0044876[495]
MGMT	O(6) metylguanine methyl transferase	O(6)benzylguanine,[18,493] Tamoxifen,[20] Lomeguatrib (PaTrin-2)[496,497]
ERCC1	nucleotide excision repair; cisplatin resistance	Cetuximab,[23,24] UCN-01[28]
XPF	nucleotide excision repair; cisplatin resistance	Cetuximab[23]
DNA polymerase α	DNA synthesis; replication and DNA repair (NER)	Aphidicolin,[498] 3-deoxyaphidicolin,[499] Aphidicolin-17-monoacetate,[499] Aphidicolin glycinate (AG; NSC 303812),[33] Dehydroaltenusin (C-12),[500,501] SQAGs,[502] Pyridoxal 5′-phosphate,[503] KAG,[504] Galactosyldiacylglycerol,[505] HMI,[506] KM043,[507] BuPdGTP,[508,509] araC,[510] Beta-lapachone,[511] Butylanilinouracil[512]
DNA polymerase β	DNA synthesis; base excision repair (BER)	SQAGs[502] Myristinin,[513] Masticadienonic acid (MA),[35] dFTTP,[514] KM043,[507] Prunasin,[515] Harbinatic acid,[516] araC,[510,517] Solanapyrone A,[518] Nervonic acid,[519] Taurospongin A,[520] Pamoic acid,[521,522] Lithocholic acid,[523] Kohamaic acid[524]
DNA polymerase δ	DNA synthesis; replication and NER	Aphidicolin,[525] Carbonyldiphosphonate[526]
DNA polymerase eta	translesion DNA polymerase	Pyrene nucleotide, [38] OXT-GTP, [39] OXT-ATP, [39] MG-132, [41] Lactacystin[41]

Table 2. Targeting DNA Repair Accessory Factors

Target	Function	Inhibitor
PARP	ribosylates proteins; promotes increased DNA accessibility in chromatin	ABT-888[527,528,422] BSI-201,[7] AG-14361,[65] AG014699,[7,529] INO-1001,[7,530,531] AZD-2281,[7,420,532] 3-aminobenzamide,[60,69,70] NU1025,[67] NU1064,[67] Phen,[66]
Fanconi anemia (FA)	the FA pathway coordinates repair of ICLs and homologous recombination	Phenylbutyrate[81] Wortmannin,[79] H-9,[79] Alsterpaullone,[79] Curcumin[79]
BRCA1	scaffolding protein coordinating DNA repair and cell cycle checkpoints	Erlotinib[82] LAQ-824,[482] Phenylbutyrate[81]
Ribonucleotide reductase (R1)	maintains a balanced supply of dNTPs needed for replication and DNA repair	Hydroxyurea[533] Gemcitabine,[94,534,535] Fludarabine,[536] Cladribine,[537] Clofarabine,[538] DMDC,[94] Caracemide,[539] Tezacitabine,[540] Triapine,[94,541] GTI-2040,[94] Didox,[542] Cisplatin[543]
Thymidylate synthase (TS)	synthesizes precursors for DNA synthesis	5-fluorouracil (5-FU)[544] Methotrexate,[545] Nolatrexed,[546] ZD9331,[547] ZD1694 (tomudex, raltiterxed),[548] OSI-7904 L,[88] Gefitinib,[549] BGC945,[550,551] Trichostatin A,[552] CB3717,[553,554] ICI D1694,[555] ITP,[556] 1843U89,[557,558] FdCMP,[559] LY231514,[560] AG337 (thymitaq),[561,562] CB30900,[563] CB300638[564]
p53R2	p53-inducible ribonucleotide reductase; enhances DNA repair	Triapine[94] Hydroxyurea,[94] Trimidox,[94] Didox,[94] DFO,[94] PIH,[94] 311,[94] Nitric oxide,[94] Alkoxyphenols[565]
proteasome	protein complex degrading proteins target with ubiquitin chains	ALLnL[118] MG-132,[566] Bortezomib (PS-341),[567,568] Lactacystin,[569] Epoxomycin,[570] CEP1612,[571] Ritonavir,[572] TP-110,[573] PR-171,[574] Physalin B,[575] TMC-95A,[114] Salinosporamide,[114,115] Cinnabaramide,[114] Homobelactosin,[114] PS-519,[114] Syringolin A,[114] Fellutaminde,[114] Aclacinomycin A,[113] Eponemycin,[113] NLVS,[113] Hypericin,[576] Carfilzomib,[115,577] Pristimerin,[578] CEP-18770,[579] S-2209[580]

Table 3. Targeting DNA Damage Signaling Proteins

Target	Function	Inhibitor
ATM	sensor of DSB/chromatin alterations and is a signal transducer; over 700 phosphorylation substrates known	KU55933[143,581] CP466722,[144] CGK 733,[164] Caffeine,[159] 17MAG,[366] 17DMAG,[370] TPA[582]
ATR	has an essential role during replication; sensor of blockage of replication and transcription	CGK 733,[164] Caffeine[159]
MRN complex	consists of Mre11, NBS, and Rad50 and is involved in the activation of ATM/ATR, cell cycle arrest, and DSB repair	Mirin,[146] Vorinostat,[149] 17MAG[366]
CHK1	has an essential role during replication; is activated by ATR by replication stress and induces intra-S and G_2/M cell cycle arrests	UCN-01[179,184,187] XL844,[186,187] Staurosporin,[184] PF-00477736,[187,583] AZD7762,[187,191] Go6976,[184] SB-218078,[184,584] ICP-1,[184] CEP-3891,[177,184] A-690002,[175] A-641397,[175] 17-AAG,[368] Geldanamycin,[369] 17DMAG[370]
CHK2	promotes but may not be required for intra-S and G2 checkpoints; promotes IR-induced p53-dependent apoptosis; thus, may not be suitable therapeutic target when combined with IR	UCN-01[180] XL844,[186] PF-00477736,[583] AZD7762,[191] CEP-6367,[184] NSC 109555[585]
p53	induces genes involved in DNA repair, cell cycle arrest, and apoptosis; direct role in repair and apoptosis	*inhibitor:* Pifitherin-α,[235] *activators:* Nutlins,[221,586] Prima-1,[207] RITA,[587] MI-219[224]

Translesion DNA polymerases (or bypass DNA polymerases) belong to a group of "emergency" polymerases that can replace replication DNA polymerases that have become blocked at lesions in the DNA template.[29] These bypass DNA polymerases promote chemotherapy tolerance in proliferating cells and could thus be considered as potential therapeutic targets.[36,37] Furthermore, since these bypass polymerases have low fidelity resulting in an increased burden of mutations, inactivation of these polymerases during chemotherapy may lower the risks of developing therapy-induced secondary tumors. The active sites of the translesion DNA polymerases are structurally quite different from the active sites of the classical replication polymerases,[29] and therefore, there is a great opportunity here to develop specific small molecule inhibitors. Compounds such as pyrene nucleotide analogues[38,39] have been shown to preferentially inhibit the function of translesion DNA polymerases and cause chain termination (Table 1). Interestingly, proteasome activity appears to be needed for efficient translesion DNA synthesis[40] and proteasome inhibitors have been shown to abrogate translesion DNA synthesis in cancer cells but, surprisingly, not in normal cells, following exposure to UV light or cisplatin.[41]

2.5. Hijacking DNA Repair Enzymes

Transcription-coupled repair (TCR) is a subpathway of NER preferentially removing transcription-blocking lesions from the DNA template.[42] Defects in this pathway enhance apoptosis induced by UV light[9,43] and cisplatin.[44] The anticancer drugs irofulven[45−47] and ecteinascidin 743 (Et743)[48−51] have been shown to cause cytotoxicity in a TCR-dependent manner in human cancer cells. Thus, the cytotoxicity of these drugs depends on an intact DNA repair pathway. Irofulven has also been shown to synergize with cisplatin[52−54] and gemcitabine[55,56] both in *in vitro* and *in vivo* tumor models. Thus, this class of drugs triggers a TCR response leading to the induction of DNA damage, but whether the actions of these drugs are tumor-selective needs further evaluation. Another approach that "hijacks" DNA repair enzymes is to introduce short DNA molecules that mimic DNA double-strand breaks. It was recently shown that these short DNA molecules, called Dbait for DSB bait, activated a full DNA damage response in cell cultures as well as *in vivo*.[57] Dbait reduced repair of radiation-induced damage and radiosensitized cells in culture. Importantly, Dbait in combination with fractionated radiation significantly enhanced the therapeutic effect in reducing the size of human xenografts in mice.[57]

3. Targeting DNA Repair Accessory Factors

3.1. PARP1

Poly(ADP-ribose)polymerase 1 (PARP1) is an abundant nuclear protein playing various roles in the sensing and repair of DNA single-strand breaks.[58] PARP1 is activated by DNA breaks within seconds[59] and ribosylates numerous target proteins such as histones, topoisomerase I, and itself. It is also thought that the activation of PARP1 is important for the completion of BER,[60] the recruitment of the MRN complex to DNA damage sites,[59] and the activation of ATM.[61]

Because of the central role of PARP1 in the sensing and repair of DNA breaks, there is a lot of interest in targeting PARP in cancer treatment.[7,62−64] PARP inhibitors have been shown to be especially useful when combined with radiation or chemotherapy[7,65−70] (Table 2). Since there are multiple members of the PARP family with overlapping functions, it may be necessary to simultaneously inhibit multiple PARP members to fully sensitize cancer cells to radiation or chemotherapy.[71] Cancer cells with defective homologous recombination are explicitly sensitive to PARP inhibitors (see section 6.1).

3.2. BRCA1/Fanconi

The BRCA1 and Fanconi anemia proteins function in a DNA damage response network important for interstrand DNA cross-link processing and homologous recombination.[72,73] Inhibition of the BRCA1/Fanconi pathway sensitizes cells to agents inducing interstrand DNA cross-links such as cisplatin, mitomycin C, and photoactivated psoralen as well as to IR and DNA synthesis inhibitors requiring homologous recombination for its resolution.[74−79] For these reasons the

Table 4. Targeting Cell Survival Proteins and Pathways

Target	Function	Inhibitor
BCL-2	antiapoptotic factor	Flavopiridol,[588,589] NS398,[590] HA14-1,[591] ABT-263,[592] ABT-737,[593] (−)-Gossypol,[594] TW-37,[595] Apogossypolone,[596,597] GX15−070,[250] Tetrocarcin A,[598] LAQ824[599]
BCL-XL	antiapoptotic factor	Flavokawain A[600] Sodium butyrate,[601] Phenylbutyrate,[480] ABT-263,[592] ABT-737,[593] (−)-Gossypol,[594] TW-37,[595] Apogossypolone,[596,597] GX15−070,[250] LAQ824,[599] Curcumin[602]
MCL1	antiapoptotic factor with a fast turnover rate	TW-37[595] Apogossypolone,[596,597] GX15−070,[250] Roscovitine,[603] Flavopiridol,[604] Leptomycin B[605]
Survivin	antiapoptotic factor	Flavokawain A[600] YM155,[606] SPC3042,[607] Gambogic acid,[251] Infliximab,[608] Farnesylthiosalicylic acid,[609] LAQ824,[599] Sodium butyrate,[610] Flavopiridol[611]
XIAP	antiapoptotic factor	Morusin[612] Flavokawain A,[600] Compound 21,[613] LAQ824,[599,614] sodium butyrate,[610] AEG 35156,[615] Embelin,[616] Roscovitine,[603] Flavopiridol,[604,611] Leptomycin B,[605] Luteolin[617]
EGFR	epidermal growth factor receptor/tyrosine kinase	Gefitinib[618] Lapatinib (GW572016),[619] BIBW2992,[272] PD153035,[620] AG1478,[621] Vandetanib (ZD6474),[275,622] HKI-272,[623] Erlotinib,[82,624] Cetuximab[23,481]
PI3K	kinase promoting cell proliferation and survival	Wortmannin,[625] LY294002,[626] BAG956,[287] NVP-BEZ235,[627] Deguelin,[289,628] Luteolin[617]
AKT	kinase activated by PI3Ks promoting cell proliferation and survival	Deguelin,[289,628] API-2,[629] Perifosine,[630,631] 3-isoquinolinylpyridine 13a,[294] Celecoxib,[296] GSK690693,[632] A-443654,[633] Luteolin,[617] TAE226,[634] SH-5[300]
mTOR	kinase responding to nutrient levels and promotes cell proliferation and survival	Rapamycin,[309,635] Temsirolimus (CCI-779),[309,636] Evirolimus (RAD-001),[309] Deforolimus (AP23573),[309] TAE226,[634] NVP-BEZ235,[627]
COX-2	promotes proliferation and survival; induces VEGF; radioresistance	NS-398,[590,637,638] Celecoxib,[318,322] Meloxicam, CAY10404,[639] SC236,[324] Etoricoxib,[318] Lumiracoxib,[318] Resveratrol[640]
VEGF	vascular endothelial growth factor; promotes angiogenesis	PTK787/ZK 222584,[641] Bevacizumab,[642,643] Axitinib (AG-013736),[644] Sunitinib,[645] Cediranib (AZD2171),[338,339,646] Pazopanib,[339,647] Endostatin,[340,648] Sorafenib,[649] Phenylbutyrate,[480] Vandetanib[275,622]
NF-kB	transcription factor that promotes growth and survival	Bay11-7082,[650] Resveratrol,[640,651] PDTC,[652] CAPE,[653] GS143,[654] Curcumin,[602] Celecoxib,[655] Phenylbutyrate,[656] PS-1145,[657] BMS-345541,[658] Quinacrine,[659] Morusin,[612] MG-132,[660] Luteolin,[617] CBLB502 (activator)[358]
heat-shock proteins hsp90	protein chaperone	Geldanamycin,[373,661] 17-AAG,[373,662] 17-DMAG,[366,370,663] SNX-2112 (5422),[664,665] Gedunin,[666] STA-9090,[667] NVP-AUY922,[665,668] Macbecin,[669] CNF2024,[665] Tanespimycin,[665] IPI-504,[665] Cisplatin,[670] Novobiocin,[670] EGCG[670]
Notch	signaling pathway important for embryonic development and maintenance of stem cells	GSI,[383,671,672] DAPT,[673] Curcumin,[674]
Hedgehog	signaling pathway important for embryonic development and maintenance of stem cells	Cyclopamine,[675,676] KAAD-cyclopamine,[392] Jervine,[392] SANT1−4,[392] CUR-61414,[677] 2-amino-thiazole,[392] IPI-269609,[678] HhAntag,[402] GDC-0449 (HhAntag691),[679]
WNT/β-catenin	signaling pathway important for embryonic development and maintenance of stem cells	FH535,[680] Quercetin,[681] ICG-001,[682] PKF115−584,[683] FJ9,[684] Hexachlorophene,[685] Endostatin,[686] Celecoxib,[687] Indomethacin,[687] Resveratrol,[687] SC-560,[687] Decursin,[688] Artesunate,[689] Curcumin[690]

BRCA1/Fanconi pathway is an attractive therapeutic target in cancer[80] (Table 2). The level of BRCA1 protein can be reduced in cells by the histone deacetylase inhibitor phenylbutyrate.[81] Furthermore, BRCA1 is sequestered to the cytoplasm of cells by treatment with the EGFR inhibitor erlotinib.[82] A screen for small-molecule inhibitors of the Fanconi anemia pathway revealed three protein kinase inhibitors as well as the natural compound curcumin.[79] It will be of interest to follow how well these inhibitors of the BRCA1/Fanconi anemia pathway will work in the clinic in combination with radiation and/or DNA cross-linkers.

3.3. Thymidylate Synthase

Thymidylate synthase (TS) plays an essential role in DNA replication and repair by synthesizing the precursor dTMP. TS is often found overexpressed in various malignancies, and it has been suggested that TS overexpression promotes

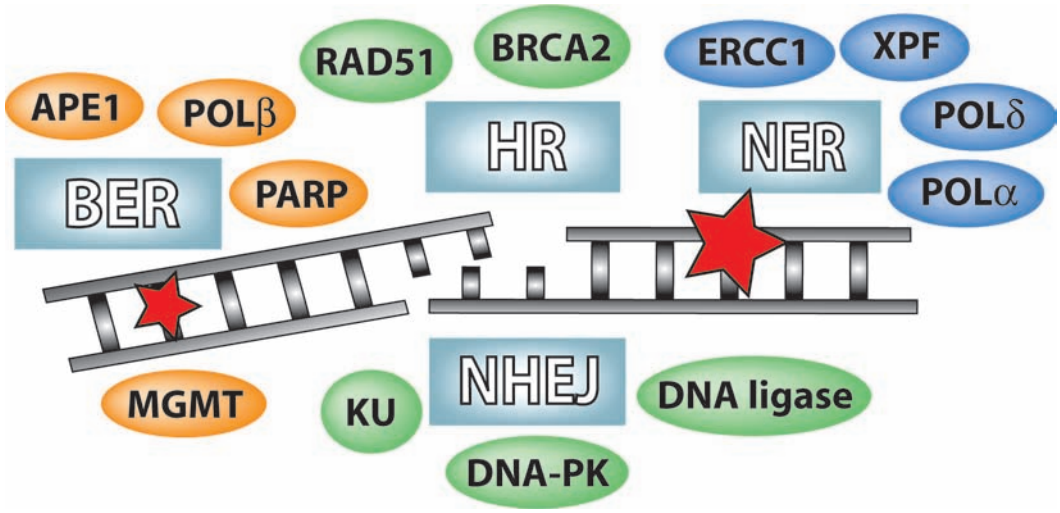

Figure 1. DNA repair as a therapeutic target. Ionizing radiation induces single- and double-strand DNA breaks as well as many types of base lesions. Base lesions and single-stranded breaks are subjected to base excision repair (BER). Drugs targeting APE1, Polβ, or PARP (Tables 1 and 2) reduce the efficiency of BER and make cells more sensitive to IR and alkylating drugs such as Temozolomide. Inhibition of the methyl transferase MGMT will also sensitize cells to alkylating agents. The most toxic lesions induced by IR are double-strand breaks (DSBs), which are repaired by either homologous recombination (HR) or nonhomologous end joining (NHEJ). Tumor cells can be sensitized to IR by inhibition of components of these pathways such as RAD51, BRCA2, KU, DNA-PK, and DNA ligase (Table 1). Finally, inactivation of components of the nucleotide excision repair (NER), such as ERCC1, XPF, Pol δ, and Pol α (Table 1), makes cells more sensitive to cisplatin and similar chemotherapeutic drugs.

cell proliferation[83] and resistance to radiation.[84] Interestingly, TS has been found to inhibit the translation of p53 mRNA, effectively suppressing p53 functions.[85,86] The role of TS in DNA synthesis, suppression of p53 function, dysregulation of cell cycle control, and the fact that TS is upregulated in many cancers makes TS an interesting therapeutic target. Many inhibitors of TS, such as 5-fluorouracil, have been developed (Table 2), and these inhibitors have been used in the clinic for decades to treat advanced colorectal cancers.[87−90] Importantly, TS inhibitors sensitize cancer cells to cisplatin[91] and radiation,[92] which may be due to the inhibition of DNA repair synthesis and suppression of p53 function, leading to abrogation of DNA repair and cell cycle arrest.

3.4. Ribonucleotide Reductase

The multisubunit enzyme ribonucleotide reductase (RR) catalyzes the reduction of ribonucleotides into their corresponding deoxyribonucleotides, which are building blocks for DNA synthesis.[93] Inhibition of RR has severe impact on DNA replication and DNA repair, and this has driven the development of a number of potent RR inhibitors (Table 2).[94,95] The RR inhibitor gemcitabine is currently used to treat a number of malignancies such as pancreatic[96] and breast cancer.[97] Gemcitabine is a powerful radiosensitizer,[98,99] and recent attempts to combine gemcitabine with inhibitors of EGFR and CHK1 to further radiosensitize tumors are promising.[100]

A p53-inducible ribonucleotide reductase, p53R2, has been shown to play an important role in supplying deoxyribonucleotides for DNA repair synthesis.[101−103] The expression of p53R2 has been found to be upregulated in various types of cancers,[104] and this upregulation has been found to correlate with advanced stage and invasion of tumors.[105−109] However, in colon cancer, p53R2 expression appears to suppress metastasis.[110] A number of inhibitors have been developed to target p53R2 (Table 2),[94,95] and inhibition of p53R2 results in sensitization to both radiation[111] and chemotherapeutic agents by the attenuation of cell cycle checkpoints and enhanced apoptosis.[104,112]

3.5. Proteasome

The ubiquitin-proteasome pathway operates as a "vacuum cleaner", regulating protein turnover in cells.[113] It is not obvious that the proteasome with its essential protein degradation function would represent a useful therapeutic target for cancer treatment. However, proteasome inhibitors have shown utility as single agents, and they preferentially kill tumor cells both *in vitro* and *in vivo*[113−116] (Table 2). Furthermore, proteasome inhibitors sensitize cancer cells to cisplatin[117−119] and to radiation.[120−122] The sensitizing role of proteasome inhibitors to DNA damaging agents is thought to be linked to the critical role of ubiquitin-mediated protein degradation in regulating the DNA damage response. For example, proteasome-mediated protein degradation is needed for homologous recombination,[123] the FA pathway,[124] nucleotide excision repair,[125] degradation of stalled RNA polymerases II,[126,127] elimination of trapped DNA topoisomerase I complexes,[128] and regulation of p53.[129,130] Furthermore, the induction of the NF-κB survival pathway by DNA damaging agents is dependent on proteosomal degradation of IκB. Thus, proteasome inhibitors would block NF-κB activation, leading to the sensitization of cells to radiation and chemotherapy.[115] The development of small-molecule inhibitors targeting specific ubiquitin ligases, rather than the proteasome itself, holds promise since such an approach could lead to the selective targeting of a subset of cancer-related proteins and should reduce dose-limiting side effects.

4. Targeting DNA Damage Checkpoint Pathways

In addition to DNA repair pathways, cells induce extensive signal transduction pathways following induction of DNA damage that leads to the activation of cell cycle checkpoints and/or apoptosis depending on the cell type and the degree of damage.[8,131,132] Forcing cancer cells to undergo apoptosis would obviously have therapeutic benefits, while induction of cell cycle arrest may increase resistance to treatment of cancer cells. Many tumor cells harbor mutations in genes coding for DNA damage response factors, such as p53, which

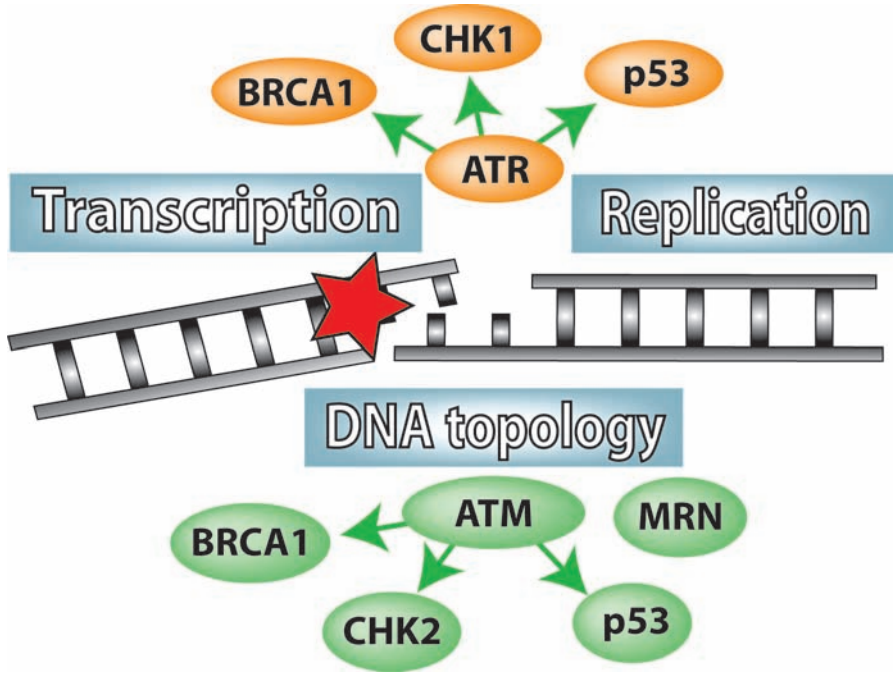

Figure 2. DNA damage checkpoint pathways as therapeutic targets. Bulky DNA adducts and DNA cross-links, induced by, for example, cisplatin or mitomycin C, cause elongation problems for both transcription and replication, leading to the activation of the ATR stress response. The phosphorylation substrates CHK1, p53, and BRCA1 promote cell cycle arrest, allowing more time for the cells to repair the DNA damage before resuming proliferation. Inactivation of these proteins with specific inhibitors (Table 3) disrupts cell cycle checkpoints, resulting in the progression of damaged cells into S-phase and mitosis with resulting increased cell death. Loss of DNA topology by induction of DNA strand breaks results in the activation of ATM and phosphorylation of CHK2, p53, and BRCA1, leading to the induction of cell cycle arrest. Inactivation of the ATM stress response pathway by specific inhibitors (Table 3) sensitizes cells to IR.

could make them more vulnerable to the effects of DNA damaging agents.[133,134] On the other hand, defects in the mitotic checkpoint have been shown to make cancer cells more resistant to certain DNA-damaging agents by escaping mitotic checkpoint-mediated apoptosis.[135] Thus, depending on the specific cellular defect in a particular tumor, the choice of therapy may have profound effects on the outcome. Because of the protective role of many of the cell cycle checkpoint responses against radiation and chemotherapy, there has been a strong interest in the development of chemical inhibitors targeting DNA damage checkpoint pathways (Figure 2 and Table 3).

4.1. ATM

Following induction of DNA strand breaks by ionizing radiation, the ATM kinase is activated by sensing alterations in the chromatin structure induced by loss of DNA topology.[136] The MRN complex, consisting of MRN11, NBS1, and RAD50, has been implicated in enhancing the activation of ATM at sites of DNA damage.[137−142] Two very specific ATM inhibitors, KU55933 and CP466722, have been shown to be effective in rapidly sensitizing cancer cells to ionizing radiation[143,144] (Table 3). Importantly, these inhibitors are reversible, making it possible to selectively target ATM during radiotherapy. Furthermore, two inhibitors of the MRN complex, mirin[145,146] and virinostat,[147−149] have been developed. It will be interesting to follow how effective these drugs are as radiosensitizers *in vivo* and in clinical trials.

4.2. ATR

Bulky DNA adducts induced by UV light or certain chemotherapeutic agents are sensed by the ATR kinase and associated factors.[150−153] The ATR kinase monitors the effect the damage has on DNA replication[154] or transcription[155] rather than sensing the damage directly (Figure 2), although there are findings showing that ATR has higher affinity for DNA containing UV lesions than undamaged DNA in *in vitro* assays.[156] While there are inhibitors of the ATR kinase available[157−164] (Table 3), inhibition of ATR is problematic because of its essential role in regulating DNA replication.[165−168] Thus, unless ATR could be targeted specifically in cancer cells or its role in the DNA damage response could be selectively targeted, ATR may be a difficult enzyme to target in the clinical setting because of toxicity to normal cells.

4.3. CHK1

Two important phosphorylation substrates of ATM and ATR are the cell cycle checkpoint kinases CHK1 and CHK2. When activated following DNA damage, these checkpoint kinases orchestrate arrests in the G_1/S, S, G_2/M, and M phases of the cell cycle.[169] CHK1 mediates checkpoint activation in the S and G_2 phases of the cell cycle by targeting the CDC25A phosphatase for degradation following DNA damage induction.[170] Inactivation of CHK1 is thought to sensitize cancer cells to DNA damaging therapeutics by not allowing these cells sufficient time to repair their DNA.[132,171] The result is that the cells enter S-phase or mitosis with unrepaired DNA, and subsequent complications lead to cell death. Furthermore, CHK1 is important for homologous recombination by activating RAD51 by phosphorylation.[172] Indeed, inhibition of CHK1 has been shown to sensitize cells to ionizing radiation and certain chemotherapeutic agents, validating CHK1 as an important therapeutic target.[100,158,162,171,173−191] In addition to playing a critical role in activating cell cycle checkpoints, CHK1 has an essential role together with ATR in regulating the progression of replication.[192−194] Many new

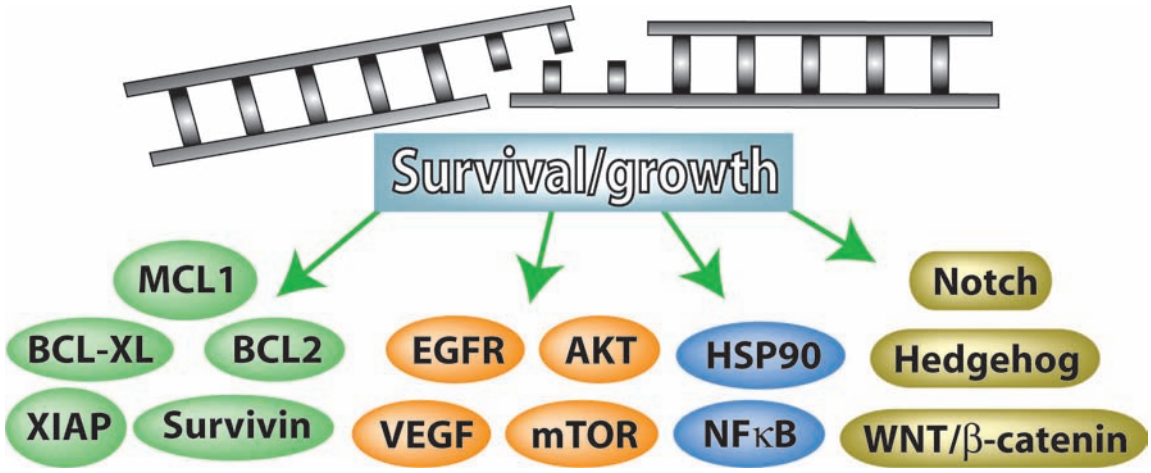

Figure 3. Survival and proliferation pathways as therapeutic targets. A common cause of cancer treatment failure is that the tumor expresses high levels of specific antiapoptotic factors (green), survival factors and growth promoting and signaling proteins (orange), transcription factors and protein chaperones (blue), or growth promoting signaling pathways (yellow). Many small-molecule inhibitors specifically targeting these factors have been developed recently (Table 4), and the efficacy of these drugs is being assessed in clinical trials as monotherapy or in combination with radiation and/or chemotherapy.

drugs that inhibit CHK1 (Table 3) are especially effective in cells defective in G_1 arrest checkpoint such as p53 mutant cells (see section 6.2).

4.4. CHK2

In contrast to CHK1, CHK2 has been shown to stimulate DNA damage-induced apoptosis and may act as a tumor suppressor.[195,196] Thus, it is possible that the targeting of CHK2 may make tumor cells less responsive to DNA -damaging therapies.[196−198] There are ongoing clinical trials employing the drugs XL844 and AZD7762, which inhibit both CHK1 and CHK2, in combination with gemcitabine.[7,186,191] It would be important to develop and test drugs that selectively inhibit CHK1 without affecting CHK2 to perhaps obtain stronger efficacies when combined with radiation and/or chemotherapy than would drugs that inhibit both kinases.

4.5. p53

There has been a lot of interest in manipulating p53 function in cancer cells to limit tumor growth and to sensitize tumors to radiation and chemotherapy.[199] The tumor suppressor p53 is an important regulator of both cell cycle checkpoints and induction of apoptosis following exposure to DNA damaging agents.[129,200] The choice of cell cycle arrest or apoptosis by p53 is dependent on the extent of damage but also on the cell type.[131] The p53 gene is mutated in more than half of all human cancers and is expressed at very high cellular levels when mutated.[201,202] One exciting strategy exploiting the high levels of p53 in cancer cells is to convert the mutated form of p53 into the wild-type conformation.[203,204] The idea here is that these compounds should be tumor-selective and would cause cancer cells to induce apoptosis as they find themselves full of active p53 proteins. The reactivation of mutant p53 in cancer cells leading to apoptosis has been shown using both peptides[205,206] and small-molecule inhibitors such as PRIMA-1[207,208] (Table 3), and this approach has shown promise in xenograft models.[208] An alternative approach is to reintroduce wild-type p53 to tumor cells to enhance the therapeutic effects of radiation[209−212] or chemotherapy.[213−216]

In cancer cells harboring wild-type p53, compounds that break the MDM2-p53 circuit can increase the cellular levels of p53. A number of new compounds have been recently developed, and they seem to have tumor-specific activities.[217−224] In some tumors, inhibition of wild-type p53 with the small-molecule inhibitor pifithirin-α has been shown to sensitize tumors to chemotherapy.[225]

Induction of cell cycle arrest by p53 is primarily confined to the G_1 phase of the cell cycle and involves the induction of the CDK-inhibitor p21.[226,227] Many studies have shown that induction of p21 and the subsequent G_1 arrest protects cancer cells from the cytotoxic action of radiation and many DNA damaging anticancer agents.[228−233] Thus, the targeting of p21 may have therapeutic benefits. Small-molecule inhibitors of p21 were recently identified,[233] and it will be interesting to assess whether these molecules have clinical utility.

While p53 can stimulate radiation and chemotherapy-induced apoptosis in cancer cells, it also plays a role as a dose-limiting factor of toxicity of normal tissues.[234] The small molecule pifithrin-α interferes with the ability of p53 to induce apoptosis by inhibiting p53 from binding to mitochondria.[235,236] When given to mice, pifithrin-α substantially protects these animals from the toxic effects of whole-body irradiation.[236] That temporary suppression of p53 function in normal tissue can be beneficial in lowering the therapeutic side effects has been verified in a mouse model in which p53 function was turned on and off at will.[237] Taken together, selective induction of p53 in tumor cells while temporarily inhibiting p53 in normal cells is a promising approach that could lead to an increase in the therapeutic window of anticancer treatments.

5. Targeting Cell Survival and Proliferation Pathways

Somewhere on their journey to malignancy, cancer cells obtain mutations that enhance cell survival and proliferation pathways.[238] There is tremendous therapeutic potential in specifically targeting these pathways to enhance DNA damage-based therapies, and many pharmaceutical companies are developing drugs that target these pathways (Figure 3, Table 4).

5.1. Apoptosis Regulators

Apoptosis is a highly regulated death program that plays important roles in normal physiology and in tumor suppression. Many cancer cells have acquired mutations leading to the overexpression of antiapoptotic factors such as BCL-2, BCL-X_L, MCL-1, Survivin, and XIAP, leading to an enhanced resistance to many anticancer therapeutic agents.[239−244] Recently, a number of small molecules have been identified that specifically target different antiapoptotic factors (Table 4). These inhibitors have been shown to sensitize cancer cells to radiation[245−248] and DNA damage-inducing chemotherapeutic agents.[249−251] An alternative approach to lower the apoptotic threshold and sensitize tumor cells to DNA damaging agents is to enhance the activity of pro-apoptotic factors such as trail.[252−257] Since many cancer cells rely on, or are "addicted" to, high expression levels of antiapoptotic factors, targeting these factors in combination with radiation or chemotherapy should have strong clinical utility in the treatment of cancer patients.

5.2. EGFR

The epithelial growth factor receptor (EGFR) integrates extracellular signals with alterations in gene expression. Activation of EGFR can lead to the induction of a number of signaling pathways such as the JAK/STAT pathway, the PI3K/AKT pathway, the RAS/MAPK pathway, and the PKC pathway.[258] The transcriptional output of these pathways involves genes associated with cell survival, proliferation, differentiation, and angiogenesis. High expression of EGFR in tumor cells has been shown to confer resistance to radiation and chemotherapeutic agents.[259−261] For these reasons, EGFR has received attention by pharmaceutical companies as an important therapeutic target, and a large selection of EGFR-targeting drugs has been developed (Table 4).

Preclinical studies have shown that inhibition of EGFR results in radiosensitization of various tumor cells expressing EGFR.[259−277] Possible mechanisms responsible for this radiosensitizing effect may be related to decreased activity of the double-strand break repair protein DNA-PK since EGFR has been shown to travel to the nucleus where it stimulates DNA-PK activity following exposure to IR.[278] In addition, recent studies have shown that the EGFR inhibitor erlotinib suppresses homologous recombination repair by cytoplasmic retention of BRCA1, making the cells more susceptible to IR.[82] Importantly, the sensitizing effect of EGFR inhibition to radiation-induced cell killing is more evident in xenograft models than in cell culture models, suggesting that the effects EGFR inhibitors have on angiogenesis and tumor invasion may be of more clinical importance than any effects on DNA damage processing.[258]

5.3. PI3K/AKT/mTOR

The PI3K/AKT/mTOR signaling pathway is frequently dysregulated in cancers.[279] Activation of the PI3K/AKT/mTOR pathway is dependent on growth factor receptors leading to the enhancement of proliferation, differentiation, and migration of cells.[280] The phosphatase PTEN, which is frequently mutated or underexpressed in many types of cancers, negatively regulates the PI3K/AKT/mTOR pathway by inhibiting PI3Ks.[281] Hyperactivation of the PI3K/AKT/mTOR pathway is associated with resistance to radiation and chemotherapy and, thus, represents a promising therapeutic target for tumor sensitization.[264,282−309] A recent study showed that cancer cells with hyperactivated AKT are hypersensitive to agents inducing reactive oxygen species (ROS), opening up some interesting new therapeutic avenues for exploration.[310]

There is currently a tremendous interest in the PI3K/AKT/mTOR pathway as a potential therapeutic target.[279−282,309,311−313] AKT has been shown to protect cells against IR by directly participating in the DNA damage response.[314] The DNA double-strand break sensor and repair protein DNA-PK and the PI3K-dependent kinase 1 (PDK1) phosphorylate AKT following IR, resulting in the localization of AKT to sites of DNA damage and activation of transcription of the cell cycle inhibitor p21.[314] Knockdown of AKT results in attenuated induction of p21 and enhanced apoptosis following IR. Another function of AKT is to regulate homologous recombination (HR) by cytoplasmic sequestering of BRCA1 and RAD51.[315] Hyperactivation of the AKT pathway results in a phenotype similar to BRCA1-deficiency with a severe defect in HR. It would be of great potential clinical benefit if small-molecule inhibitors could be developed that target the apoptosis-protecting role of AKT without negating its HR-suppressing function. Such compounds should lead to a strong sensitization of cancer cells to treatments requiring HR such as IR, cisplatin, mitomycin C, and PARP inhibitors. With the development of novel reporter molecules for AKT activity that can be imaged noninvasively in tumors,[316] high-throughput screening of chemical libraries for new small-molecule inhibitors of the PI3K/AKT/mTOR pathway can be conveniently performed in cell cultures and target inhibition can be validated *in vivo*.

5.4. COX-2

Cyclooxygenase-2 (COX-2) is involved in the production of prostanoids, such as prostaglandin, which are chemokines that can promote inflammation. Because of its pro-inflammation activity, many pharmaceutical drugs have been developed to target COX-2 activity.[317,318] These inhibitors have been used in cancer treatment due to the frequent overexpression of COX-2 in cancer and to the strong link between inflammation and cancer.[319] When combined with radiation or chemotherapy, COX-2 inhibitors have been found to promote DNA damage-induced cell killing of cancer cells.[320−329] A potential mechanism of sensitization of COX-2 inhibitors to DNA damaging agents may be that loss of COX-2 attenuates DNA repair.[322]

5.5. VEGF

The vascular endothelial growth factor (VEGF) is secreted from growing tumors to stimulate angiogenesis. Blockage of VEGF can be accomplished by neutralization of VEGF ligands or VEGF receptors by specific antibodies or inhibition of VEGF activation and signaling using specific kinase inhibitors.[330] Inhibition of VEGF reduces angiogenesis and suppresses tumor growth *in vivo*,[331] and clinical trials employing VEGF-targeting therapies have shown efficacy toward advanced-stage cancers.[330] However, the beneficial effect of these anti-VEGF agents cannot be attributed to inhibition of angiogenesis alone, as additional pathways are thought to be involved.[330] The apoptotic threshold of cancer cells and endothelial cells may be affected by VEGF inhibitors since VEGF normally promotes the expression of

the antiapoptotic factors BCL-2, Survivin, XIAP, and AKT.[330] The apoptosis-protective effect of VEGF may also explain why VEGF-targeted therapies sensitize cancer cells to radiation[264,332−340] and chemotherapy.[341−344]

5.6. NF-κB

Nuclear factor-kappa B (NF-κB) is a transcription factor that promotes the expression of genes regulating a number of processes including cell growth, differentiation, and apoptosis. NF-kB is activated by stresses, such as DNA damage,[345,346] leading to its nuclear localization and transactivation of target genes.[347] Induction of NF-κB following exposure to radiation or chemotherapy promotes cell survival, while inhibition of NF-κB activation augments the therapeutic response. The key mechanism of NF-κB activation is the phosphorylation of the inhibitory factor IκB by the IKK kinase, leading to the degradation of the IκB protein.[347] There are many potential strategies to abrogate NF-κB activation with the most promising target being the IKK kinase.[347] Many preclinical studies have verified that NF-κB is a valid therapeutic target with NF-κB inhibitors sensitizing cancer cells to both radiation and chemotherapy.[348−357] An alternative approach to increase the therapeutic window of radiation or chemotherapy would be to make normal tissue cells more resistant to radiation or chemotherapy by activation of NF-κB. Indeed, activation of the NF-κB pathway by the polypeptide drug CBLB502 has been shown to protect normal tissues against radiation.[358]

5.7. HSP90

The heat-shock protein 90 (HSP90) is a molecular chaperone interacting with "client proteins" regulating their folding, stability, and transport.[359,360] HSP90 has ATPase activity and binding, and hydrolysis of ATP leads to a conformational change of the HSP90 protein required for its chaperone activity. HSP90 is frequently dysregulated and hyperactive in cancer cells because of the high frequency of mutations in these cells, leading to the production of misfolded proteins subjected to HSP90 processing.[360] Because of the hyperactivity of HSP90 in cancer cells, HSP90 inhibitors preferentially target cancer cells.[359] In addition, many of HSP90 clients have oncogenic functions that cancer cells become "addicted" to, and loss of HSP90-mediated stabilization of these factors selectively affects cancer cells.[360] In addition to oncogenic clients, HSP90 clients also include a number DNA damage response factors such as p53,[361−363] FANCA,[364,365] the MRN complex,[366,367] and CHK1.[368−370] As expected, inhibitors of HSP90 sensitize cells to chemotherapy[371,372] and IR.[366,367,370,373−378] Because of the broad inhibitory effects on both oncogenes and DNA repair factors, inhibitors of HSP90 show great promise for combination cancer treatments.

5.8. Notch Signaling Pathway

The Notch signaling pathway plays important roles in development and in adult tissue homeostasis by the maintenance of stem cells.[379,380] Upregulation of this pathway is very common in tumors of the breast,[381] prostate,[382] colon, and pancreas and in melanoma and hematological malignancies.[383,384] It is thought that hyperactivation of the Notch signaling pathway results in increased proliferation[384] and enhanced angiogenesis.[385]

The Notch pathway is upregulated by chemotherapy, leading to the induction of proteins enhancing cell survival.[386] Inhibition of the Notch pathway by down-regulation of Notch by siRNA[387] or by treatment with a Notch-1 inhibitor[386] sensitizes cancer cells to chemotherapeutic agents such as cisplatin. Potential mechanisms by which Notch influences the response to DNA-damaging agents is via the induction of the cell cycle inhibitor p21,[388] by inhibition of p53 function,[389] and/or by upregulation of DNA repair and survival pathways.[386,387] These effects by Notch activation suggest that Notch is a promising therapeutic target for the sensitization to DNA-damaging agents, and this exciting area awaits further exploration.

5.9. Hedgehog Signaling Pathway

The Hedgehog signaling pathway regulates tissue patterning during embryonic development and plays an important role in stem cell maintenance.[390,391] Hedgehog proteins are secreted proteins that bind to the membrane-bound patched-1 protein, leading to the activation of the transcription factor GLI.[392] Aberrant hyperactivity of the Hedgehog signaling pathway is common in many cancers and results in a hyperproliferative phenotype driven by GLI-mediated induction of *cyclin D*, *E*, and *Myc*.[392,393] The Hedgehog pathway is often induced early in carcinogenesis,[394] and it is possible that activation of the Hedgehog pathway allows for oncogenes such as RAS to break through the DNA damage response barrier by suppressing the function of p53[395] and the ATR signaling pathway.[396]

In addition to cyclopamine, many small-molecule inhibitors and antibodies that target the Hedgehog signaling pathway have been recently developed (Table 4). Inhibition of the Hedgehog signaling pathway sensitizes cancer cells to IR[397] and paclitaxel but not gemcitabine or cisplatin.[398] Surprisingly, one study shows that activation of the Hedgehog pathway in mouse embryonic fibroblasts or human HEK293 cells, which normally show low Hedgehog activities, resulted in radiosensitization due to an impaired DNA damage response.[396]

It has been shown that Hedgehog activity is greatly enhanced in tumors 6−8 days after radiation therapy, suggesting that the cells that survived and repopulated the tumor have a hyperactive Hedgehog signaling pathway.[399] It is possible that the abrogation of p53 function by the activated Hedgehog promotes survival following radiation and allows these cells to repopulate the tumor.[395] Since Hedgehog signaling is involved in maintaining the cancer stem cell population,[400] it is possible that it is the stem cell compartment that preferentially expands following radiation treatment, as has been noted for glioblastoma.[401] A recent interesting study using antibodies (HhAntag) antagonizing the Hedgehog pathway showed that neutralization of cancer-secreted Hedgehog proteins reduced cancer growth not by inhibiting tumor cell proliferation *per se* but through the abrogation of the tumor growth-supporting role of neighboring stroma cells.[402]

5.10. WNT/β-catenin Signaling Pathway

Like the Hedgehog and Notch signaling pathways, the WNT/β-catenin pathway is essential for normal development and the maintenance of tissue stem cells.[403−406] This pathway is activated by the binding of the WNT ligand to its membrane receptor complex, resulting in the inhibition of

the β-catenin destruction complex and subsequent transactivation of β-catenin target genes promoting proliferation.[403] The WNT/β-catenin pathway is frequently hyperactive in many types of malignancies such as colon and liver cancer, leukemia and melanoma,[407] pancreatic cancer,[408] and breast cancer.[381] The hyperactive state is due to mutations resulting in constitutive active WNT receptors, abrogated destruction complexes,[409] or constitutive active/stable β-catenin proteins.[403]

Cells with an activated WNT/β-catenin pathway are hyperresistant to radiation[410−412] and chemotherapeutic agents such as cisplatin.[413,414] Exposure of human fibroblasts to IR activates β-catenin via a WNT-mediated mechanism, and this activation may promote survival.[412] Forced expression of β-catenin results in the induction of p53, resulting in cell senescence or apoptosis.[415,416] In order for tumor cells with activated β-catenin signaling to grow and progress, the p53 tumor-suppressing pathway needs to be inactivated. An interesting finding is that activation of the Hedgehog signaling pathway, which is an event that often precedes the activation of the β-catenin pathway in carcinogenesis, suppresses p53[395] and, thus, would allow for the β-catenin to promote proliferation of the tumor cells unopposed by p53.

6. Exploiting DNA Damage Response Defects in Cancer

The pathways that respond to DNA damage ensure that cells maintain genetic stability by promoting DNA repair, activating cell cycle checkpoints, or inducing cells to undergo apoptosis. A critical driving force in the development of malignant disease is that cells need to acquire a genetic instability phenotype to generate multiple mutations subjected to selective evolution.[11,12] Thus, tumors often have defects in one or more DNA damage response pathways, and this presents a great opportunity for the exploration of these "weaknesses" therapeutically.[7]

6.1. BRCA1/BRCA2 Deficiencies

Mutations in the BRCA1 or BRCA2 genes, which are common in breast and ovarian cancers, result in a deficiency in conducting homologous recombination repair (HR). This pathway is required for the resoution of DNA interstrand cross-links induced by chemotherapeutic agents such as cisplatin and mitomycin C, for the repair of DNA double-strand breaks specifically during the S and G_2 phases of the cell cycle, and to resolve complications occurring during replication.[13,14,417] Oxidative DNA damage occurring endogenously in cells is repaired primarily through base excision repair (BER). If the BER pathway is abrogated by, for example, inhibition of PARP, the unrepaired lesion will cause complications during replication, requiring processing by HR. Thus, tumor cells defective in HR are exceptionally sensitive to PARP inhibitors since neither BER nor HR would be functional.[418−422] PARP inhibitors are currently being clinically evaluated as monotherapy in patients with BRCA1 and BRCA2 defective tumors.[7] It has been shown that hypoxia causes the downregulation of HR proteins such as BRCA1 and RAD51.[423,424] It would be interesting to therapeutically exploit whether PARP inhibitors may selectively kill hypoxic regions of tumors.[425]

6.2. Mutated p53

The p53 gene is mutated in over 50% of human cancers, and it is thought that cancers harboring wild-type p53 alleles are likely to have gene mutations in genes compromising the activation or function of the p53 pathway.[201,426] Since p53 responds to DNA damage by activating cell cycle checkpoints and promoting DNA repair, mutations compromising p53 function will prohibit the cells from correctly responding to DNA damage.[131] Indeed, for some tumor cell types, a mutant p53 phenotype predisposes the cells to chemotherapy-induced cell kill.[427] Furthermore, loss of p53-mediated G_1 arrest will force cells to rely on a G_2/M cell cycle arrest to avoid mitotic catastrophe. However, if the G_2/M checkpoint is targeted by, for example, CHK1 inhibitors, p53-deficient cancer cells will lose their ability to arrest in G_2/M following radiation or chemotherapy.[175] Thus, the combination of Chk1 inhibitors and radiation therapy should be selectively toxic to p53-defective tumor cells since normal tissues with wild-type p53 would be able to arrest in G_1.[175,185,428] The selective targeting of mutant p53 in tumors by p53-reactivating agents, such as small peptides or PRIMA-1,[205−208] or the UMP synthesis inhibitor *N*-phosphonacetyl-L-aspartate (PALA)[429−431] are other promising approaches by which cancer-specific defects in p53 are exploited and converted into potential clinical utility.[208]

6.3. BRCA/Fanconi Defects

Ovarian, lung, and oral cancer cells frequently have defects in the BRCA1/Fanconi DNA damage response pathway, making them selectively sensitive to treatment with cisplatin or mitomycin C.[77,432] However, if the tumor is not eliminated by the first line treatment, recurring tumors have a high likelihood of being refractory to cisplatin treatment due to reactivation of the Fanconi pathway by demethylation of the *fancF* gene.[77] Similarly to ovarian cancers, some head and neck cancers are hypersensitive to cisplatin, which in part appears to be due to a defect in the expression of BRCA1.[433] It may be of value to examine the status of the BRCA1/Fanconi pathway in tumors to determine which patients would most benefit from cisplatin/mitomycin C therapy.

6.4. Abrogated ATM Function

ATM is frequently mutated or dysregulated in human cancers.[3,434−442] Since the ATM kinase is involved in orchestrating DNA damage responses following exposure to agents inducing DNA strand breaks, it is expected that ATM-defective tumors are radiosensitive.[439,443] Thus, tumors defective in ATM function would be good candidates for radiotherapy. However, if a patient has a suboptimal ATM response in normal tissues due to heterozygosity or downregulation by epigenetic factors, there is a potential increased risk that the radiation treatment may induce late effects[444,445] or secondary cancers,[446] although some ATM variants have been associated with a reduced risk of contracting secondary tumors.[447] Further studies are needed to resolve whether ATM defects in tumors can be exploited therapeutically and how ATM heterozygosity in normal tissues contributes to treatment complications.

6.5. Mismatch Repair Deficiencies

Defects in DNA mismatch repair (MMR) are common in colorectal cancer and produce a microsatellite instability

(MSI) phenotype, which is used as a diagnostic tool for MMR defects in tumors.[448] Furthermore, hypoxia has been shown to suppress expression of MMR proteins in cells, and therefore, hypoxic regions of tumors may have relatively poor MMR activity.[449,450] Alkylating agents inducing O^6-methylguanine adducts are more toxic to cells harboring functional MMR potentially due to a futile MMR-induced repair response.[451] Alternatively, the binding of MMR proteins to O^6-methylguanine adducts leads to the induction of DNA damage signaling and apoptosis[452,453] via MMR-mediated blockage of transcription.[454] However, agents inducing DNA interstrand cross-links[455] or inhibiting DNA synthesis[455] preferentially kill tumor cells with defective MMR. Furthermore, gemcitabine preferentially radiosensitizes MMR-defective cancer cells,[456] and MMR-deficiency leads to hypersensitivity to carboxyamidotriazole (CAI).[457] Thus, by confirming the MSI phenotype of the tumor or by locating hypoxic regions of tumors, treatments that selectively target either MMR-proficient or MMR-deficient cells should be considered to improve therapy.

6.6. Exploiting Oncogenic Stress

Tumor growth and progression is promoted by oncogenes that drive cells into S-phase. However, this entry into S-phase is premature and results in complications during replication, a phenomenon termed "replication stress".[458,459] The replication stress activates a DNA damage response that acts as a barrier for further tumor development. Upregulation of the Hedgehog pathway, which is often an early event in cancer progression,[394] may overcome the growth suppression induced by the oncogenic stress by abrogating p53 function.[395] Regardless of the mechanism responsible for suppressing the DNA damage response during tumor progression, the activated oncogene is expected to continue to drive cells prematurely into S-phase, causing DNA damage. Thus, tumor cells continuously induce DNA damage, and if the repair machinery that resolves this damage could be specifically targeted, tumor cells would theoretically be selectively killed. Compounds inhibiting CHK1 or the replication licensing system[460] would be of great interest to test for selective toxicity of cells subjected to oncogene-induced replication stress. Future studies need to elucidate the mechanisms responsible for replication stress and the identity of the enzymes participating in the resolution of these replication problems so that targeted therapies could be developed.

6.7. Targeting Cancer Stem Cells

Many tumor types have a subpopulation of cells, termed cancer stem cells, which are thought to drive the growth of the tumor.[461] However, some cancers, such as melanoma, appear to contain cells that are all capable of growing the tumor.[462] Interestingly, the population of cells identified as cancer stem cell has in some reports been shown to be more resistant to radiation or chemotherapy than the non-stem cell population of the tumor.[401,463−468] It was suggested that cancer stem cells have a more easily triggered DNA damage response, providing better protection against DNA-damaging agents.[401] This enhanced protection may be related to a more open chromatin structure of cancer stem cells, which promotes a more efficient DNA damage signaling than cells with a more compact chromatin.[469] However, DNA repair pathways do not appear to be more efficient in cancer stem cells than in non-stem cells.[470] Interestingly, glioma cancer stem cells have been found to be preferentially sensitive to Temozolomide by an unknown mechanism.[471] Other potential mechanisms to target cancer stem cells are through inhibition of the Notch, Hedgehog, or WNT/β-catenin pathways, since they are all critical in maintaining stem cell populations.[400,405,472] Indeed, inhibition of the Hedgehog pathway by cyclopamine preferentially hits cancer stem cells in glioblastoma.[473] Efforts to further identify genes and gene products specifically expressed and utilized by cancer stem cells should help in the development of novel therapies specifically targeting cancer stem cells.

7. Conclusions

We are in an exciting phase in cancer research with a rapid pace of discovery driven by new technologies. Recent studies have shed light on the complexity of tumor biology, showing that tumors rarely have similar sets of mutations in common.[1−3] However, when placing the various tumor mutations into functional pathways, a more manageable picture emerges with about 12 core pathways abrogated in the majority of the tumors.[1] Thus, it may be possible after identifying the pathway(s) altered in a particular tumor to tailor therapies to specifically block that pathway(s). The DNA damage response is one of these core pathways found to be frequently dysregulated in cancer.[1] Proteins participating in this pathway are expected to be important therapeutic targets for the sensitization of tumor cells to radiation or chemotherapy. The targeting of the DNA damage response in cancer stem cells may be of particular importance, since these cells are often found to be more resistant to radiation and chemotherapy than other tumor cells.

The fact that many tumors have defects in DNA repair pathways and/or cell cycle checkpoints presents unique opportunities for therapeutic exploitation. Likewise, oncogene-driven induction of "DNA damage" sets tumor cells apart from normal cells, and with a better understanding of the mechanisms involved in the repair of these lesions, tumor-selective therapies may be developed. Aristotle once said: *"We make war that we may live in peace"*. By applying novel strategies involving inhibitors of the DNA damage response in combination with radiation or chemotherapy, we may improve the chances of peace by winning the war on cancer.

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