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Disruption of Protein–DNA Interactions: An Opportunity for Cancer Chemotherapy

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1. Introduction

The use of inhibitors, both natural and synthetic has been a mainstay in the biochemical analysis of cellular pathways from glycolysis, the TCA cycle and the electron transport chain to DNA replication, cell signaling and apoptosis. With advents in screening technology, robotics and combinatorial chemistry, the field of chemical genetics was born. The development and use of small molecule inhibitors (SMIs) to modulate the activities of proteins has provided a wealth of knowledge on a variety of pathways and enhanced drug development targeting novel proteins and activities. The effectiveness of targeting enzyme-substrate interactions is well established and only more recently have protein-protein interactions been effectively targeted with SMIs (Saha et al., 2010; Huang et al., 2008; De et al., 2009; Ballatore et al., 2010; Yang et al., 2010; Weber, 2010). While targeting protein-DNA interactions has been considered by some to be "undrugable interactions" we and others have succeeded in developing SMIs capable of inhibiting these often complex interactions. The ability to develop inhibitors of protein-DNA complex formation capable of *in vivo* activity opens up an entire new class of targetable molecule interactions for potential therapeutic benefit. One could envision inhibiting proteins involved in transcription in addition to DNA replication, DNA repair and recombination. This review will summarize the recent successes in targeting protein-DNA interactions and draw the distinction between those agents that inhibit these interactions directly versus those that reduce protein-DNA interactions via indirect mechanisms. We also highlight the development of DNA repair inhibitors focusing on the clinical utility of targeting DNA repair for cancer therapy.

2. Inhibitors of DNA replication, repair and recombination

Numerous DNA repair pathways are required for genomic stability and chromosome maintenance. Defects or deficiencies in DNA repair proteins, machinery and activity contribute to mutation driven carcinogenesis and the development of cancer. The importance of DNA repair has also been well established in the treatment response in numerous cancer types including testicular, ovarian and lung where defects in DNA repair increase the effectiveness of DNA damaging therapies. Exploiting the inherent genome instability in certain cancers via synthetic lethality targeting novel DNA repair proteins has progressed to clinical trials and holds the potential to significantly impact cancer treatment. First demonstrated in BRCA1/2-mutant breast cancer, targeting DNA repair with SMIs of

poly-ADP-ribose polymerase (PARP) proved clinically effective. While the exact mechanisms of PARP inhibition have not been completely elucidated, the idea of targeting DNA repair is gaining traction in both the laboratory and clinic. Supporting this is the recent editorial from Bruce Alberts in *Science* suggesting that all cancers will display some defect in DNA repair (Alberts, 2009). Some success in early phase trials has propelled this avenue of research though the number of targets is still limited.

Target	Inhibitor	Reference
PARP-1	NU1085	Griffin et al., 1996; Delaney et al., 2000
	NU1064	Bowman et al., 1998
	NU1025	Bowman et al., 1998; Delaney et al., 2000
	PD128763	Delaney et al., 2000
	AG14361	Calabrese et al., 2004
	ABT-888	Donawho et al., 2007
	AG14447	Thomas et al., 2007
RPA	MCI	Anciano et al., 2010
	TDRL-505	Shuck et al., 2010
XPA	TDRL-X80	Neher et al., 2010
DNA-PK	NU7441	Hardcastle et al., 2005; Leahy et al, 2004
	NU7026	Veuger et al., 2003
ATM	KU-55933	Hickson et al., 2004
C-Met	MP470	Qi et al., 2009
Stat3	Galiellalactone	Hellsten et al., 2008; Weidler, et al., 2000
	Falvopiridol	Lee et al., 2006
	IS3295	Turkson et al., 2005
	CPA-1 , CPA-7	Turkson et al., 2004
	Platinum (V) tetracholoride	Turkson et al., 2004
NF-kB	Pristimerin	Lu et al., 2010
	KINK-1	Schon et al., 2008
	DHMEQ	Ariga et al., 2002
NOTCH	SAHM1	Moellering et al., 2009
HOXA13	lactam carboxamide	Ng et al., 2007

Table 1. Small molecule inhibitors of DNA repair proteins and transcription factors.

2.1 PARP1 inhibitor – targeting single strand break repair

Poly ADP-ribose polymerase (PARP) is a nuclear protein which binds to single-strand breaks (SSBs) in the DNA and signals downstream repair proteins to the site of damage, initiating DNA repair. PARPs direct involvement in SSB repair is the synthesis of ADP-

ribose polymers, utilizing NAD^+ as a substrate, which aids in DNA repair and cellular signaling (Calabrese et al., 2004). PARP also plays a role in the homologous recombination (HR) repair pathway (Helleday, 2010) and has been suggested to play a role in the alternative non-homologous end joining pathway (A-NHEJ) (Wang et al., 2006). The indirect role PARP plays in the HR pathway is through its ability to recognize SSBs. In the absence of PARP SSBs accumulate resulting in an increased number of collapsed replication forks which require DNA repair. Therefore, chemotherapeutics which elicit their toxic effects by damaging the DNA, have increased potency in combination treatment with PARP inhibitors due to a decrease in DNA repair and an accumulation of collapsed replication forks (Thomas et al., 2007). This increase in DNA damage results in cell death, which is a favorable outcome in the treatment of cancer. Researchers have used this knowledge to initiate the development of PARP inhibitors and over the past four decades numerous PARP inhibitors have entered clinical trials, some of which have been successfully incorporated into chemotherapeutic regimens.

Initial PARP inhibitors were analogues of nicotinamide whose activities were useful for *in vitro* studies but were found to be of little clinical value. A second generation of inhibitors, which included benzimidazole-carboxamides, quinazolin-4-[3H]-ones and isoquinoline derivatives (NU1085, NU1025, PD128763) were shown to increase radio- and chemosensitivity *in vitro* (Delaney et al., 2000). NU1025 sensitized tumor cell lines to temozolomide and camptothecin, yet the specificity of NU1025 was not developed enough for use in preclinical trials. AG14361, a PARP inhibitor identified by a PARP1 activity assay, exploits the PARP1-catalyzed NAD-dependent incorporation of poly(ADP)ribose to histones (Thomas et al., 2007). Briefly, the incorporation of ^{32}P-ADP-ribose into an insoluble material is measured following the transfer of radiolabeled phosphate from ^{32}P-NAD. Data from this assay demonstrate a decrease in ADP transfer, suggestive of the inhibition of PARP1 activity. Additionally, AG14361 treatment increased a cells' susceptibility to three chemotherapeutics irinotecan, γ-irradiation and temozolomide with an IC_{50} value below 5 nM (Calabrese et al., 2004). Although a number of PARP inhibitors have entered preclinical and clinical trials, most of these are competitive inhibitors with NAD+ and there is no data demonstrating disruption of the PARP-DNA interaction by SMIs. This is consistent with the separation of activities between the two zinc finger DNA binding domains and the catalytic domain though recent evidence proposes a model for the DNA dependent catalytic activity involving a DNA bound Zn domain 1 interaction with another critical domain required for catalytic activity (Langelier et al., 2011). How this is regulated by SMI binding again is yet to be determined.

Currently there are over 40 ongoing clinical trials focusing on PARP inhibitors and patient response. Olaparib, a novel PARP1 inhibitor has entered into clinical trials and in conjunction with BRCA1/2 mutations has proven to increase efficacy of treatments and is in Phase II clinical trials. ABT-888 has been shown to not only inhibit PARP1 activity but to also inhibit PARP2 activity based on a PARP enzyme assay using purified protein (Donawho et al., 2007; Penning et al., 2009). More recently crystal structure data provided a potential mechanism for this specificity (Karlberg et al., 2010) and highlights the deep binding pocket that allow low nM inhibitors to be developed (Figure 1). While ABT-888 has entered into early phase clinical trials the true target remains to be determined (Kummar et al., 2010).

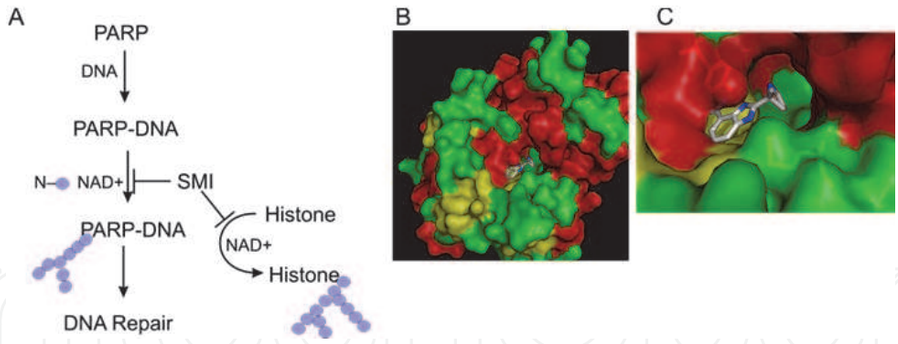


Fig. 1. Small Molecule Inhibitor of PARPs DNA Repair Activity. A) Depicted is the inhibitory effect of a general PARP SMI which disrupts the PARP catalyzed addition of poly(ADP)ribose onto various substrates or PARP itself. Disruption of this activity results in a decrease in DNA repair. B, C) Structural analysis of PARP- ABT-888 complex . PARP is colored according to secondary structure with red indicating α-helix, yellow β-sheet and green unstructured. ABT-888 is colored by element.

2.2 RPA inhibitors – targeting nucleotide excision repair, homologous recombination repair and DNA replication

Replication protein A (RPA) is involved in nearly all DNA metabolic pathways. It's involvement in the nucleotide excision repair (NER) pathway and the HR repair pathway is particularly important in the context of genome stability. RPA is the major human single strand DNA binding protein and participates in DNA replication at the fork, stabilizing single-stranded DNA (Wold, 1997). In NER RPA interacts with undamaged single strand DNA following the recognition of damaged nucleotides by Xeroderma Pigmentosum Group C (XPC), Rad23B and Centrin 2 in the initial steps of the NER pathway. RPA, together with the Xeroderma Pigmentosum Group A (XPA) protein and Transcription Factor II H (TFIIH), form the preincision complex of the NER pathway which is necessary for the proper functioning of the NER machinery (Araujo et al., 2000; Shuck et al., 2008). This preincision complex further guides the placement of downstream proteins such as Xeroderma Pigmentosum Group F (XPF) and Xeroderma Pigmentosum Group G (XPG) the proteins responsible for excising the damaged nucleotides. RPA also plays an indirect role in the HR repair pathway by interacting with Rad51 which initiates the HR pathway and promotes DNA strand exchange (Stauffer and Chazin, 2004; Sigurdsson et al., 2001). Disruption of RPA's DNA binding activity via a SMI would disrupt the formation of a functional NER preincision complex and decrease the efficiency of the NER machinery. In relation to cancer therapy, a decrease in NER efficiency is beneficial since this is the main pathway utilized for the removal of bulky DNA adducts, such as those resulting from cisplatin treatment.

Cisplatin is a common chemotherapeutic used as front line treatment for a number of cancers including those associated with the head and neck, non-small cell lung cancer (NSCLC), and testicular cancer. Cisplatin has a >90% cure rate for the treatment of testicular cancer (Einhorn, 2002); however in the case of NSCLC the response to cisplatin treatment varies significantly (Simon, 2008). Recurrence and resistance to cisplatin treatment are two significant clinical issues. In the cell, cisplatin elicits its toxic effect by forming covalent adducts with purine residues within the DNA. The NER preincision complex recognizes these bulky adducts and initiates the removal of the damaged nucleotides. Therefore,

inhibiting the NER machinery would result in an accumulation of cisplatin lesions on genomic DNA resulting in increased efficacy following treatment.

TDRL-505 – Recently a number of putative SMIs of RPA's DNA binding activity were identified and a subset of these putative inhibitors were analyzed *in vitro*. One inhibitor, TRDL-505, demonstrated an inhibitory effect on RPA's DNA binding activity as shown by electrophoretic mobility shift assays (EMSA) and by fluorescence polarization assays using both single- and double-strand DNA substrates with an IC_{50} value of 12.9 μM (Shuck and Turchi, 2010). This reversible RPA inhibitor disrupted not only the interaction of full-length RPA but also of the p70 domain of RPA with DNA (Figure 2). The p70 domain of RPA contains two of the main OB-folds which are involved in the RPA-DNA interaction (Bochkarev and Bochkareva, 2004). After demonstrating that TRDL-505 reduced the formation of an RPA-DNA complex, *in vivo* studies were initiated to study the cellular effect of TDRL-505. Although single agent treatment of lung cancer cell lines H460 and A549 with TDRL-505 resulted in a G1 arrest and increased non-apoptotic cellular death, combination treatment with cisplatin resulted in a synergistic level of efficacy in both cell lines. Other *in vivo* analyses, such as immunofluorescence and foci formation demonstrated both a decrease in cellular concentration of RPA and foci formation following treatment with TDRL-505, suggesting that TDRL-505 may be affecting the NER activity and the replication activity of RPA (Shuck and Turchi, 2010). Although a number of *in vitro* and *in vivo* studies have demonstrated not only an interaction between TRDL-505 and RPA but also a synergistic effect increasing cisplatin efficacy, the molecule interactions between RPA and TDRL-505 have not been determined. Further, mouse model studies, in addition to clinical testing, are necessary to further characterize the inhibitory effect of TDRL-505. The initial data, however, provide substantial support for studies involving SMIs, which interact directly with proteins in the NER pathway, specifically those necessary for the preincision complex formation.

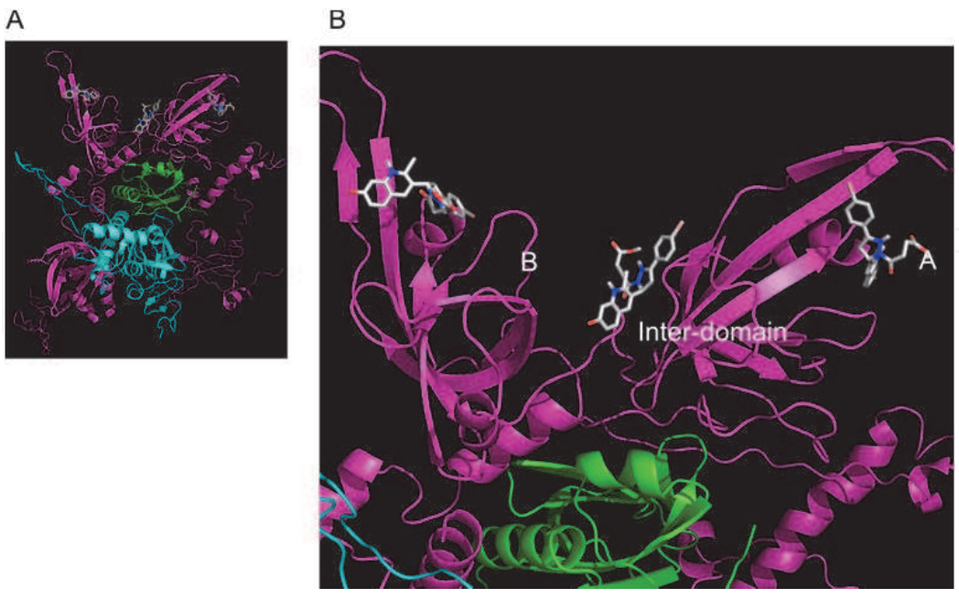


Fig. 2. Interaction of TDRL-505 with Replication Protein A. TDRL-505 is an *in vitro* characterized inhibitor of RPA's DNA binding activity. The modeled image demonstrates the potential interaction between TDRL-505 and RPA.

MCI – A second class of RPA inhibitors, containing a central isoborneol compound, irreversibly inhibit RPA's DNA binding activity *in vitro* (Anciano Granadillo et al., 2010).
This class of SMIs demonstrated an IC_{50} value below 5 μM and in some cases as low as 1 μM, depending on the cell line analyzed. Following single agent treatment, this class of compounds induced a classical apoptotic response and lengthened either G1 or S phases of the cell cycle. Furthermore, this class of compounds synergized with cisplatin following combination treatment and a sequential dosing schedule in which cisplatin was the first drug employed. Taken together, this data suggests that this class of isoborneol compounds may be employed as effective single agent chemotherapeutics or in combination with current chemotherapy drugs such as cisplatin. However, the MCI SMIs have potential off-target cellular effects, which render the compounds more effective, further analyses studying the direct *in vivo* targets of the MCI SMIs is necessary to form solid conclusions as to the exact mechanisms of the inhibitors.
More recently, novel SMIs of the N-terminal domain of RPA70, which is responsible for numerous protein-protein interactions important for DNA damage signaling and damage response, were identified using in silico and *in vitro* methodologies (Glanzer et al., 2011). One specific SMI, NSC15520, disrupted the RPA-p53 and RPA-Rad9 interactions but did not affect RPAs ability to bind to ssDNA. Although this SMI needs to be further characterized, this data demonstrates the feasibility of targeting protein-DNA interactions for therapeutic benefit.

2.3 XPA inhibitors – targeting nucleotide excision repair

XPA's only known role is in the NER pathway and this protein is essential for the formation of the preincision complex following damage recognition. Previous studies have demonstrated that a decrease in XPA expression in testicular cancer cell lines leads to a decrease in NER capacity and an increase in cisplatin efficacy (Koberle et al., 2006; Welsh et al., 2004; Koberle et al., 1999). Small molecules docked against XPA's minimal DNA binding domain (MBD), via *in silico* screening, led to the identification of a number of compounds with the potential to disrupt XPA's DNA binding activity (Neher et al., 2010). Primary screening, consisting of fluorescence polarization using a single stranded oligonucleotide containing a fluorescein label, identified 1 compound TDRL-X80, which disrupted the formation of the XPA-DNA complex (Neher et al., 2010).
TDRL-X80 - Fluorescence polarization and ELISA based assays were used to study the disruption of the XPA-DNA interaction in the presence of TDRL-X80. The assays were performed using single-, double-strand, and double-strand cisplatin-damaged DNA; and with all three substrates the XPA-DNA interaction was reduced with an IC_{50} value near 30 μM. Modeling of TDRL-X80 with XPA's MBD demonstrated that TDRL-X80 was in proximity to interact with Lysine 137 possibly disrupting XPA's DNA binding ability (Figure 3). These data provide support for the accuracy of the novel *in silico* screen in addition to providing a SMI of XPA's DNA binding activity. In addition, the data suggest the importance of Lys 137 in XPA's DNA binding activity rendering this amino acid potentially important for XPA's DNA binding function; however further analyses are necessary before this conclusion can be made. The possibility remains that *in vivo* TDRL-X80 may reduce the formation of a stable preincision complex, involving XPA and therefore reduce the NER capacity. If this occurs, as seen with the testicular data provided above, combination treatment with TDRL-X80 and cisplatin should increase the efficacy of drug treatment reducing cell division and increasing apoptosis.

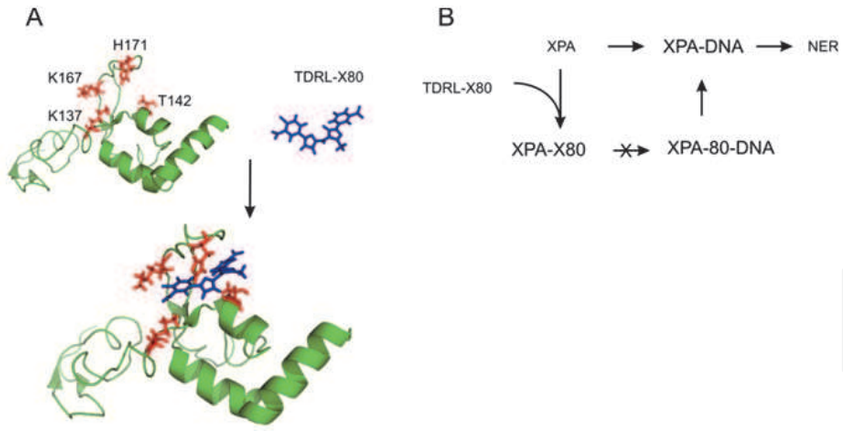


Fig. 3. Putative Interactions between TDRL-X80 and Amino Acids Localized in XPA's Minimal DNA Binding Domain. TDRL-X80 was modeled in silico in XPA's minimal DNA binding domain and amino acids within proximity are highlighted and may be potentially important for the XPA-X80 interaction.

2.4 DNA-PK inhibitors – targeting non-homologous end joining double strand break repair via ATP competitive inhibitors

DNA-PK, a heterotrimeric protein complex consisting of Ku70/80 and DNA-PKcs, plays an important role in the NHEJ pathway and the repair of double strand breaks (DSBs) by interacting with the free ends of genomic DNA and recruiting downstream end processing proteins such as artemis and fill-in/ligation proteins such as the XRCC4/Ligase IV complex (Pawelczak et al., 2010). Inhibiting proteins involved in the NHEJ pathway would result in a decrease in the repair of DNA DSBs and an accumulation of DNA damage, resulting in cellular death or apoptosis. DNA DSBs can be caused by a number of agents, including ionizing radiation (IR), which is commonly used for cancer therapy. IR treatment not only directly causes DSBs but also induces free radicals and reactive oxygen species which in turn may damage the DNA, creating abasic sites. IR, therefore, results in DNA ends which are difficult to ligate and require significant processing, which is the function of the NHEJ pathway. Thus, by decreasing the efficiency of the NHEJ pathway an increase in the effectiveness of IR may be possible. A number of SMIs of DNA-PK have been identified and extensively characterized *in vitro* and *in vivo*, although none target the DNA-PK-DNA interaction. Most of the inhibitors identified to date are competitive with the ATP substrate and do not appear to impact the necessary interaction of DNA-PK with DNA.

Wortmannin, one of the first identified DNA-PK inhibitors is an irreversible inhibitor that displays non-competitive kinetics, while competing with ATP (Izzard et al., 1999). The lack of specificity while limiting the utility of this agent as a chemical genetic probe, did provide key structural information used for the synthesis of analogs. Similarly other early PI-3K inhibitors, OK1035 and LY249002 were useful structurally but had limited utility to probe DNA DSB repair (Take et al., 1995, Hollick et al., 2003). Second generation ATP competitive inhibitor NU-7026 ((2-(morpholin-4-yl)-benzo[h]chromen-4-one) was shown to be more selective and more potent (Hollick et al., 2003). 2-N-morpholino-8-dibenzothiophenyl-chromen-4-one (NU7441) also based on LY294002 (Hardcastle et al., 2005), was shown to be more potent and more specific for DNA-PK with an IC_{50} value of 14 nM as demonstrated in an ELISA-based assay (Leahy et al., 2004). With low nM activity and increased specificity

these agents were active as radiosensitizers and sensitized cells to etoposide, a common chemotherapeutic that indirectly induces DNA DSBs (Zhao et al., 2006). These data support the possibility that NU7441 is an effective SMI of DNA-PK and in combination treatment with current chemotherapeutic regimens, such as IR or etoposide treatment, a decrease in repair would result in an increase in treatment efficacy. Continued development of both classes of inhibitors including NU7613 continue to target the ATP binding pocket of DNA-PK and result in increased potency and selectivity while also increasing cellular activity (Clapham et al., 2011; Cano et al., 2010; sage-El et al., 2008; Hollick et al., 2007; Griffin et al., 2005), however, their true utility as therapeutic agents awaits clinical assessment.

2.5 ATM inhibitors – targeting the DSB DNA damage response

The role of Ataxia telangiectasia mutated (ATM) in DSB repair has been studied in detail. This protein kinase plays an important role in the signaling cascade initiated in response to DNA DSBs. As mutation in ATM results in hypersensitivity to IR, similar to DNA-PK, chemical inhibition is a means of radiosensitizing cells to radiation treatment. Initial work also focused on non-specific inhibitors including wortmannin and caffeine. More recently a small molecule, KU-55933 (2-morpholin-4-yl-6-thianthren-1-yl-pyran-4-one), was identified and from a screen of a combinatorial library and characterization revealed potent and specific inhibition of ATM (Hickson et al., 2004). Specificity for ATM was 100x greater than that for any other tested proteins in the PIKK family and demonstrated an IC_{50} value of ~12.9 nM. Cells treated with KU-55933 after IR demonstrated a significant downregulation of the IR-induced phosphorylation of p53. Furthermore, UV-induced phosphorylation events were not altered by the addition of KU-55933 following UV damage, suggesting that KU-55933 is a specific inhibitor of ATM and not interacting indirectly with proteins in the NER pathway, which is used to repair UV-damaged DNA. Additional cell cycle analysis demonstrated that KU-55933 alone had no effect on the cell cycle; however, KU-55933 treatment following IR results in a shift to the G2/M phase in contrast to the G2/S or G2/M phase with IR treatment alone and KU-55933 did not alter the cell cycle for fibroblast cells even after IR treatment, again suggesting specificity and direct target effects by this ATM inhibitor. More recently, KU-55933 was observed to induce apoptosis as a single agent and ATM regulation of AKT was suggested to mediate this effect (Li and Yang, 2010). A similar effect was also observed with KU-60019, an improved more potent inhibitor (Golding et al., 2009). The mechanism of these inhibitors has not been described in detail however, these SMIs are based on the LY294002 compound (see section 2.4) and therefore one would expect both KU-55933 and KU-60019 to be competitive inhibitors with respect to ATP. Very similar results were also observed with another ATM inhibitor identified by screening a focused library (Rainey et al., 2008). Similar to DNA-PK inhibitors the utility of these as radiosensitizing agents for cancer therapy remains to be determined.

2.6 Indirect targeting of Rad51 via receptor tyrosine kinase inhibitors

Rad51 is a critical protein in homologous recombination (HR) and homology directed repair. RAD51 binds RPA coated single stranded DNA and mediates the search for homology. Rad51 is overexpressed in a variety of cancers and has been proposed to be a target for cancer therapy. Despite these intriguing data, no direct Rad51 inhibitors have been described to date. Rad51 however has been found to be down regulated in cells treated with an inhibitor of the c-Met Receptor tyrosine kinase (RTK). RTKs are involved in the

regulation of numerous cellular processes such as cell growth, differentiation and repair of damaged DNA. Additionally, overexpression and mutation of tyrosine kinases have been shown to be involved in the progression of many cancers. c-Met, one such RTK has been implicated in tumorigenesis and has recently become a target for SMIs (Eder et al., 2009; Welsh et al., 2009). The SMI, MP470 was designed as a general RTK inhibitor and was initially shown to inhibit c-Met in addition to other RTKs (Qi et al., 2009). More specifically, MP470 inhibits c-Met tyrosine kinase phosphorylation and has been shown to sensitize cells to IR and platinum-based therapies in addition to inducing apoptosis (Qi et al., 2009). Cells treated with MP470 were not only shown to have a reduction in c-Met but also a slight reduction in Akt- and IR-induced Rad51 expression, which is involved in the repair of DSB. Literature suggests that MP470 may impart its function by modulating Rad51 expression in a dose dependent manner; however, data supporting this statement remain sparse at best. Although MP470 has advanced to clinical trials, the plethora of indirect effects make determination of the contribution of HR repair to any observed activity nearly impossible to determine. Thus validation of Rad51 as a clinical target for cancer therapy will likely require an agent that directly targets this protein and its role in HR.

3. Inhibitors of transcription factors

Myriad of human diseases are associated with irregular transcription factor activity making this class of proteins and complexes highly desirable targets for therapy. Many factors however, have led some to consider these targets as "undruggable". The complexity of the interactions involving multi-point contact over large surfaces and lack of small pockets and crevices in which to design SMI's are only a few of the issues needed to be addressed. While not comprehensive, below we highlight a few of these efforts towards targeting the transcription factors and identify those with direct action blocking protein-DNA interactions versus indirect action.

3.1 Stat3 transcription factor

Signal transducer and activator of transcription 3 (Stat3) is a member of the Stat protein family that acts as a transcription activator. In response to cytokines and growth factors, Stat3 is activated by phosphorylation on tyrosine 705, and forms homo- or hetero-dimers via reciprocal interaction between its Src homology 2 (SH2) domain and the phosphorylated tyrosine residues. Stat3 dimers then translocate into the nucleus, where they bind to specific promoter sequences activating transcription. Stat3 target genes have been identified and include regulators of crucial steps in proliferation and survival, metastasis and angiogenesis, and immune evasion (reviewed in ref (Bowman et al., 2000; Darnell, Jr., 1997; Hsieh et al., 2005; Ihle, 1996). Constitutive activation of Stat3 has been observed in various human cancers such as breast, lung, head and neck, and prostate cancers and correlates with poor prognosis of these diseases (Bowman et al., 2000). Subcutaneously-injected cells expressing constitutively-activated Stat3 also formed tumors in xenograft animal models (Bromberg et al., 1999). Selective inhibition of aberrant Stat3 activity has been reported to inhibit cell proliferation and induce apoptosis in a variety of cancer cell lines (Yue and Turkson, 2009). Thus, Stat3 is one of the promising targets for antineoplastic drug discovery. Indeed, inhibitors directed against the Stat3 pathway have recently entered into clinical trials. For example, a phase-1 study of OPB-31121 in patients with advanced solid tumors is currently

recruiting participants. OPB-31121 appears to strongly inhibit Interleukin 6 (IL-6)-induced phosphorylation of Stat3, thereby inducing tumor cell apoptosis and regression. A variety of Stat3 inhibitors have been previously identified, although targeting the upstream kinases for Stat3 activation such as Janus kinase inhibitor AG490 (Burke et al., 2001), WP1066 (Iwamaru et al., 2007), TG101209 (Ramakrishnan et al., 2010) and AZD1480 (Hedvat et al., 2009) or upstream factors for its expression such as antisense oligonucleotides (Kunigal et al., 2009; Ling and Arlinghaus, 2005) have been considered and tested (Yue and Turkson, 2009). The following discussion focuses on the inhibitors specifically targeting protein-protein and protein-DNA interactions (Figure 4). For inhibitors directed against protein-protein interactions the first proof-of-concept approach was peptidic and peptidomimetic inhibitors mimicking the sequence that binds to the Stat3 SH2 domain disrupting Stat3 dimerization. These inhibitors include small peptides PpYLKTK (Turkson et al., 2001), pYLPQTV (Ren et al., 2003), certain peptide aptamers (Nagel-Wolfrum et al., 2004) and mimetics ISS610 (Turkson et al., 2004a). However, these inhibitors face challenges in membrane permeability and stability. Although the mimetics such as ISS610 have improved inhibition of Stat3 and selectivity over Stat1 and Stat5 in *in vitro* DNA-binding assays, their intracellular activity remains low as it cannot be efficiently taken up by cells (Turkson et al., 2004a). Nevertheless, these studies show that targeting the SH2 domain and dimerization of Stat3 is feasible. Recently, computational approaches and assay-based screening have been used to identify several potential SMIs targeting the SH2 domain. These SMIs include S3I-M2001 (Siddiquee et al., 2007b), STA-21 (Song et al., 2005; Chen et al., 2007), S3I-201 (Siddiquee et al., 2007a; Fletcher et al., 2009; Lin et al., 2009), Stattic (Schust et al., 2006), and catechol containing compounds (Hao et al., 2008). Additionally, these SMIs appear to inhibit Stat3 dimerization and have anti-proliferative effects on cancer cells. Although these inhibitors exhibited better cell permeability, stability and bioavailability than the peptidic and peptidomimetics, their moderate activities at medium to high micromolar levels will likely limit their clinical development.

Although the DNA-binding domain of transcription factors has been long considered undrugable, the inhibition of the DNA-binding activity of Stat3 for drug discovery has been tested. Galiellalactone (Weidler et al., 2000; Hellsten et al., 2008), flavopiridol (Lee et al., 2006) and a class of platinum (IV) compounds including IS3295 (Turkson et al., 2005), CPA-1, CPA-7 and platinum (V) tetrachloride (Turkson et al., 2004b), and decoy oligodeoxynucleotides (Xi et al., 2005; Zhang et al., 2007; Gu et al., 2008; Sun et al., 2008; Zhang et al., 2010; Barton et al., 2004) were found to interfere with Stat3 binding to DNA as well as induce cell growth inhibition and apoptosis of human breast, lung and prostate cancer cells (Hellsten et al., 2008; Barton et al., 2004; Zhang et al., 2010; Zhang et al., 2007; Xi et al., 2005; Sun et al., 2008; Gu et al., 2008; Turkson et al., 2004b; Turkson et al., 2005; Lee et al., 2006). Some of these inhibitors have been tested in animal models and they appear to cause regression of xenograft tumors. These findings suggest that the DNA-binding domain of Stat3 is likely drugable. Recently, using computation-based drug screening, targeting the DNA-binding site of Stat3, we identified Stat3-specific SMIs that were able to inhibit cell proliferation and induce cellular apoptosis of human breast and lung cancer cells at sub-micromolar concentrations (un-published data). Further investigation of these DNA-binding inhibitors of Stat3 will likely result in promising candidates for therapeutic development. However, more studies are clearly needed to assess further the therapeutic suitability of these agents and establish a pharmacologic and toxicity profile.

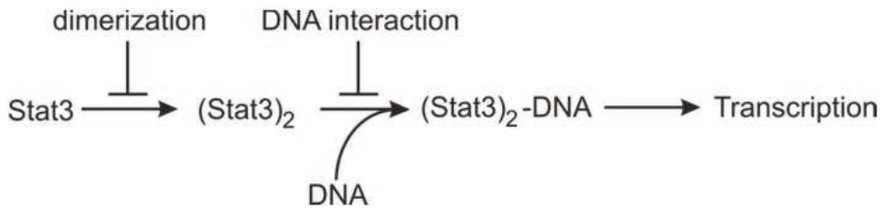


Fig. 4. Inhibitors of Transcription Factor Stat3. SMIs have been developed against Stat3's protein-protein and more recently protein-DNA interactions. Recently identified Stat3 inhibitors have demonstrated a decrease in the Stat3-DNA interaction and are being further characterized.

3.2 Direct inhibition of HOXA13-DNA interaction

HOXA13 is a member of the homeobox family of transcription factors involved in the regulation of development and has been found to play a role in the progression of a number of cancers (bate-Shen, 2002). These characteristics, like those of many transcription factors, make HOXA13 a viable target for inhibition towards therapeutic treatment of human cancer. As mentioned above, targeting the transcription factor-DNA interaction remains difficult but of high importance; therefore, a number of molecules with high complexity were designed to inhibit general transcription factors. An inhibitor of the HOXA13-DNA interaction was identified via a high-throughput screen of a library of lactam carboxamides (Ng et al., 2007). Researchers utilized a fluorescence polarization assay to screen the compounds and identified two lactam carboxamides which disrupted the HOXA13-DNA interaction. One identified inhibitor was further analyzed and demonstrated an IC_{50} value of ~6.5 μM. In addition, using a gene reporter assay, which places the HOXA13 transcription factor in control of the expression of luciferase, researchers demonstrated an increase in luciferase experssion following the addition of the HOXA13 inhibitor (Ng et al., 2007). Although the data presented suggest the disruption of the HOXA13-DNA interaction, there is very little additional information regarding this inhibitor. Although further biochemical studies need to be performed to confirm the inhibitor activity of this lactam carboxamide on HOXA13, these data provide support for the utility of high-throughput screens and the importance of inhibition of transcription factor-DNA interactions.

3.3 Targeting Notch transcription complexes

Notch proteins are membrane bound receptors, which are expressed during organogenesis and throughout adult tissues. Cell communication occurs when a Notch receptor interacts with a Notch ligand. Once activated, Notch is cleaved and then able to translocate into the nucleus to activate target genes by forming a complex with the DNA-bound transcription factor CSL (Schwanbeck et al., 2010). The Notch-CSL-DNA complex then recruits co-activator proteins to ultimately stimulate transcription. Notch proteins play important roles in a number of cellular processes such as cellular differentiation and proliferation, for example, increased Notch expression correlates with a predisposition for cancers (Weng et al., 2004; O'Neil et al., 2007). Targeting Notch transcription was achieved with an α-helical peptide designed to bind the Notch-CSL-DNA complex termed SAHM1. SAHM1 was able to compete with the co-activator MAMl1 in vitro and in cellular assays, capable of repressing Notch target gene expression (Moellering et al., 2009). Perhaps even more impressively, treatment of T-ALL cancer cells resulted in decreased proliferation in cell

culture models and also inhibited leukemic progression in an in vivo mouse model (Moellering et al., 2009). While this agent does not directly inhibit DNA binding of the transcription complex, the ability to target a DNA-bound factor on DNA represents a novel and exciting possibility of targeting other DNA bound proteins.

3.4 NF-kB inhibitor

Nuclear transcription factor-kappa B (NF-kB) has been shown to be activated in numerous tumors found in the breast, colon, prostate and skin (Amiri et al., 2004). This pleotropic pathway has been the subject of intense study and inhibitors of NF-kB signaling have been reported from numerous laboratories (Karin et al., 2004). The vast majority of these agents have been identified in cell based screening using reporter assays. While inhibition of NF-kB DNA binding activity is reported for many of these, there is a scarcity of data supporting a direct interaction NF-kB with any of these compounds. Again owing to the complexity of the system, there are numerous up-stream cellular events that could lead to reduced NF-kB DNA binding activity as measured in cell extracts prepared from treated cells. A number of indirect NF-kB inhibitors has been identified such as pristimerin, an inhibitor of NF-kB-1 kinase (KINK-1)(Schon et al., 2008; Lu et al., 2010). While, the data demonstrate that cells treated with pristimerin had less NF-kB activation, this is an indirect effect, which, while being therapeutically useful, is not mediated by a direct interaction with NF-kB. Similarly, research has clearly demonstrated that DHMEQ, a derivative of the antibiotic epoxyquinomicin C, which was studied as an inhibitor of NF-kB (Matsumoto et al., 2000), does not directly disrupt NF-kB interactions, rather it inhibits NF-kB activation by eliminating the nuclear translocation of NF-kB via inhibition of the tumor necrosis factor-alpha (Yamamoto et al., 2008; Cardile et al., 2010). Recently, screening of a library of FDA approved compounds for their ability to inhibit NF-kB signaling was reported and 19 drugs were identified that inhibited NF-kB signaling with IC_{50} values near 20 μM (Miller et al., 2010). Although the 19 drugs identified as NF-kB inhibitors are currently approved for clinical use they were not originally identified for direct interaction with NF-kB. Therefore, further characterization of each of the drugs is necessary to gain insight into their exact biological and molecular mechanisms before any cellular or physiologic effects can be attributed to inhibition of NF-kB.

4. Conclusion

The molecular interactions between proteins and DNA have been investigated for decades in the context of nearly every nuclear DNA metabolic pathway. The results obtained have provided significant insight and advances to the scientific community and generated considerable biochemical, structural and physiological knowledge. In the last decade a researchers began the search for inhibitors of such protein-DNA interactions and have found a number of inhibitors, which are able to disrupt these critical interactions. While there is a wide range of implications, this review has focused on the potential clinical utility associated with the disruption of protein-DNA interactions as a means to treat cancer. Cancer associated deaths remain the number one cause of mortality in the US and resistance to current chemotherapeutics remains a major clinical hurdle. Sensitizing cancer cells to treatment with DNA damaging chemotherapeutics holds great value, and disruption of protein-DNA interactions via SMIs is one way to achieve this result. The development of small drug-like molecules targeting protein-DNA interactions represent a new paradigm for disrupting cellular processes toward clinical utility.

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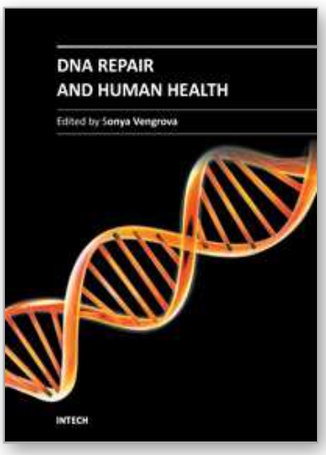
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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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