PROSPECTS
Journal of Cellular Biochemistry 115:611–624 (2014)

Journal of Cellular Biochemistry

Prospects on Strategies for Therapeutically Targeting Oncogenic Regulatory Factors by Small-Molecule Agents

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ABSTRACT

Although the Human Genome Project has raised much hope for the identification of druggable genetic targets for cancer and other diseases, this genetic target-based approach has not improved productivity in drug discovery over the traditional approach. Analyses of known human target proteins of currently marketed drugs reveal that these drugs target only a limited number of proteins as compared to the whole proteome. In contrast to genome-based targets, mechanistic targets are derived from empirical research, at cellular or molecular levels, in disease models and/or in patients, thereby enabling the exploration of a greater number of druggable targets beyond the genome and epigenome. The paradigm shift has made a tremendous headway in developing new therapeutic agents targeting different clinically relevant mechanisms/pathways in cancer cells. In this Prospects article, we provide an overview of potential drug targets related to the following four emerging areas: (1) tumor metabolism (the Warburg effect), (2) dysregulated protein turnover (E3 ubiquitin ligases), (3) protein–protein interactions, and (4) unique DNA high-order structures and protein–DNA interactions. Nonetheless, considering the genetic and phenotypic heterogeneities that characterize cancer cells, the development of drug resistance in cancer cells by adapting signaling circuitry to take advantage of redundant pathways or feedback/crosstalk systems is possible. This "phenotypic adaptation" underlies the rationale of using therapeutic combinations of these targeted agents with cytotoxic drugs. J. Cell. Biochem. 115: 611–624, 2014.

KEY WORDS: WARBURG EFFECT; E3 LIGASES; PROTEIN–PROTEIN INTERACTIONS; PROTEIN–DNA INTERACTIONS; DNA QUADRUPLEX

In light of remarkable technological breakthroughs in cancer "omics," the past decade has witnessed tremendous progress in our understanding of cancer biology [Vucic et al., 2012]. These advances have also been translated into new cancer biomarkers and therapeutic targets, leading to a shift in the paradigm of drug discovery toward a target-based rational design approach in lieu of empirical structure–activity relationship-based lead modifications. Such a paradigm is epitomized by the FDA's approvals of more than 10 kinase inhibitors that target mutational activation of kinase signaling in various types of malignancies [Zhang et al., 2009; Dar and Shokat, 2011], including *BCR–ABL* fusion in chronic myelogenous leukemia [Druker et al., 2001], *BRAF* mutations in melanomas [Flaherty et al., 2010], *EGFR* mutations in a subset of lung adenocarcinoma [Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004], and *ALK* fusion in lung cancer [Koivunen et al., 2008].

Although these new therapeutic agents have led to improved clinical outcomes for many cancer patients, kinase inhibitors face two major challenges in clinical development, that is, specificity for target versus off-target kinases and emergence of drug resistance. Most kinase inhibitors developed so far act by competing with ATP for the ATP-binding sites located at the hinge region of target kinases [Zhang et al., 2009]. As there are a total of 518 kinases encoded in the human genome [Venter et al., 2001], it is inevitable that many of these drugs show complex clinical pharmacology in vivo by targeting multiple kinases [Zhang et al., 2009; Dar and Shokat, 2011], which raises potential concerns of untoward side effects arising from this polypharmacology. However, from a clinical perspective, such multikinase inhibitors might be therapeutically advantageous through enhanced efficacy by targeting a spectrum of kinases involved in cancer pathogenesis and progression. Examples include sorafenib [Ahmad and Eisen, 2004] and sunitinib [Fabian et al., 2005], both of which suppress tumor proliferation and angiogenesis by blocking multiple kinase pathways, including those mediated by RAF-kinase, vascular endothelial growth factor receptor (VEGF)2, VEGF3, platelet-derived growth factor receptor-β, KIT, and FLT3. With regard to drug resistance, cancer cells acquire a resistant

Grant sponsor: National Institutes of Health; Grant numbers: CA112250, CA158807; Grant sponsor: Stefanie Spielman Fund for Breast Cancer Research; Grant sponsor: Lucius A. Wing Endowed Chair Fund.

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Manuscript Received: 20 October 2013; Manuscript Accepted: 22 October 2013
Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 25 October 2013
DOI 10.1002/jcb.24704 • © 2013 Wiley Periodicals, Inc.

phenotype to kinase inhibitors under selective pressure, in part, through target amplification or mutations at the gate-keeper residues that abrogate drug binding [Zhang et al., 2009]. Alternatively, cancer cells might adapt their signaling circuitry to develop compensatory mechanisms by taking advantage of redundant signaling pathways or feedback/crosstalk systems to counteract drug actions [Logue and Morrison, 2012].

Another frontier that has progressed rapidly in cancer therapeutic development is epigenetic-modulating drugs [Rodríguez-Paredes and Esteller, 2011]. The cancer epigenome is characterized by global changes in the patterns of DNA methylation and histone modifications arising from dysregulated expression of DNA methyltransferases (DNMTs) and histone-modifying enzymes, including histone acetyltransferases (HATs)/deacetylases (HDACs), lysine- and arginine-specific methyltransferases (HMTs)/demethylases (HDMs), kinases/phosphatases, and so on [Kouzarides, 2007]. Dysregulation of any of these epigenetic enzymes through mutations or altered expression results in aberrant gene expression associated with typical cancer traits. More important, in contrast to genetic mutations, the reversible nature of epigenetic changes in the patterns of DNA methylation and histone acetylation/methylation underlies the impetus of targeting this epigenetic machinery, particularly DNMTs [Heyn and Esteller, 2012; Singh et al., 2013] and HDACs [Marks, 2010], in cancer cells to restore the epigenome to its normal state. In the past few years, the epigenetic field has generated 4 FDA-approved drugs for the treatment of subtypes of leukemia and lymphoma, including the DNMT inhibitors 5-azacytidine (azacitidine, Vidaza) and 5-aza-2′-deoxycytidine (decitabine, Dacogen) for myelodysplastic syndrome and the HDAC inhibitors SAHA (vorinostat, Zolinza) and depsipeptide (romidepsin, Istodax) for the rare cutaneous T cell lymphoma and other hematological malignancies.

Although the biology of other epigenetic enzymes remains less well defined, inhibitors of many of these enzymes, especially those of sirtuins, HATs, HMTs, and HDMs, have shown promising preclinical tumor-suppressive efficacy in vitro and/or in vivo [Rodríguez-Paredes and Esteller, 2011].

HOW MANY DRUGGABLE ANTICANCER TARGETS ARE THERE? GENOME- VERSUS MECHANISM-BASED TARGETS

Although the Human Genome Project has raised much hope/hype for the identification of druggable genetic targets for cancer and other diseases, this genetic target-based approach, however, has not improved productivity over the traditional approach. This discrepancy might, in part, be attributable to the complex process of in vitro and in vivo validation of these targets in relevant cell and transgenic animal models [Sams-Dodd, 2005]. Analyses of known human target proteins of currently marketed drugs reveal that these drugs target only a limited number of proteins as compared to the whole proteome. For example, a comprehensive analysis of all FDA-approved small-molecule drugs, a total number of 1,204, by Overington et al. [2006] indicated that these drugs, including 5 kinase inhibitors acting on 18 protein kinases, targeted 207 distinct human genome-derived proteins [Hopkins and Groom, 2002], a small number in comparison to the estimated 30,000 human protein-coding genes [Overington et al., 2006]. The majority of these 207 drug-targeted proteins in human cells fall into the following categories: G protein-coupled receptors, ligand-gated ion channels, nuclear receptors, phosphodiesterases, proteases, protein kinases, voltage-gated ion channels, and enzymes involved in DNA synthesis/mitosis [Overington et al., 2006]. With the exception of kinases, the identification of these targets, prior to the Human Genome Project, were based on laboratory or clinical findings associated with various pathological conditions. From a translational perspective, this mechanism-based approach avoids the one-gene-one-disease hypothesis, and can be applied much more broadly in the context of target identification.

In contrast to genome-based drug targets, mechanistic targets are derived from empirical research, at cellular or molecular levels, in disease models and/or in patients, thereby enabling the exploration of a greater number of druggable targets. This approach is illustrated by the therapeutic targeting of the Warburg effect by developing inhibitors of enzymes involved in glucose metabolism in tumor cells. In addition, a number of molecular defects resulting from dysregulated protein turnover or interactions with other macromolecules (proteins and DNA) have also been interrogated as targets (Fig. 1), which are delineated as follows.

THE WARBURG EFFECT (TUMOR METABOLISM): GLYCOLYTIC ENZYMES AS TARGETS

Cells undergoing malignant transformation often exhibit a shift in cellular metabolism from oxidative phosphorylation to glycolysis, known as the Warburg effect, to gain growth advantage [Kroemer and Pouyssegur, 2008; Vander Heiden, 2011]. This glycolytic shift enables cancer cells to adapt to low-oxygen environments, to produce biosynthetic building blocks needed for cell proliferation, to acidify the local environment to facilitate tumor invasion, and to generate NADPH and glutathione through the pentose phosphate shunt to increase resistance to oxidative stress. As the Warburg effect is considered a fundamental property of neoplasia, targeting glycolysis represents a therapeutically relevant strategy for cancer treatment [Eisenstein, 2012]. Thus, development of small-molecule agents that target various aspects of glucose metabolism has been the focus of many recent investigations, which are summarized in Table I.

The emerging view of cancers as a metabolic disease opens up opportunities for the development of new strategies for cancer therapy. Many of the tumor metabolism-targeted agents listed in Table I exhibit in vivo efficacy alone or in combination with chemotherapeutic drugs in advanced cancers. Although it is generally believed that interference with energy metabolism gives rise to ATP depletion and metabolic stress, leading to cell death, data from this and other laboratories indicate that reduction of glycolytic rate by energy restriction elicits the activation of multiple signaling pathways, including those mediated by the NAD^+-dependent HDAC Sirt1 (silent information regulator 1), AMPK, and endoplasmic reticulum (ER) stress [Wei et al., 2010]. This complicated signaling network affects many aspects of cellular functions in cell cycle regulation, survival, and aggressive phenotype, culminating in cancer cell death through autophagy and apoptosis. Thus, it is plausible to achieve

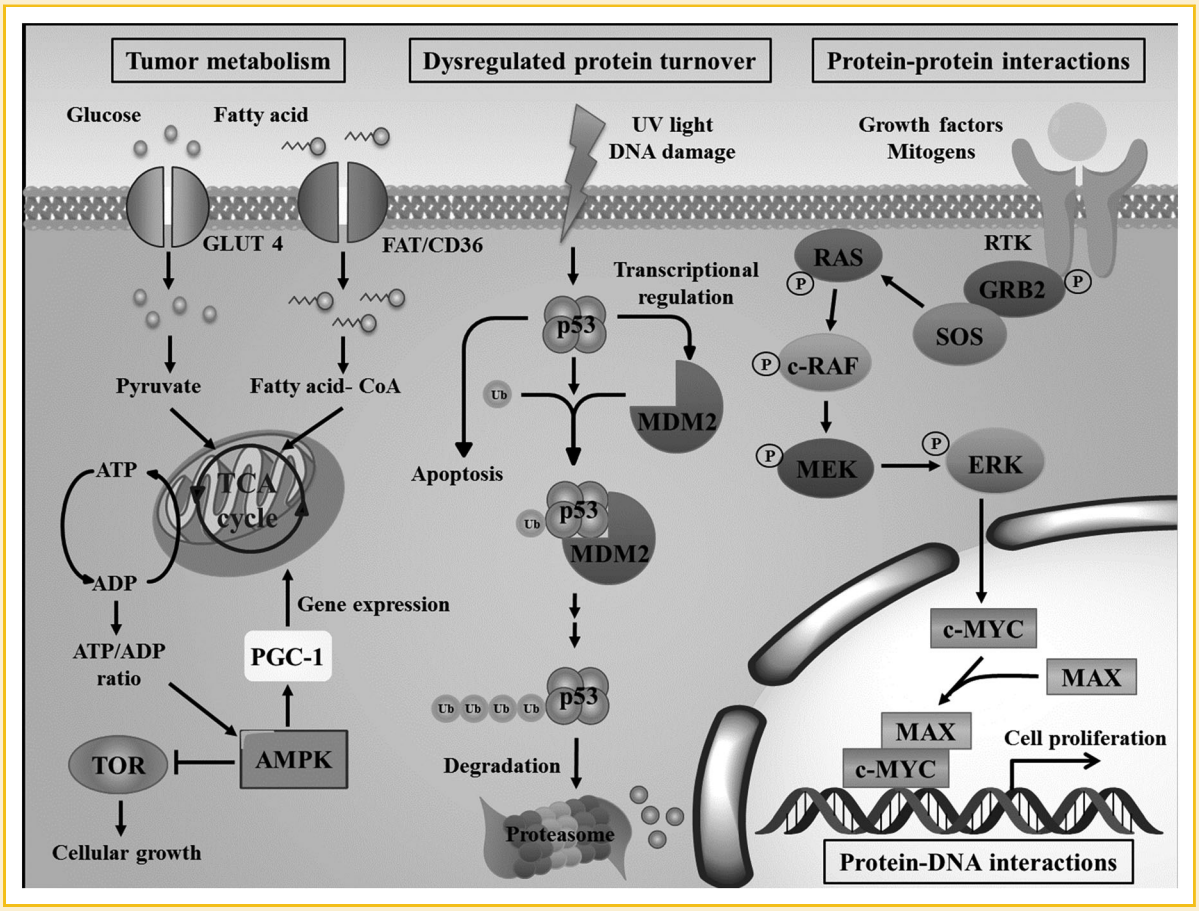

Fig. 1. Pathways identified by a mechanism-based approach as promising targets for anticancer therapy. Pathways associated with energy metabolism, protein turnover, and protein–protein and protein–DNA interactions can be dysregulated in cancer cells, and involve multiple potentially druggable targets.

synergy in killing cancer cells by using metabolism-targeted agents with other molecularly targeted agents, such as kinase inhibitors or HDAC inhibitors. Further understanding of the signaling mechanisms underlying the antitumor effects of these tumor metabolism-targeted agents will help foster novel strategies for cancer therapy.

DYSREGULATED PROTEIN TURNOVER: ONCOGENIC E3 LIGASES AS TARGETS TO RESTORE DYSREGULATED PROTEIN FUNCTION

The ubiquitin-proteasome system (UPS) plays a pivotal role in the regulation of key cellular functions, including cell cycle control, DNA repair, and growth factor receptor signaling, through targeted degradation of regulatory proteins [Devoy et al., 2005]. UPS-mediated protein degradation consists of two sequential steps initiated by ubiquitination of the target protein, followed by proteolysis via the 26S proteasome complex. The targeted ubiquitination is mediated through the concerted action of three enzymes: E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and E3 ubiquitin ligase (Fig. 3) [Nakayama and Nakayama, 2006]. In the past few years, inhibitors targeting different components of this ubiquitination system have been developed. For example, a mechanism-based neddylation inhibitor, MLN4924, was developed to target NEDD8 activating enzyme, an essential component of the NEDD8 conjugation pathway that controls the activity of the cullin-RING subtype of ubiquitin ligases [Soucy et al., 2009], while small-molecule inhibitors of murine double minute 2 protein (Mdm2) have progressed into preclinical/clinical development (see discussion below). From a therapeutic perspective, relative to E1 and E2, E3 ligases are of particular interest as drug targets for their role in conferring the selectivity for protein ubiquitination [Nalepa et al., 2006].

E3 ligases can be divided into three groups: the RING-finger E3s, the HECT (homologous to E6-AP COOH-terminus)-domain E3s, and the U-box E3s, each of which is characterized by a distinct protein interaction domain (RING-finger, HECT, or U-box domain) that serves to bind E2 ligases. As these E2-interacting domains are highly conserved, the specificity of E3 ligases is conferred by a variable substrate recognition motif that determines which substrate is to be ubiquitinated. Consequently, while proteasome inhibitors block the degradation of all ubiquitinated proteins indiscriminately, targeting a single E3 ligase allows for selective stabilization of a subset of ubiquitinated proteins. In light of this increased specificity,

TABLE I. Small-Molecule Agents Targeting Glucose Metabolism

Target (small-molecule agents)	Mode of action
1. Glucose intake	
Glufosfamide[a]	Glufosfamide is a covalent conjugate of glucose with an ifosfamide mustard. Cancer cells preferentially take up glufosfamide, which is metabolized to release a cytotoxic compound, isophosphoramide, to kill cancer cells. This agent has undergone clinical trials in solid tumors, alone or in combination with gemcitabine, with low to modest activities [Chiorean et al., 2008; Ciuleanu et al., 2009]
2. Adenosine monophosphate-activated protein kinase (AMPK)	
5-Amino-imidazole-4-carboxamideribo-nucleotide (AICAR)	AICAR is widely used experimentally to activate AMPK and effectively inhibits the growth of established tumor cells in vitro and in vivo [Xiang et al., 2004; Rattan et al., 2005; Swinnen et al., 2005; Buzzai et al., 2007]
Metformin and its analogues phenformin and biguanide	Epidemiologic data have suggested the chemopreventive potential of metformin in breast cancer [Evans et al., 2005], which is supported by its in vivo efficacy in suppressing breast xenograft tumor growth in nude mice [Liu et al., 2009]. At the molecular level, metformin suppresses cancer cell growth by inhibiting mTOR-dependent translation initiation through AMPK activation [Zakikhani et al., 2006; Dowling et al., 2007], or through the phosphorylating inactivation of acetyl-CoA carboxylase accompanied by suppression of fatty acid synthase, leading to growth inhibition through the blockade of lipogenesis [Xiang et al., 2004; Guo et al., 2009]
OSU-53	OSU-53, developed in the authors' laboratory, is an allosteric activator of AMPK by binding to the auto-inhibitory domain [Guh et al., 2010]. Thus, it directly activates the kinase activity of the recombinant AMPK $\alpha 1\beta 1\gamma 2$ with EC_{50} of 0.3 μM relative to 8 μM for AMP. This AMPK activator inhibits cancer cell proliferation by targeting both metabolic and oncogenic signaling pathways [Lee et al., 2011]. Especially noteworthy is that OSU-53 blocks Akt signaling via a protein phosphatase 2A-dependent pathway
3. Glucose transporters	
CG-5	CG-5, a peroxisome proliferator-activated receptor γ-inactive ciglitazone derivative, is a promising energy restriction-mimetic agent (ERMA) with high 20- and 1,000-fold higher potency than resveratrol and 2-DG, respectively [Wei et al., 2010; Wang et al., 2012a]. CG-5 inhibits glucose metabolism through effects at different molecular levels, including the cellular uptake of glucose, inhibition of Akt, and the transcription of genes associated with glycolysis and energy metabolism. Further investigation of additional mechanisms is currently underway
Silybin	Silybin, a flavonoid natural product, is widely used to treat hepatocellular carcinoma and cirrhosis-associated insulin resistance. A recent study indicates that silybin and its derivative dehydrosilybin inhibit cellular glucose uptake by directly interacting with GLUT transporters [Zhan et al., 2011]
Resveratrol	Resveratrol has been reported to target cancer cells, in part, by mimicking energy restriction [Baur and Sinclair, 2006; Cucciolla et al., 2007; Bishayee, 2009; Lin et al., 2010]. Many studies show the anti-cancer activity of resveratrol in vitro and in animal models [Jang et al., 1997]. With the exception of skin and gastrointestinal tract tumors [Athar et al., 2007], resveratrol showed no activity against the growth of existing tumors, in part, due to its poor systemic bioavailability [Wenzel et al., 2005; Niles et al., 2006; Boocock et al., 2007]
4. Hexokinase II (HK II)	
Lonidamine	Inhibition of the mitochondrial-bound HK II not only affects glucose metabolism but also increases the sensitivity of cancer cells to apoptosis by facilitating the docking of Bax on the HK II-binding partner voltage-dependent anion channel (VDAC) [Mathupala et al., 2006]. Phase II trials with the combination of lonidamine and cytotoxic chemotherapy was active against advanced nonsmall cell lung cancer and ovarian cancer [Portalone et al., 1999; De Lena et al., 2001]. However, in the absence of cytotoxic drugs, lonidamine showed little activity against nonsmall cell lung cancer or glioblastoma multiforme [De Marinis et al., 1999; Oudard et al., 2003]
3-Bromopyruvate (3-BrPA)	3-BrPA is an alkylating agent with structural similarity to lactate, which may enter cancer cells on the same transporter that exports lactate and then induce ATP depletion [Ko et al., 2004]. 3-BrPA showed in vitro and in vivo efficacy in suppressing the growth of hepatocellular carcinoma [Kim et al., 2007b] and breast cancer [Buijs et al., 2009]
5. Phosphohexose isomerase	
2-Deoxyglucose (2-DG)	2-DG blocks glycolysis through the inhibition of phosphohexose isomerase [Sols and Crane, 1954; Tower, 1958], which leads to depletion of ATP and glucose derivatives required for protein glycosylation. 2-DG also induces unfolded protein response (UPR), as does low glucose stress [Hightower, 1990; Little et al., 1994]. 2-DG effectively blocks growth of rat fibrosarcoma [Kern and Norton, 1987], hepatocellular carcinoma [Cay et al., 1992; Geschwind et al., 2004], and other tumors by itself or in combination with other chemotherapeutic agents [Maher et al., 2004; Maschek et al., 2004]
6. Lactate dehydrogenase A (LDH-A)	
FX-11	Treatment of P493 human lymphoma B cells with FX11 reduced ATP levels and caused oxidative stress-induced cell death, and inhibited the progression of human lymphoma and pancreatic xenograft tumor growth [Le et al., 2010]
7. Pyruvate kinase	
TLN-232 (or CAP-232)	The M2 splice isoform of pyruvate kinase has been reported to play an important role in cancer metabolism and tumor growth [Christofk et al., 2008]. TLN-232 is a cyclic heptapeptide targeting M2PK, which is currently undergoing a small phase II study in metastatic melanoma [Hersey et al., 2009]

TABLE I. (*Continued*)

Target (small-molecule agents)	Mode of action
8. Pyruvate dehydrogenase kinase (PDK) Dichloroacetate (DCA)	DCA has been proposed as a novel and relatively non-toxic anti-cancer agent that can reverse the glycolytic phenotype in cancer cells through the inhibition of PDK [Michelakis et al., 2008]. DCA has been in clinical use since 1969 for the treatment of lactic acidosis, and is currently undergoing clinical trials to evaluate its toxicity in cancer patients
9. Monocarboxylate transporter 1 (MCT1) α-Cycno-4-hydroxy-cinnamate (CHC)	Inhibition of MCT1 by CHC induced a switch from lactate-fueled respiration to glycolysis in oxygenated tumor cells, and suppressed lung and colon xenograft tumor growth [Sonveaux et al., 2008]
10. ATP citrate lyase SB-204990	Inhibition of ATP citrate lyase by SB-204990 blocks cytosolic acetyl-CoA production and lipid synthesis, thereby inhibiting proliferation and survival of tumor cells displaying aerobic glycolysis in vitro and in vivo [Hatzivassiliou et al., 2005]

[a]Structures of all chemical compounds mentioned in this review are listed in Figure 2.

it is more therapeutically advantageous to target E3 ligases, as compared to the proteasome, to increase the stability/activity of selected tumor-suppressive proteins.

Among the three groups of E3 ligases, RING-finger E3 ligases have received much attention in the development of small-molecule inhibitors, which are represented by inhibitors of Mdm2 and S-phase kinase associated protein 2 (Skp2) in light of their well-characterized roles in regulating the degradation and/or activity of the tumor suppressors p53 [Kubbutat et al., 1997] and p27 [Carrano et al., 1999], respectively. The therapeutic targeting of Mdm2, Skp2, and other E3 ligases involved in regulating the stability of oncogenic or tumor-suppressive proteins are addressed as follows.

Mdm2

At the cellular level, Mdm2 and p53 are mutually regulated through an autoregulatory feedback loop: in response to stress signals, p53 transcriptionally activates Mdm2 gene expression, and in turn Mdm2 inhibits the transcriptional activity and promotes the ubiquitin-dependent proteasomal degradation of p53 [Wang et al., 2012b]. Thus, dysregulation of this regulatory loop results in malignant transformation of normal cells. Among all E3 ligases identified, Mdm2 is the most intensely pursued target, leading to the development of several structurally distinct classes of inhibitors, at least six of which have progressed into clinical trials in advanced solid tumors or acute myelogenous leukemia [Zhao et al., 2013]. Mechanistically, Mdm2 inhibitors are classified into two categories: inhibitors of the Mdm2-p53 protein–protein interactions, such as Nutlin-3 [Vassilev et al., 2004] and most other Mdm2 inhibitors [Zhao et al., 2013], and inhibitors of the Mdm2 E3 ligase activity [Yang et al., 2005].

Recently, MdmX, an Mdm2 homolog, has also received considerable attention as a target for therapeutic development [Zhao et al., 2013] because of its non-redundant and essential role as a negative regulator of p53 [Finch et al., 2002)]. MdmX has no E3 ligase activity, but forms heterodimers with Mdm2 through their RING domains to increase Mdm2 E3 ligase activity [Tanimura et al., 1999]. However, due to the high degree of sequence homology between Mdm2 and MdmX, many small-molecule inhibitors that were designed to target MdmX-p53 interactions also showed high affinity with Mdm2, thus becoming MdmX/Mdm2 dual inhibitors.

Skp2

Substantial evidence indicates that Skp2, a Skp1-Cul1-F-box (SCF) E3 ubiquitin ligase, acts as an oncoprotein by targeting a wide range of signaling effectors, such as the tumor suppressor p27 [Carrano et al., 1999], for degradation. Moreover, it was demonstrated that Skp2 facilitates the activation of Akt through ubiquitination downstream of ErbB receptor signaling in Her2-positive breast cancer [Chan et al., 2012], and that Skp2 represents a key component for the Mre11/Rad50/NBS1 (MRN) complex-mediated ATM activation in response to DNA double-strand breaks through NBS1 ubiquitination [Wu et al., 2012]. Together, this oncogenic E3 ligase represents an important target for cancer drug discovery [Frescas and Pagano, 2008; Wang et al., 2012c].

Data from the authors' laboratory indicate that downregulation of Skp2 represents a cellular response in cancer cells to energy restriction induced by CG-5 (a novel glucose transporter inhibitor) and 2-deoxyglucose [Wei et al., 2012]. This Skp2 downregulation was attributable to Sirt1-dependent suppression of COP9 signalosome (Csn)5 expression in response to CG-5, leading to increased cullin 1 neddylation in the SCF protein complex and consequent Skp2 destabilization. This finding provides a proof-of-concept that the oncogenic Csn5/Skp2 signaling axis represents a "druggable" target by using this novel glucose transporter inhibitor. More recently, a Skp2 inhibitor, 3-(1,3-benzothiazol-2-yl)-6-ethyl-7-hydroxy-8-)1-piperidinylmethyl)-4H-chromen-4-one (compound #25), that selectively inhibited Skp2 E3 ligase activity, but not other SCF complexes, was identified using high-throughput in silico screening [Chan et al., 2013]. This Skp2 inhibitor phenocopied the effects observed upon genetic Skp2 deficiency, such as suppressing survival and Akt-mediated glycolysis and triggering p53-independent cellular senescence, and showed antitumor efficacy in multiple animal models.

β-TRANSDUCIN REPEAT-CONTAINING PROTEIN (β-TrCP)

Besides Skp2, another SCF E3 ligase that has received much attention is β-TrCP. In contrast to Skp2, the role of β-TrCP as a therapeutic target remains controversial because it plays a dichotomous role, either oncogenic or tumor-suppressive, in a cellular context-dependent manner considering its diverse substrate spectrum [Frescas and Pagano, 2008]. Although evidence suggests its oncogenic character is mediated through the activation of NF-κB signaling

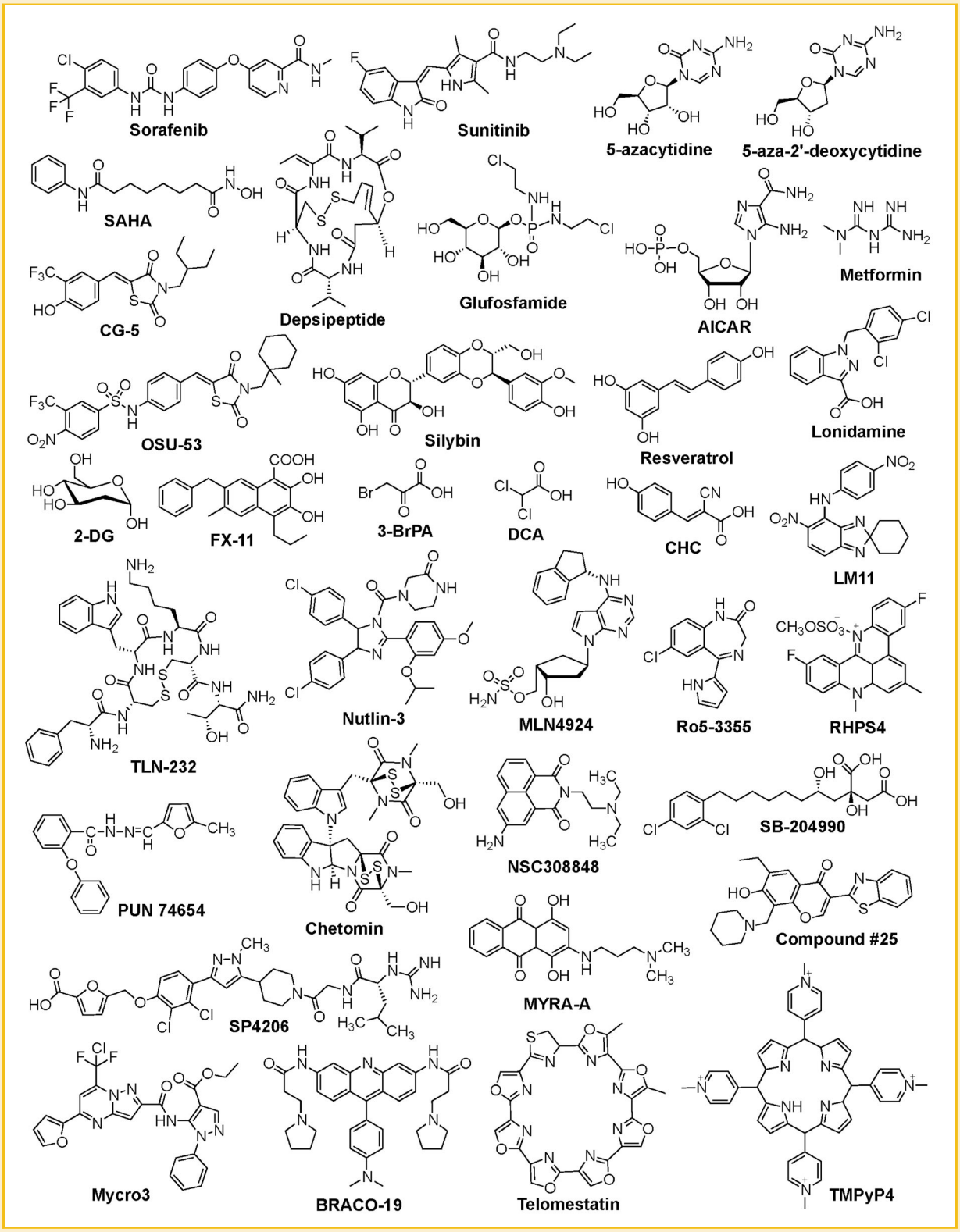

Fig. 2. Structures of all of the small-molecule agents mentioned in this article.

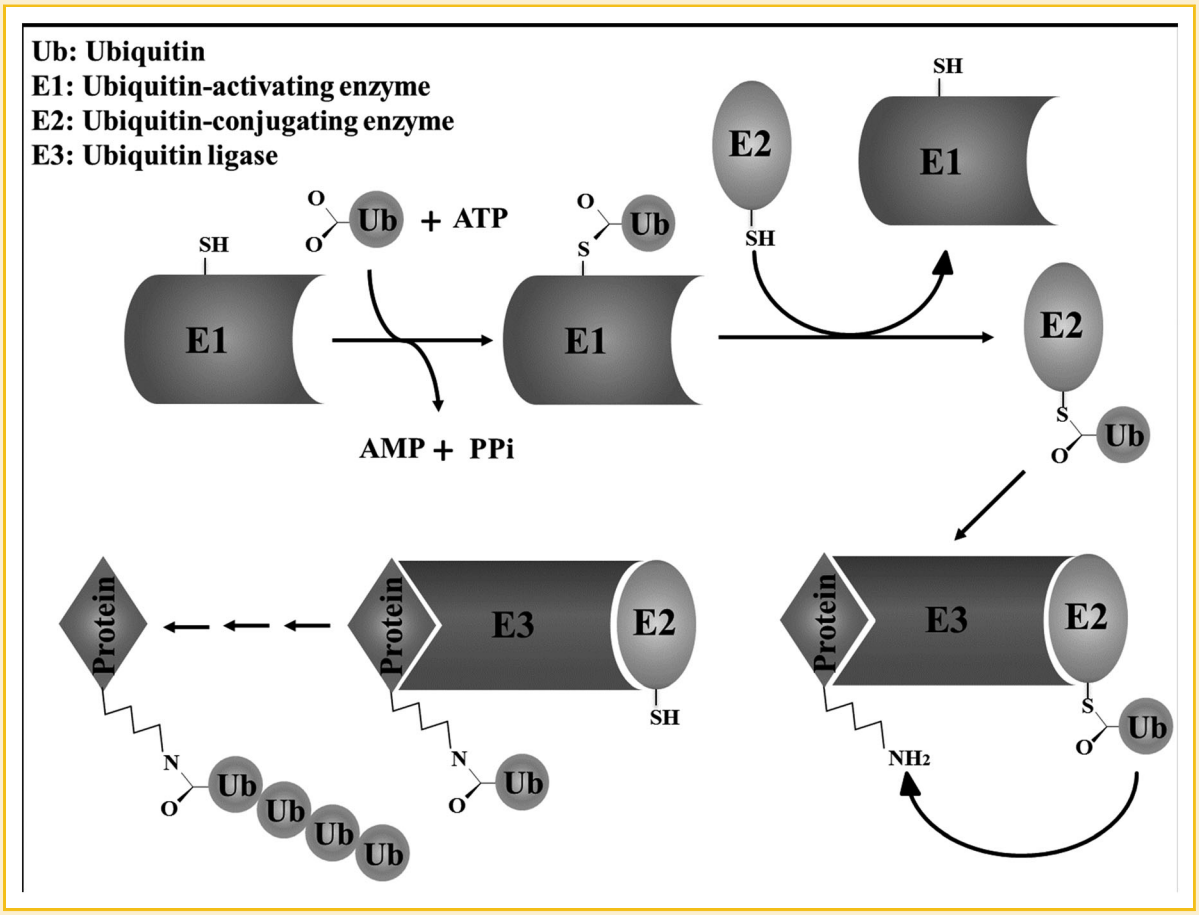

Fig. 3. Diagram depicting the ubiquitination of a target protein. The protein is ubiquinated by the concerted actions of three enzymes (E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and E3 ubiquitin ligase) which marks it for subsequent degradation by the 26S proteasome complex.

[Fuchs et al., 2004], β-TrCP also facilitates the degradation of a wide array of tumor-promoting proteins, including β-catenin [Hart et al., 1999], Snail [Yook et al., 2006], ATF4 [Lassot et al., 2001], cdc25A [Jin et al., 2003], Mcl-1 [Ding et al., 2007], cyclin D1 [Wei et al., 2008], and Sp1 [Wei et al., 2009], thereby suppressing cancer cell proliferation and invasion. The authors previously demonstrated that treatment of cancer cells with the glucose transporter inhibitor CG-5 led to decreased Skp2 accompanied by upregulated β-TrCP expression, as Skp2 targets β-TrCP for degradation via a cyclin-dependent kinase 2-dependent mechanism [Wei et al., 2012]. Mechanistic evidence indicates that this β-TrCP upregulation underlies the suppressive effect of CG-5 on cancer cell proliferation. Together, these findings raise a question of whether the inhibition of β-TrCP-mediated ubiquitination represents a therapeutically relevant strategy for cancer treatment.

CASITAS B-LINEAGE LYMPHOMA (c-Cbl)

Is a RING-type E3 ligase involved in ubiquitination and degradation of BCR–ABL, EGFR, and a series of other receptor and non-receptor protein kinases [Lu and Hunter, 2009]. Thus, wild type c-Cbl has been proposed to function as a tumor suppressor. A recent report indicates that arsenic sulfide (As_4S_4) upregulated the expression of c-Cbl by blocking its self-ubiquitination/degradation through the RING finger binding, thereby inducing degradation of BCR-ABL in chronic myelogenous leukemia (CML) [Mao et al., 2010]. This finding provides a molecular basis to design small-molecule agents that activate c-Cbl through a similar mode of mechanism.

TARGETING PROTEIN–PROTEIN INTERACTIONS

The concept of targeting protein–protein interactions has been demonstrated by therapeutic antibodies, which block ligand-mediated activation of growth factor or cytokine receptors. In contrast, even just a decade ago, it was generally perceived unfeasible to develop selective small-molecule compounds that could interfere with protein–protein interactions effectively, of which the reason is multifold [Arkin and Wells, 2004]. For example, the interface involved in the protein–protein complex formation is typically large and associated with diverse protein topologies, and small molecules would have to compete with macromolecular partners for binding. However, recent advances in structural biology and bioinformatic analysis indicate that a few amino acids at the interface ("binding hotspots") contribute to the majority of the binding energy in protein–

TABLE II. Examples of Targeting Protein–Protein Interactions by Small-Molecule Inhibitors

Protein–protein interaction	Clinical relevance
Arf/ARNO [Viaud et al., 2007]	Arf1, a major regulator of cellular traffic, is activated by the Sec7 catalytic domain of its guanine nucleotide exchange factor ARNO [D′Souza-Schorey and Chavrier, 2006]. In silico screening of a flexible pocket near the Arf1/ARNO interface led to the identification of LM11 [Viaud et al., 2007]. In vitro cell-based assays indicated that LM11 impaired Arf-dependent trafficking structures at the Golgi and inhibited ARNO-dependent migration of MDCK cells, confirming that ARNO is a target of LM11 in cells
BRCT/p-BACH1 [Simeonov et al., 2008]	The C-terminal portion of BRCA1 (BRCT) is a key tumor suppressor protein with diverse function, and its interaction with the phosphoprotein p-BACH1 is implicated in the DNA damage response and repair signaling pathways [Kim et al., 2007a]. Inhibitors of this interaction are useful to study BRCA1′s role in cancer and to potentially sensitize tumors to chemotherapeutic agents
BH3-only proteins/pro-survival Bcl-2 family members [Lessene et al., 2008; Vogler et al., 2009; Azmi et al., 2011; Billard, 2013]	Members of the B-cell lymphoma 2 (Bcl-2) family are important regulators of apoptotic cell death. The BH3-only Bcl-2 family members (NOXA, BAD and BIM) can trigger apoptosis by binding to the prosurvival members of this family (Bcl-2, Bcl-XL, Bcl-W, Mcl-1, and A1), thus neutralizing their functional activity. The "BH3 mimetic" concept is to develop small molecules capable of mimicking BH3-onlyproteins and thus inducing apoptosis, which has generated a large number of Bcl-2 inhibitors, some of which are currently undergoing preclinical/clinical development
β-Catenin/Tcf4 [Trosset et al., 2006]	Targeting the interaction between β-catenin and Tcf members is considered a therapeutically relevant anticancer strategy in light of the role of this interaction in mediating the Wnt signaling pathway, which is constitutively activated in colorectal and other types of cancer [MacDonald et al., 2009]. The Tcf3/Tcf4-binding surface on β-catenin contains a well-defined hot spot around residues K435 and R469. A virtual screening of a library collection of 17,700 compounds by docking into this hot spot resulted in the identification of three Tcf4-competitive compounds with the tightest binder PUN 74654 having a K_D of 450 nM [Trosset et al., 2006]
eIF4E/eIF4G [Moerke et al., 2007]	Assembly of the eIF4E/eIF4G complex has a central role in the regulation of gene expression at the level of translation initiation. Through a high-throughput screening assay, 4EGI-1 and structurally related small-molecule inhibitors of theeIF4E/eIF4G interaction were identified [Moerke et al., 2007]. 4EGI-1 inhibited cap-dependent translation but not initiation factor-independent translation, and inhibited expression of oncogenic proteins encoded by weak mRNAs
HIF-1α/p300 [Kung et al., 2004]	Chetomin, a fungal metabolite, was identified through high-throughput screening of libraries consisting of over 500,000 natural products and synthetic compounds for inhibitors ofHIF-1α/p300 interactions that regulate HIF-1 transcriptional activity. Chetomin exhibited in vivo efficacy in suppressing xenograft tumor growth in different animal models, in part, by blocking HIF-1 transcriptional activity through the disruption of HIF-1α/p300 interactions
IAPs/apoptosis effectors [Wright and Duckett, 2005; LaCasse et al., 2008]	The inhibitor of apoptosis (IAP) family members, defined by the presence of a baculovirus IAP repeat (BIR) protein domain, are key regulators of cytokinesis, apoptosis and signal transduction. Specific IAPs regulate cell division, caspase activity or survival pathways mediated through binding to their BIR domains, and/or through their ubiquitin-ligase RING domain activity. These protein–protein interactions are the subject of intense investigations for therapeutic development. Several IAP protein-targeted agents are currently evaluated in early clinical trials
IL-2/IL-2Rα [Thanos et al., 2006]	Overexpression of the interleukin-2 receptor (IL-2R)α in tumor cells is associated with tumor progression and a poor patient prognosis, and binding of IL-2 to IL-2Rαleads to activation of several proliferative and anti-apoptotic intracellular signaling pathways. A small-molecule, SP4206, was discovered through fragment-based drug design to bind IL-2Rα with high affinity (K_D, 70 nM) [Braisted et al., 2003; Raimundo et al., 2004]. This high affinity of ligand binding might be attributable to the ability of SP4206 to target virtually the same critical "hot-spot" residues on IL-2 that drive binding of IL-2Rα [Thanos et al., 2006]
c-Myc/Max [Berg, 2011]	c-Myc is involved in fundamental cellular processes including cell cycle progression, growth, oncogenic transformation, and apoptosis [Adhikary and Eilers, 2005]. It forms heterodimers with Max to regulate the transcription of target genes. Several c-Myc-Max dimerization inhibitors have been developed, which target the association of the basic helix–loop–helix leucine zipper (HLH-LZ) domains of these two proteins through chemical library screening [Berg, 2011]. An optimized representative c-Myc-Max dimerization inhibitor, Mycro3, showed good potency and selectivity at concentrations of 10–40 μM against c-Myc in cellular assays [Kiessling et al., 2007]
The Notch transcription factor complex [Moellering et al., 2009]	Notch proteins regulate conserved pathways governing cell differentiation, proliferation, and death Gain-of-function mutations in the Notch pathway are causally linked to cancer. Synthetic, cell-permeable, stabilized α-helical peptides were developed to target a critical protein–protein interface of the Notch transactivation complex [Moellering et al., 2009]. Treatment of leukemic cells with these peptides caused potent Notch-specific antiproliferative effects in vitro and in vivo
RUNX1/CBFβ [Cunningham et al., 2012]	Transcription factors RUNX1 and CBFβ form a heterodimer for DNA binding and regulation of gene expression. Evidence suggests that interaction between these two transcription factors plays a crucial role in the pathogenesis of core binding factor (CBF) leukemias, for which the treatments are associated with significant morbidity and mortality, with a 5-year survival rate of 50%. High-throughput screening of a large compound library netted an inhibitor, Ro5-3355, that preferentially killed human CBF leukemia cell lines, rescued preleukemic phenotype in a RUNX1–ETO transgenic zebra fish, and reduced leukemia burden in a mouse CBF leukemia model [Cunningham et al., 2012]

protein interactions [Valkov et al., 2012]. This paradigm shift in combination with advances in computation- and chemical library-based high-throughput screening technologies has proven the feasibility of developing small-molecule inhibitors of protein–protein interactions [Blundell et al., 2006; Berg, 2008b; Fry, 2008; Valkov et al., 2012]. To date, therapeutic development targeting a number of protein–protein interactions has been the focus of many recent reports (Table II). Especially noteworthy is that at least two BH3 mimetics, (−)-gossypol and ABT-263 (Navitoclax), have advanced to clinical trials [http://clinicaltrials.gov].

TARGETING UNIQUE DNA HIGH-ORDER STRUCTURES AND PROTEIN–DNA INTERACTIONS

A large portion of currently used chemotherapeutics, such as platinum drugs, alkylating agents, topo II poisons, and DNA intercalating agents, act by inhibiting DNA replication and cell division through their reactions with DNA [Sheng et al., 2013]. However, relative to proteins, DNA historically has not been as well recognized as a mechanistic target for structure-based drug design for a number of reasons. First, the highly charged nature of DNA renders ligand recognition of target DNA less discriminative/specific. Second, transcription factors have generally been considered undruggable due to lack of suitable assay methods. In recent years, advances in nucleic acid chemistry and molecular and structural biology have created opportunities for potential drug discovery, which is addressed as follows.

TARGETING THE DNA QUADRUPLEX

G-quadruplexes (also known as G-tetrads or G_4-DNA) are higher-order DNA structures formed from guanine (G)-rich sequences that are capable of forming a four-stranded structure (Fig. 4) [Burge et al., 2006]. Four guanine bases can associate through Hoogsteen hydrogen bonding to form a square planar structure called a G-tetrad, and two or more G-tetrads can stack on top of each other to form a G-quadruplex.

Potential G-quadruplex sequences have been identified in eukaryotic telomeres, and more recently in non-telomeric genomic DNA, for example, in the nuclease-hypersensitive promoter regions of many genes, such as *c-myc*, chicken β-globin gene, human ubiquitin-ligase RFP2, and the protooncogenes *c-kit*, *bcl-2*, *vegf*, *H-ras*, *N-ras*, and *K-ras* [Burge et al., 2006; Neidle, 2009]. As G-quadruplexes exhibit diverse topologies and structures, targeting these high-order DNA structures for selective therapeutic intervention represents a feasible strategy since it is reasonable to assume that each target G-quadruplex has a unique architecture. Consequently, small-molecule agents capable of stabilizing a G-quadruplex structure in upstream regions essential to the promoter activity of a protooncogene will result in down-regulation of its gene expression. This premise provides a mechanistic rationale to identify ligands for selective G-quadruplex binding [Neidle, 2009], of which the proof-of-concept is provided by several small-molecule G-quadruplex-stabilizing agents, including RHPS4 [Leonetti et al., 2004], BRACO-19 [Burger et al., 2005], telomestatin [Miyazaki et al., 2012], and TMPyP4 [Le et al., 2013], with interesting antitumor activities associated with telomere capping alteration and/or inhibition of various protooncogenes, such as *c-myb* and *bcl-2*.

TARGETING PROTEIN–DNA INTERACTIONS

In addition to blocking protein–protein interaction as discussed above, the function of transcription factors can also be inhibited by disrupting their interactions with DNA [Berg, 2008a]. For example, c-Myc could be targeted by blocking its dimerization with Max (Table II), or by inhibiting the recruitment of c-Myc-Max dimers to

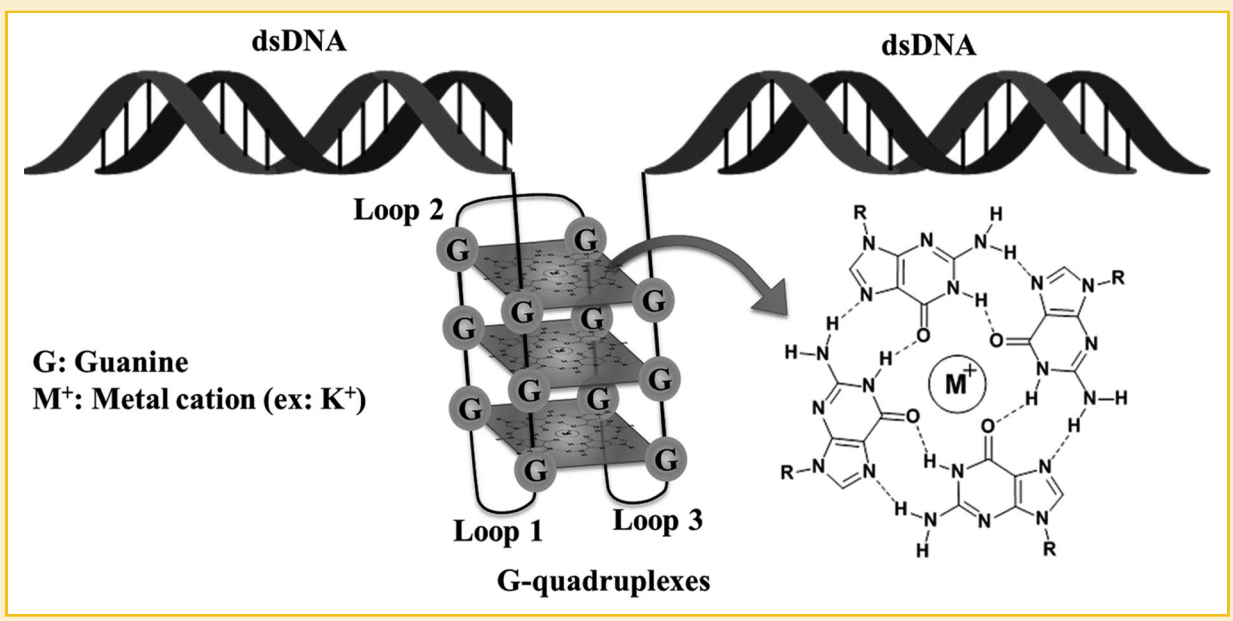

Fig. 4. Diagram of the structure of a DNA G-quadruplex.

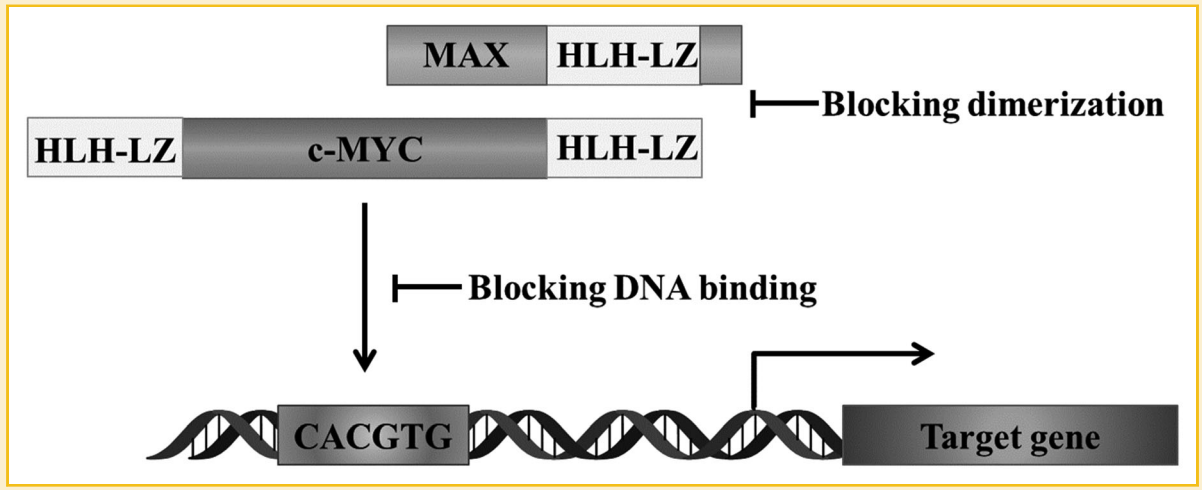

Fig. 5. Schematic diagram depicting the strategies for developing c-Myc inhibitors by targeting dimerization or DNA binding. HLH-LZ, the basic helix–loop–helix leucine zipper domain.

their DNA recognition motif, that is, the E-box element (5′-CACGTG-3′), to block c-Myc-induced transcriptional activation of target genes (Fig. 5).

The latter strategy was demonstrated by the identification of two DNA binding inhibitors of c-Myc/Max dimers, MYRA-A [Mo and Henriksson, 2006], and NSC308848 [Mo et al., 2006]. Evidence suggests that MYRA-A might target DNA-binding domains of c-Myc-Max dimers, in lieu of the DNA recognition motif.

Similar approaches were also taken to design inhibitors of other transcription factors, including hypoxia-inducible factor (HIF)-1 and signal transducer and activator of transcription (STAT)3, by targeting their dimerization or DNA binding, which have led to the identification of HIF-1 and Stat3 inhibitors targeting either mechanism [Berg, 2008a].

OUTLOOK

The paradigm shift in drug discovery toward a target-based approach in the past decade has made a tremendous headway in developing new therapeutic agents targeting different clinically relevant signaling mechanisms/pathways in cancer cells. However, despite apparent advantages of targeted therapies, challenges remain in improving clinical outcomes, which is, in part, attributable to the genetic and, equally important, phenotypic heterogeneities of cancer cells. Assumptions are made that gain/loss of function of a particular target protein or pathway is the major cause for the pathogenesis or progression of cancer. However, under targeted therapy-imposed selective pressure, cancer cells might adapt their signaling circuitry to develop compensatory mechanisms by taking advantage of redundant signaling pathways or feedback/crosstalk systems to develop drug resistance. Such a "phenotypic adaptation" represents a major challenge for targeted therapy, which underlies the rationale of using a therapeutic combination with cytotoxic drugs.

ACKNOWLEDGMENTS

Work in my research group is supported by NIH grants CA112250 and CA158807, the Stefanie Spielman Fund for Breast Cancer Research, and the Lucius A. Wing Endowed Chair Fund at The Ohio State University Medical Center.

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