Exploiting synthetic lethal interactions for targeted cancer therapy

Citation: Reinhardt, H. Christian et al. "Exploiting Synthetic Lethal Interactions for Targeted Cancer Therapy." Cell Cycle 8.19 (2009): 3112–3119.

As Published: http://dx.doi.org/10.4161/cc.8.19.9626

Publisher: Landes Bioscience

Persistent URL: http://hdl.handle.net/1721.1/73619

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Published in final edited form as:
Cell Cycle. 2009 October 1; 8(19): 3112–3119.

Exploiting synthetic lethal interactions for targeted cancer therapy

H. Christian Reinhardt[1,†], **Hai Jiang**[1,†], **Michael T. Hemann**[1,*], and **Michael B. Yaffe**[1,2,3,*]

[1] The Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA USA

[2] Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA USA

[3] The Broad Institute, Massachusetts Institute of Technology, Cambridge, MA USA

Abstract

Emerging data suggests that synthetic lethal interactions between mutated oncogenes/tumor suppressor genes and molecules involved in DNA damage signaling and repair can be therapeutically exploited to preferentially kill tumor cells. in this review, we discuss the concept of synthetic lethality, and describe several recent examples in which this concept was successfully implemented to target tumor cells in culture, in mouse models, and in human cancer patients.

Keywords

DNA damage; signaling; cell cycle checkpoints; synthetic lethality; MAPKAP kinase-2; ATM; Chk2

Targeting Cancer Genes

Cancer is a collection of different genetic diseases.[1,2] During tumor development incipient cancer cells undergo a multistep mutational process during which they acquire a set of genetic and/or epigenetic lesions, which ultimately result in the cancerous state.[1] These mutations provide the cancer cell with a set of traits that have been termed the "*hallmarks of cancer*"—potential for unlimited proliferation, mitogen-independent proliferation, escape from apoptotic and anti-proliferative signals, immune evasion, sustained angiogenesis and tissue invasion and metastasis.[1] These cancer phenotypes are thought to be the consequence of gain of function of oncogenes or loss of function of tumor suppressor genes.[3] Due to recent technological advances such as next generation sequencing, we are beginning to understand the complex genetic changes that ultimately result in cancerous growth.[4-10] Cancer-associated mutations can be classified into (1) so-called "driver" mutations, which are essential for malignant growth and (2) passenger mutations, which appear to be functionally less significant.[10] Recent large-scale tumor genome re-sequencing efforts have begun to shed light on the identity and frequency of driver lesions and the signaling pathways that they are involved in. Although the true number of potential driver lesions still remains a matter of active debate, it appears that there is a limited number of high-frequency mutations that can be classified as driver lesions.[2,4-10] Analysis of breast and colon tumors, for example, showed that each individual tumor harbors ~50–80 mutations, with on average

[*]Correspondence to: Michael B. Yaffe and Michael T. Hemann; myaffe@mit.edu hemann@mit.edu.
[†]These authors contributed equally to this work.

less than 15 being considered to be driver mutations.[8] This small number of driver mutations present within any individual tumor are believed to affect a finite number of relatively well conserved "core" signaling pathways, that have been re-wired within cancer cells,[2,5,8] including those involved in cell cycle control, DNA damage responses, integrin-mediated cell adhesion, apoptosis, TGFβ signaling, Wnt/Notch signaling, Hedgehog signaling and Ras signaling.[5] Therapeutic targeting of these re-wired oncogenic signaling networks holds great promise for cancer therapy.

The driver lesions underlying the oncogenic signaling network state can be further sub-classified into those that are potentially direct drug targets and others for which pharmacological manipulation is more difficult. Inhibition of "druggable" driver lesions, such as the BCR-Abl fusion protein (Imatinib), the mutant or amplified EGF receptor (Gefitinib, Erlotinib), or HER2 (Trastuzumab) are prime examples of successful therapeutic targeting of critical signaling molecules in cancer.[11-13] In contrast, the development of inhibitory molecules targeting non-kinase oncogenes, such as Myc and Ras has proven to be much more difficult, even when enzymes that are responsible for critical post-translational modifications of these oncogenes, such as those involved in Ras farnesylation are targeted.[14]

In addition to oncogene addiction, tumor cells commonly display hypersensitivity to tumor suppressor genes. Studies in genetically engineered mouse models of cancer have shown that, depending on the tissue of origin, re-expression of p53 in preexisting tumors lacking p53 induces widespread apoptosis or senescence of these tumors.[15-17] However, due to well-established problems in gene delivery, therapeutic restoration of commonly lost tumor suppressor genes, such as *p53*, *Rb*, *ATM*, *p16^{INK4A}* or *BRCA1/2* is currently not a viable option for cancer therapy.

The Concept of Synthetic Lethality

While cancer-driving genetic lesions clearly promote the oncogenic state, they are also commonly associated with dependencies that are specific to these lesions and absent in normal non-cancerous cells. In recent years the phenomenon of synthetic lethality, which has its roots in genetic experiments mainly performed in yeast and fruit flies, has been successfully revisited in the context of cancer therapy. Two genes are said to interact in a 'synthetic lethal' fashion, when mutation of either gene in isolation is compatible with viability, but simultaneous mutation is lethal.[18-24] In an extension of this terminology, two genes are said to be "synthetic sick," if simultaneous mutation of two genes reduces cellular fitness without being lethal.[18] Synthetic lethal or sick genetic interactions have been widely reported for loss of function mutations, but can also involve gain of function mutations.[18,25-27] Thus, the protein products of genes that are in synthetic lethal or sick interactions with known, non-druggable cancer-driving mutations should represent ideal anti-cancer drug targets for two reasons: First, a synthetic lethality-driven therapeutic regimen is an elegant way to indirectly target non-druggable cancer-promoting lesions by virtue of pharmacological inhibition of druggable synthetic lethal interactors. The second advantage lies in the exquisite selectivity that should be achievable by exploiting true synthetic lethal interactions for anti-cancer therapy. By definition, pharmacological abrogation of the protein product of a gene that is synthetic lethal with a given mutated cancer gene will selectively kill cancer cells, but will be tolerated by healthy cells that lack the cancer cell-specific mutation.

Components of the DNA damage response network and the DNA repair pathways are among the most commonly lost genes in human tumors.[28-36] It is thought that these deficiencies in the DNA damage response contribute to the tumorigenic process by promoting a 'mutator' phenotype that allows the acquisition of additional genetic lesions

that fuel the process of malignant transformation. On the other hand, based on the concept of synthetic lethality, these loss of function mutations in the DNA damage response may also provide ample opportunity to selectively target the tumor. With the advent of new technologies amenable for high throughput screening, the search for synthetic lethal interactions in mammalian cells is now becoming feasible. Recent studies performed in *cerevisiae*, for example, have shown that for 74 genes that (C) are known to be involved in the maintenance of genomic stability, 4956 unique synthetic lethal interactions exist.[37] These 4956 unique synthetic lethal interactions involve 875 different genes.[37] Given the high degree of conservation between the DNA damage response in yeast and man, it is tempting to speculate that a similar number of synthetic lethal relationships can be identified in human cells. In the last five years we have witnessed the first successful translations of the concept of synthetic lethality into novel cancer treatment strategies.[18,38-41]

Synthetic Lethality between *BRCA1/BRCA2* and *PARP1*

In a series of recent papers, Ashworth, Jackson, Helleday and colleagues reported a synthetic lethal interaction between Poly(ADP-ribose) polymerase (PARP1) and the high-penetrance breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2*[38,39] (Fig. 1). Both *BRCA1* and *BRCA2*-deficient cells display a defect in the error-free homologous recombination (HR) repair mechanism for DNA double strand breaks (DSBs).[42,43] This defect results in the repair of DSBs by error-prone repair mechanisms, such as single strand annealing (SSA) and non-homologous end joining (NHEJ), which ultimately results in increased genomic instability.[42,44] PARP1 on the other hand is a critical component of the base excision repair (BER) mechanism, which is important for the repair of DNA single strand lesions.[43] Farmer et al. and Bryant et al. observed that cells exposed to PARP1 inhibitors formed robust nuclear γ-H2AX foci, suggesting that inhibition of PARP1-dependent repair processes resulted in the formation of DNA lesions such as DSBs and collapsed replication forks that are normally repaired by HR.[38,39] Wildtype cells, or cells that were hemizygous null for *BRCA1* or *BRCA2* displayed only slightly reduced survival after up to 24 hours of PARP inhibition.[39] In contrast, cells that were *BRCA1* or *BRCA2*-deficient showed a dramatically increased loss of viability after PARP inhibition.[39] This increased death of *BRCA1* or *BRCA2*-deficient cells after PARP inhibition could be explained by the lack of HR activity in those cells, as evidenced by an absence of PARP1 inhibitor-induced Rad51 foci formation. In contrast, Rad51 foci could readily be detected in wildtype cells.[39] Although alternative error-prone repair processes such as NHEJ and SSA could, in principle, still be operative in these cells, the presence of large-scale genomic damage likely results in excessive chromosomal instability and cell death. These findings strongly suggested that PARP inhibition might be an ideal therapeutic strategy for the treatment of HR-impaired *BRCA1* or *BRCA2*-deficient cancers, based on a synthetic lethal interaction between these genes (Fig. 1). Consequently, PARP inhibitors are being rapidly evaluated in clinical trials.[40,42] The first results from a phase I trial involving 60 patients have recently been reported. The PARP inhibitor Olaparib showed limited adverse effects and had activity in tumors with *BRCA1* or *BRCA2* mutations.[40] However, these results have to be taken with some caution, since recent reports using cell culture systems showed that PARP inhibitor-treated *BRCA2*-deficient cancer cells acquire resistance through secondary intragenic deletions in *BRCA2*, which result in expression of new, HR-competent BRCA2 isoforms.[45,46] Furthermore, while *PARP1*-deficient mice are viable and fertile, they appear to be predisposed for the development of mammary carcinomas.[47,48] This might be an indication that long-term PARP inhibitor treatment should be avoided.

Synthetic Lethality between *p53* and *MK2* in the Context of DNA Damage

The concept of synthetic lethality can also be applied to situations where cells are facing extrinsic cellular stress, such as that induced by DNA-damaging chemotherapy. The homozygous loss of a given tumor suppressor gene *A* might not dramatically increase the chemosensitivity of tumor cells compared to wildtype cells. However, pharmacological inhibition of the product of gene *B* that engages in a synthetic lethal relationship with *A* might be detrimental for the survival of these tumor cells following chemotherapy treatment. Thus, in the context of DNA-damaging anti-cancer therapy, synthetic lethal interactions might be exploited to selectively sensitize cancer cells to genotoxic stress. These considerations led us, and others, to explore the effects of combinatorial loss of function experiments in tumor cells. We started by focusing on cells that were deficient for the prominent tumor suppressor gene *p53*, which is lost in approximately 30% of all human tumors.[49] We then identified multiple components of the DNA damage response signaling network that are synthetic lethal with loss of *p53* in the context of DNA damaging chemotherapy, namely the protein kinases MK2, ATM and Chk2.[50,51]

The DNA damage signaling response has traditionally been divided into two major branches: The ATM pathway, acting through the downstream effector kinase Chk2, and the ATR upstream kinase, acting through Chk1. Some crosstalk exists between the ATM/Chk2 and ATR/Chk1 pathways, particularly when signaling through one pathway is partially or totally deficient.[34,52-55] Normally, these pathways appear to have distinct functions with only partial functional overlap in response to particular forms of DNA damage especially at later stages in the cell cycle.[56] Different types of genotoxic stress are preferentially channeled through one or the other of these two pathways. The ATM/ Chk2 pathway is activated primarily in response to DSBs, such as those formed by topoisomerase-2 inhibitors, while the ATR/Chk1 pathway is activated by bulky DNA lesions induced by UV-light, and in response to replication fork collapse during S-phase.[52,57] We initially identified MK2, as a downstream effector kinase in the DNA damage response.[50,58] MK2 is a component of the p38 signaling pathway and is activated directly downstream of p38. The p38/MK2 signaling complex is considered to be a general stress response pathway, which is activated in response to a variety of stimuli including various toxins, osmotic stress, heat shock, reactive oxygen species, cytokines and DNA damage.[59] Activation of the p38/MK2 complex in response to genotoxic stress depends on the canonical DNA damage response kinases ATM and ATR, indicating that this general stress response pathway is recruited as part of the DNA damage response.[50,60,61] One prominent target of the DNA damage effector kinases Chk1, Chk2 and MK2 are members of the Cdc25 family of dual specificity phosphatases.[62] Phosphorylation and inhibition of Cdc25 by Chk1, Chk2 and/ or MK2 ultimately prevents activation of the Cdk-Cyclin com- into S-phase, S-phase pro- plexes that mediate transition from G_1 gression and mitotic entry, thereby establishing G_1, intra-S-phase and [63,64] Other critical targets for G_2/M cell cycle checkpoints. MK2-dependent cell cycle arrest probably exist, but have not yet been reported.

The context-dependent role for MK2 in cell survival following genotoxic stress was investigated using RNAi-mediated depletion of MK2 in p53-proficient and p53-deficient settings.[50] Knockdown of MK2 dramatically sensitized p53-deficient murine embryonic fibroblasts (MEFs), and H-Ras^{V12}-driven p53-deficient allografts to the cytotoxic effects of the cross-linking agent cisplatin and the topoisomerase II inhibitor doxorubicin.[50] In contrast, loss of MK2 in p53-proficient cells did not result in increased cell death.[50] Further investigation into the mechanistic details of this synthetic lethal interaction between *MK2* and *p53* revealed that MK2-depletion dramatically reduced phospho-rylation of Cdc25A and B, on the same phospho-acceptor sites that are targeted by Chk1 and Chk2. This suggests that MK2-dependent phosphorylation of Cdc25A/B might be required for functional $^{G}{}_{1}$/S

and G_2/M cell cycle checkpoints in cisplatin or doxorubicin-treated p53-deficient cancer cells.[50] The inability of MK2-depleted p53-deficient cells to execute functional cell cycle checkpoints following genotoxic stress resulted in mitotic cell death that involved activation of caspase-3, indicating that the cells were dying by mitotic catastrophe.[50,65]

Synthetic Lethality between *ATM/Chk2* and *p53* in the Context of DNA Damage

The observation that *MK2* displays synthetic lethality with *p53* prompted us to search for additional synthetic lethal interactors of *p53* in the DNA damage response network. We chose to limit this analysis to protein kinases, since these are potentially druggable targets. Analyzing a large panel of human and murine cell lines, we demonstrated that loss of ATM or Chk2 strongly increased the sensitivity of p53-deficient cells to doxorubicin-induced cell death.[51] This observation is in line with an earlier report indicating that $p53^{-/-};ATM^{-/-}$ MEFs are significantly more sensitive to topoisomerase I and II inhibitors than p53-deficient MEFs with retained ATM function.[66] In contrast, loss of ATM or Chk2 in p53-proficient cells not only failed to increase the cytotoxic response to doxorubicin, but actually made the cells resistant to chemotherapy.[51] Similar observations were made in vivo using allograft tumors in $NCR^{nu/nu}$ mice and syngeneic transplants of Eμ-myc-driven lymphomas. RNAi-mediated ATM depletion strongly sensitized p53-deficient H-Ras^{V12}-driven allografts and p53-deficient Eμ-myc lymphomas while ATM depletion in a p53-proficient setting conferred *resistance*. We were able to extend these results obtained in cell culture and mouse models to human cancer patients by analyzing the 10-year survival of a large cohort of chemotherapy-treated breast cancer patients. Patients with tumors that lost either ATM or p53 in isolation had a significantly reduced survival after chemotherapy compared to patients with tumors that displayed normal levels of ATM and p53. Furthermore, those patients who had wild-type p53 and mutant ATM had the worst prognosis of all, suggesting that in the setting of a non-mutated form of p53, ATM activity is important for chemotherapy-induced cytotoxicity. On the other hand, patients with tumors that displayed dysfunctional ATM/ Chk2 *and* p53, albeit exceedingly rare, showed increased survival compared to patients with tumors that had normal ATM and p53 levels.[51] These observations clearly indicate that synthetic lethality, as a conceptual process, is not simply the synergy of two deleterious alterations. Here, Jiang, Reinhardt et al. demonstrated that isolated loss of *ATM* or *p53* promotes chemo resistance, while the combined loss of *ATM* and *p53* results in markedly increased chemo sensitivity—the exact opposite phenotype.[51]

The mechanism underlying the synthetic lethality between *ATM/Chk2* and *p53* is reminiscent of what has been observed for the interaction between *MK2* and *p53*. In response to doxorubi-cin, ATM-depleted *p53* null cells are unable to execute a functional G_2/M cell cycle checkpoint and display features of mitotic catastrophe.[51]

Abrogation of ATM or Chk2 in p53-proficient cells and tumors resulted in substantially increased resistance to doxorubicin—the exact opposite effect of the synthetic lethality that was seen in p53-deficient settings. This surprising observation could be explained by the finding that loss of ATM in p53-proficient cells dramatically and selectively reduced the DNA damage-induced expression of the pro-apoptotic target genes *Puma* and *Noxa*, while expression of the cell cycle arrest-mediating p53 targets *p21* and *Gadd45α* was maintained. Thus, the protective cell cycle arresting function of p53 remains intact in ATM-depleted cells, while the pro-apoptotic p53 response is selectively blunted. It remains unclear whether this selective loss of the p53-mediated induction of *Puma* and *Noxa* after doxorubicin is a direct consequence of reduced ATM-mediated phosphorylation of p53 on Ser-15 (Ser-18 in mouse p53). Given that this site can also be phosphorylated by the two other DNA damage-activated phosphatidyl-inositol-3-kinase-like protein kinases (PIKKs) ATR and DNA-PKcs

this might be unlikely. However, the relative contribution of Ser-15 phosphorylation should be tested using cells from mice in which endogenous *p53* has been replaced with the Ser-18 to Ala mutant. If the sole mechanism of doxorubicin resistance in ATM-depleted p53-proficient tumors is loss of Ser-18 phosphory-lation, then the Ser-18 to Ala mutant should phenocopy the loss of ATM. Alternatively, ATM might be involved in recruiting p53 to the promoters of its pro-apoptotic target genes via a mechanism that is independent of direct p53 phosphorylation. This could be tested using chromatin immunoprecipitation assays to compare the promoter occupancy of p53 substrate genes in ATM-proficient and ATM-depleted cells and tumors.

Both MK2 and Chk2 activation after doxorubicin exposure requires the presence of functional ATM.[62] The observation that ATM, Chk2 and MK2 display synthetic lethality with *p53* in the context of DNA-damaging chemotherapy, might suggest that synthetic lethality with *p53* is a generalizable feature of all cell cycle checkpoint signaling pathways, including the ATR/Chk1 branch. In support of this hypothesis, RNAi-mediated Chk1 depletion has been shown to increase the sensitivity of p53-deficient prostate cancer cells to doxorubicin.[67] However, when considering Chk1 as a chemo-sensitizing drug target, care should be taken to consider the potential adverse effects of such a treatment strategy. There is an accumulating body of evidence that global Chk1 inhibition using small molecule inhibitors might be limited by undesired side-effects or the development of secondary malignancies. Disruption of either ATR or Chk1 in mice, for instance, results in embryonic lethality.[68-70] Furthermore, WAP-Cre-driven conditional loss of *Chk1* in mammary epithelial tissue is lethal in a homozygous setting, and results in progressive DNA damage and uncontrolled premature mitotic entry in heterozygous animals,[71] while Chk1 inhibition with small molecule inhibitors in cultured human cells leads to severe stress and cell death even in the absence of additional genotoxic stress.[72] In contrast to what has been described for *ATR* or *Chk1*, mice in which *ATM*, *Chk2* or *MK2* have been constitutively deleted are viable.[73-75] These observations, together with the data discussed above, strongly suggest that ATM/Chk2 and MK2 might be safer drug targets, than ATR/Chk1 for the development of chemo-sensitizing therapies in the treatment of p53-deficient cancers. It remains to be seen whether loss or inhibition of Chk1 or MK2 in p53-proficient settings promotes chemo-resistance, similar to what has been described for ATM and Chk2.

Chemosensitivity is Determined Early during Tumor Development

ATM and *p53* have been reported as frequently mutated in human cancers. We performed expression analysis for ATM and p53 on a large panel of diverse human epithelial tumor specimens and found aberrant expression of ATM and p53 in ~9% and ~29%, respectively. These numbers are in excellent agreement with recent large-scale lung adenocarcinoma re-sequencing efforts that have shown *ATM* and *p53* to be mutated in ~8% and ~30% of cases.[4] Interestingly, both studies independently demonstrated—with high statistical significance—that the combined loss of *ATM* and *p53* is an exceedingly rare event.[4] There are at least two possible explanations for the apparent under-representation of combined loss of *ATM/Chk2* and *p53*. Two recent studies have shown that ATM, Chk2 and p53 activation can frequently be observed in early pre-neoplastic lesions and that these proteins constitute a checkpoint response to prevent further malignant transformation.[36,76] These studies, in conjunction with data from the recent report by Jiang, Reinhardt et al. suggest that inactivation of ATM, Chk2 or p53 is sufficient to abolish this early tumor checkpoint and allow further progression even in the face of oncogene-induced replicative stress and DNA damage.[51] Hence, loss of either protein would be selected for and additional losses of components of this checkpoint might not confer additional selective advantage. However, based on the synthetic lethal interaction between ATM/Chk2 and p53 in the context of DNA damage described by Jiang, Reinhardt et al. an alternative explanation for the underrepresentation of combined ATM/Chk2 and

p53 deficiency in human tumors might be that loss of both ATM/Chk2 *and* p53 inappropriately sensitized the tumors to the effects of oncogenic stress-induced DNA damage occurring during tumor evolution, likely as a result of mitotic catastrophe.[51] This hypothesis should be tested in vivo using models in which *ATM/Chk2* and *p53* can be inactivated prior to activation of a potent, replicative stress-inducing oncogene, such as *mos*. If DNA damage induced by oncogene activation is indeed lethal for incipient tumor cells that have lost *ATM/Chk2* and *p53*, one would expect a substantially reduced number of tumors compared to a situation in which *ATM/Chk2* or *p53* have been lost in isolation.

Synthetic Lethality as a Means to Sensitize Chemo-Resistant Cancers

The data provided by Jiang, Reinhardt et al. strongly suggests that loss of *ATM/Chk2* in the setting of wild-type *p53* not only confers resistance to DNA-damaging chemotherapy in different mouse models of cancer, but also indicates that these mutations in human tumors are associated with a significantly impaired response to chemotherapy and reduced patient survival.[51] While inhibition of ATM/Chk2 or MK2 in p53-deficient tumors provides an elegant synthetic lethality-based strategy to sensitize these tumors for DNA-damaging chemotherapy (Fig. 2), a different approach has to be taken to sensitize inherently chemotherapy-resistant ATM-deficient tumors with retained p53 function.

In addition to a well-documented role in mediating cell cycle arrest after genotoxic stress, ATM also mediates DSB repair. There is strong evidence for a role of ATM in HR-mediated DSB repair,[77-80] with a less pronounced effect on NHEJ-mediated DSB repair.[78,80-84] Since ATM-deficient cancer cells with preserved p53 function must repair doxorubicin-induced DSBs to ensure long-term survival, they likely rely extensively on alternative, error-prone DSB repair pathways, such as NHEJ to compensate for the HR defect that is present in ATM-deficient cells. DSB repair by NHEJ involves binding of the non-catalytic subunits Ku70 and Ku80 as a heterodimer to the free DNA ends, followed by recruitment of the catalytic subunit DNA-PKcs. DNA-PKcs activity is essential for XRCC4 and Lig4-mediated re-joining of the broken ends during the NHEJ process.[85-88] Data now provided by Jiang, Reinhardt et al. showed that the DNA-PKcs-dependent NHEJ pathway becomes essential for the cellular survival of doxorubicin-treated *p53* wildtype tumor cells that lack ATM function.[51] A synthetic lethal interaction between *DNA-PKcs* and *ATM* in the presence of doxorubicin-induced DSBs was formally established by the observation that RNAi or small molecule inhibitor-mediated suppression of DNA-PKcs signaling specifically sensitized ATM-depleted p53 wild-type cancer cells for doxorubicin-induced cell death both in vitro and in vivo. In contrast, in the presence of functional ATM, inhibition of DNA-PKcs did not have a sensitizing effect. Interestingly, when DNA-PKcs was inhibited in p53-deficient cancer cells no significant doxorubicin sensitization was seen regardless of ATM status. These observations are in line with a previous report from Gurley et al. who described early embryonic lethality (E7.5) in *ATM*$^{-/-}$*;DNA-PKcs*$^{-/-}$ double knockout mice.[89] These data strongly suggest that the NHEJ pathway serves as a backup pathway for DSB repair in HR-deficient cells that have managed to survive by virtue of intact p53 function. This is strikingly analogous to the role of the HR pathway as a backup pathway for unrepaired DSBs that result from PARP inhibition, as discussed above. Thus, while isolated loss of *ATM* appears to protect cancer cells from genotoxic stress by selectively blunting the pro-apoptotic p53 response, it renders these cells exquisitely susceptible to DNA-PKcs inhibition in the context of DNA-damaging chemotherapy. *DNA-PKcs*-deficient mice are viable and do not exhibit an increased incidence of tumorigenesis, further suggesting that DNA-PKcs might be a safe drug target for chemo sensitization of *ATM*-deficient tumor cells with retained p53 function (Fig. 2).[90]

Interestingly, a recent report by Callén et al. suggests that inhibition of DNA-PKcs in *ATM*-deficient thymocytes protects these cells from ionizing radiation (IR)-induced apoptotic cell death, which was likely due to a repression of p53-dependent induction of pro-apoptotic target genes, such as *Puma* and *Noxa*.[91] At first glance these results are in contrast to what was reported by Jiang, Reinhardt et al.[51] however, these differences may be cell or DNA damaging-agent specific. Jiang, Reinhardt et al. used MEFs and lymphoma cells that were experiencing potent oncogenic stress in their analysis and DNA damage was induced by doxorubi-cin.[51] Callén et al. used normal primary T-cells in combination with IR. Since DNA damage response networks are extensively rewired in cancer cells, these findings lend further credence to the concept of differential synthetic lethality effects between normal and transformed cells.

Future Directions

The first applications of the concept of synthetic lethality discussed here are focused on loss of function mutations in tumor suppressor genes.[38,39,50,51] However, there are reports indicating that the concept of synthetic lethality is applicable to gain of function mutations, as well.[18] Thus, the same principles that were discussed above could be used to determine patient-specific therapies for tumors that are driven by 'non-druggable' lesions, such as *Ras* mutation or *Myc* amplification. The Elledge, Hahn and Gilliland labs recently successfully applied large-scale RNAi screening technology to look specifically for synthetic lethal interactors of mutant K-Ras,[92,93] and identified the kinase STK33 and Plk1 as potentially druggable targets in these mutant tumor types.

The major challenge in the area of synthetic lethal approaches to cancer treatment remains the identification of synthetic lethal pairs, since these interactions are often non-intuitive. New technologies, such as genome-wide RNAi screening and next generation sequencing of cell lines and primary tumor samples, in combination with the use of cell lines carrying well-defined oncogenic lesions, such as activating *K-Ras* mutations should allow the systematic search for new synthetic lethal relationships. Newly identified synthetic lethal interactions could be rapidly evaluated for their potential clinical efficacy using well-characterized mouse models of cancer providing that they faithfully recapitulate therapeutic aspects of the human disease.

Acknowledgments

We apologize to our colleagues for the omission of many important contributions to the field, and their references, due to space limitations. We thank the members of the Hemann and Yaffe laboratories for helpful discussions. This work was supported by the NIH (GM68762, CA112967, ES015339 to M.B.Y.), the NIH Integrative Cancer Biology Program grant (U54-CA112967-03 to M.T.H. and M.B.Y.), the Deutsche Forschungsgemeinschaft (RE2246/1-1 to H.C.R.), the Deutsche Nierenstiftung (to H.C.R.) and the David H. Koch Fund (to H.C.R. and M.B.Y.).

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70. [PubMed: 10647931]
2. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009;136:823–37. [PubMed: 19269363]
3. Hahn WC, Weinberg RA. Modelling the molecular circuitry of cancer. Nat Rev Cancer 2002;2:331–41. [PubMed: 12044009]
4. Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature 2008;455:1069–75. [PubMed: 18948947]
5. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 2008;321:1801–6. [PubMed: 18772397]

6. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807–12. [PubMed: 18772396]
7. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, et al. The consensus coding sequences of human breast and colorectal cancers. Science 2006;314:268–74. [PubMed: 16959974]
8. Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, et al. The genomic landscapes of human breast and colorectal cancers. Science 2007;318:1108–13. [PubMed: 17932254]
9. Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, et al. Patterns of somatic mutation in human cancer genomes. Nature 2007;446:153–8. [PubMed: 17344846]
10. Greenman C, Wooster R, Futreal PA, Stratton MR, Easton DF. Statistical analysis of pathogenicity of somatic mutations in cancer. Genetics 2006;173:2187–98. [PubMed: 16783027]
11. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561–6. [PubMed: 8616716]
12. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26:3291–310. [PubMed: 17496923]
13. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169–81. [PubMed: 17318210]
14. Fritz G. Targeting the mevalonate pathway for improved anticancer therapy. Curr Cancer Drug Targets. 2009
15. Martins CP, Brown-Swigart L, Evan GI. Modeling the therapeutic efficacy of p53 restoration in tumors. Cell 2006;127:1323–34. [PubMed: 17182091]
16. Ventura A, Kirsch DG, McLaughlin ME, Tuveson DA, Grimm J, Lintault L, et al. Restoration of p53 function leads to tumour regression in vivo. Nature 2007;445:661–5. [PubMed: 17251932]
17. Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature 2007;445:656–60. [PubMed: 17251933]
18. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689–98. [PubMed: 16110319]
19. Dobzhansky T. Genetics of natural populations XIII. Recombination and variability in populations of Drosophila Pseudoobscura. Genetics 1946;31:269–90.
20. Friend SH, Oliff A. Emerging uses for genomic information in drug discovery. N Engl J Med 1998;338:125–6. [PubMed: 9420347]
21. Guarente L. Synthetic enhancement in gene interaction: a genetic tool come of age. Trends Genet 1993;9:362–6. [PubMed: 8273152]
22. Hartman, JLt; Garvik, B.; Hartwell, L. Principles for the buffering of genetic variation. Science 2001;291:1001–4. [PubMed: 11232561]
23. Kamb A. Mutation load, functional overlap and synthetic lethality in the evolution and treatment of cancer. J Theor Biol 2003;223:205–13. [PubMed: 12814603]
24. Lucchesi JC. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanfgaster*. Genetics 1968;59:37–44. [PubMed: 5683639]
25. Kroll ES, Hyland KM, Hieter P, Li JJ. Establishing genetic interactions by a synthetic dosage lethality phenotype. Genetics 1996;143:95–102. [PubMed: 8722765]
26. Li JJ, Herskowitz I. Isolation of ORC6, a component of the yeast origin recognition complex by a one-hybrid system. Science 1993;262:1870–4. [PubMed: 8266075]
27. Measday V, Hieter P. Synthetic dosage lethality. Methods Enzymol 2002;350:316–26. [PubMed: 12073321]
28. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 2007;7:937–48. [PubMed: 18034184]
29. Frebourg T, Friend SH. Cancer risks from germline p53 mutations. J Clin Invest 1992;90:1637–41. [PubMed: 1430194]
30. Lavin MF, Shiloh Y. The genetic defect in ataxia-telangiectasia. Annu Rev Immunol 1997;15:177–202. [PubMed: 9143686]

31. Lehmann AR. DNA repair-deficient diseases, xero-derma pigmentosum, Cockayne syndrome and tricho-thiodystrophy. Biochimie 2003;85:1101–11. [PubMed: 14726016]
32. Nevanlinna H, Bartek J. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene 2006;25:5912–9. [PubMed: 16998506]
33. O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. Nat Genet 2003;33:497–501. [PubMed: 12640452]
34. Shiloh Y. ATM and related protein kinases: safeguarding genome integrity. Nat Rev Cancer 2003;3:155–68. [PubMed: 12612651]
35. Taylor AM, Groom A, Byrd PJ. Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis. DNA Repair 2004;3:1219–25. [PubMed: 15279810]
36. Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 2005;434:864–70. [PubMed: 15829956]
37. Pan X, Ye P, Yuan DS, Wang X, Bader JS, Boeke JD. A DNA integrity network in the yeast *Saccharomyces cerevisiae*. Cell 2006;124:1069–81. [PubMed: 16487579]
38. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913–7. [PubMed: 15829966]
39. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917–21. [PubMed: 15829967]
40. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009
41. Kennedy RD, Chen CC, Stuckert P, Archila EM, De la Vega MA, Moreau LA, et al. Fanconi anemia pathway-deficient tumor cells are hypersensitive to inhibition of ataxia telangiectasia mutated. J Clin Invest 2007;117:1440–9. [PubMed: 17431503]
42. Martin SA, Lord CJ, Ashworth A. DNA repair deficiency as a therapeutic target in cancer. Curr Opin Genet Dev 2008;18:80–6. [PubMed: 18343102]
43. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366–74. [PubMed: 11357144]
44. Tutt AN, Lord CJ, McCabe N, Farmer H, Turner N, Martin NM, et al. Exploiting the DNA repair defect in BRCA mutant cells in the design of new therapeutic strategies for cancer. Cold Spring Harb Symp Quant Biol 2005;70:139–48. [PubMed: 16869747]
45. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, et al. Resistance to therapy caused by intragenic deletion in BRCA2. Nature 2008;451:1111–5. [PubMed: 18264088]
46. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 2008;451:1116–20. [PubMed: 18264087]
47. Wang ZQ, Auer B, Stingl L, Berghammer H, Haidacher D, Schweiger M, et al. Mice lacking ADPRT and poly(ADP-ribosyl)ation develop normally but are susceptible to skin disease. Genes Dev 1995;9:509–20. [PubMed: 7698643]
48. Tong WM, Yang YG, Cao WH, Galendo D, Frappart L, Shen Y, Wang ZQ. Poly(ADP-ribose) polymerase-1 plays a role in suppressing mammary tumourigenesis in mice. Oncogene 2007;26:3857–67. [PubMed: 17160013]
49. Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat 2007;28:622–9. [PubMed: 17311302]
50. Reinhardt HC, Aslanian AS, Lees JA, Yaffe MB. p53-deficient cells rely on ATM- and ATR-mediated checkpoint signaling through the p38MAPK/MK2 pathway for survival after DNA damage. Cancer Cell 2007;11:175–89. [PubMed: 17292828]
51. Jiang H, Reinhardt HC, Bartkova J, Tommiska J, Blomqvist C, Nevanlinna H, et al. The combined status of ATM and p53 link tumor development with therapeutic response. Genes Dev. 2009

52. Abraham RT. Cell cycle checkpoint signaling through the ATM and ATR kinases. Genes Dev 2001;15:2177–96. [PubMed: 11544175]
53. Bartek J, Lukas J. Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell 2003;3:421–9. [PubMed: 12781359]
54. Kastan MB, Lim DS. The many substrates and functions of ATM. Nat Rev Mol Cell Biol 2000;1:179–86. [PubMed: 11252893]
55. Shiloh Y. ATM and ATR: networking cellular responses to DNA damage. Curr Opin Genet Dev 2001;11:71–7. [PubMed: 11163154]
56. Jazayeri A, Falck J, Lukas C, Bartek J, Smith GC, Lukas J, et al. ATM- and cell cycle-dependent regulation of ATR in response to DNA double-strand breaks. Nat Cell Biol 2006;8:37–45. [PubMed: 16327781]
57. Zhou BB, Elledge SJ. The DNA damage response: putting checkpoints in perspective. Nature 2000;408:433–9. [PubMed: 11100718]
58. Manke IA, Nguyen A, Lim D, Stewart MQ, Elia AE, Yaffe MB. MAPKAP kinase-2 is a cell cycle check-point kinase that regulates the G_2/M transition and S phase progression in response to UV irradiation. Mol Cell 2005;17:37–48. [PubMed: 15629715]
59. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev 2001;81:807–69. [PubMed: 11274345]
60. Raman M, Earnest S, Zhang K, Zhao Y, Cobb MH. TAO kinases mediate activation of p38 in response to DNA damage. EMBO J 2007;26:2005–14. [PubMed: 17396146]
61. Perfettini JL, Nardacci R, Bourouba M, Subra F, Gros L, Seror C, et al. Critical involvement of the ATM-dependent DNA damage response in the apop-totic demise of HIV-1-elicited syncytia. PLoS ONE 2008;3:2458.
62. Reinhardt HC, Yaffe MB. Kinases that control the cell cycle in response to DNA damage: Chk1, Chk2 and MK2. Curr Opin Cell Biol 2009;21:245–55. [PubMed: 19230643]
63. Donzelli M, Draetta GF. Regulating mammalian checkpoints through Cdc25 inactivation. EMBO Rep 2003;4:671–7. [PubMed: 12835754]
64. Rudolph J. Cdc25 phosphatases: structure, specificity and mechanism. Biochemistry 2007;46:3595–604. [PubMed: 17328562]
65. Castedo M, Perfettini JL, Roumier T, Andreau K, Medema R, Kroemer G. Cell death by mitotic catastrophe: a molecular definition. Oncogene 2004;23:2825–37. [PubMed: 15077146]
66. Fedier A, Schlamminger M, Schwarz VA, Haller U, Howell SB, Fink D. Loss of atm sensitises p53-deficient cells to topoisomerase poisons and antime-tabolites. Ann Oncol 2003;14:938–45. [PubMed: 12796033]
67. Mukhopadhyay UK, Senderowicz AM, Ferbeyre G. RNA silencing of checkpoint regulators sensitizes p53-defective prostate cancer cells to chemotherapy while sparing normal cells. Cancer Res 2005;65:2872–81. [PubMed: 15805289]
68. Brown EJ, Baltimore D. ATR disruption leads to chromosomal fragmentation and early embryonic lethality. Genes Dev 2000;14:397–402. [PubMed: 10691732]
69. Liu Q, Guntuku S, Cui XS, Matsuoka S, Cortez D, Tamai K, et al. Chk1 is an essential kinase that is regulated by Atr and required for the G(2)/M DNA damage checkpoint. Genes Dev 2000;14:1448–59. [PubMed: 10859164]
70. Takai H, Tominaga K, Motoyama N, Minamishima YA, Nagahama H, Tsukiyama T, et al. Aberrant cell cycle checkpoint function and early embryonic death in Chk1(−/−) mice. Genes Dev 2000;14:1439–47. [PubMed: 10859163]
71. Lam MH, Liu Q, Elledge SJ, Rosen JM. Chk1 is hap-loinsufficient for multiple functions critical to tumor suppression. Cancer Cell 2004;6:45–59. [PubMed: 15261141]
72. Syljuasen RG, Sorensen CS, Hansen LT, Fugger K, Lundin C, Johansson F, et al. Inhibition of human Chk1 causes increased initiation of DNA replication, phosphorylation of ATR targets, and DNA breakage. Mol Cell Biol 2005;25:3553–62. [PubMed: 15831461]
73. Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D. Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects and thymic lym-phoma. Genes Dev 1996;10:2411–22. [PubMed: 8843194]

74. Hirao A, Cheung A, Duncan G, Girard PM, Elia AJ, Wakeham A, et al. Chk2 is a tumor suppressor that regulates apoptosis in both an ataxia telangi-ectasia mutated (ATM)-dependent and an ATM-independent manner. Mol Cell Biol 2002;22:6521–32. [PubMed: 12192050]

75. Kotlyarov A, Neininger A, Schubert C, Eckert R, Birchmeier C, Volk HD, et al. MAPKAP kinase 2 is essential for LPS-induced TNFalpha biosynthesis. Nat Cell Biol 1999;1:94–7. [PubMed: 10559880]

76. Gorgoulis VG, Vassiliou LV, Karakaidos P, Zacharatos P, Kotsinas A, Liloglou T, et al. Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature 2005;434:907–13. [PubMed: 15829965]

77. Luo CM, Tang W, Mekeel KL, DeFrank JS, Anne PR, Powell SN. High frequency and error-prone DNA recombination in ataxia telangiectasia cell lines. J Biol Chem 1996;271:4497–503. [PubMed: 8626804]

78. Morrison C, Sonoda E, Takao N, Shinohara A, Yamamoto K, Takeda S. The controlling role of ATM in homologous recombinational repair of DNA damage. EMBO J 2000;19:463–71. [PubMed: 10654944]

79. Xie A, Puget N, Shim I, Odate S, Jarzyna I, Bassing CH, et al. Control of sister chromatid recombination by histone H2AX. Mol Cell 2004;16:1017–25. [PubMed: 15610743]

80. Kuhne M, Riballo E, Rief N, Rothkamm K, Jeggo PA, Lobrich M. A double-strand break repair defect in ATM-deficient cells contributes to radiosensitivity. Cancer Res 2004;64:500–8. [PubMed: 14744762]

81. Dar ME, Winters TA, Jorgensen TJ. Identification of defective illegitimate recombinational repair of oxidatively-induced DNA double-strand breaks in ataxia-telangiectasia cells. Mutat Res 1997;384:169–79. [PubMed: 9330613]

82. Bredemeyer AL, Sharma GG, Huang CY, Helmink BA, Walker LM, Khor KC, et al. ATM stabilizes DNA double-strand-break complexes during V(D)J recombination. Nature 2006;442:466–70. [PubMed: 16799570]

83. Riballo E, Kuhne M, Rief N, Doherty A, Smith GC, Recio MJ, et al. pathway of double-strand break rejoining dependent upon ATM, Artemis and proteins locating to gamma-H2AX foci. Mol Cell 2004;16:715–24. [PubMed: 15574327]

84. Yuan SS, Chang HL, Lee EY. Ionizing radiation-induced Rad51 nuclear focus formation is cell cycle-regulated and defective in both ATM(−/−) and c-Abl(−/−) cells. Mutat Res 2003;525:85–92. [PubMed: 12650908]

85. DeFazio LG, Stansel RM, Griffith JD, Chu G. Synapsis of DNA ends by DNA-dependent protein kinase. EMBO J 2002;21:3192–200. [PubMed: 12065431]

86. Lees-Miller SP, Meek K. Repair of DNA double strand breaks by non-homologous end joining. Biochimie 2003;85:1161–73. [PubMed: 14726021]

87. Spagnolo L, Rivera-Calzada A, Pearl LH, Llorca O. Three-dimensional structure of the human DNA-PKcs/Ku70/Ku80 complex assembled on DNA and its implications for DNA DSB repair. Mol Cell 2006;22:511–9. [PubMed: 16713581]

88. Smith GC, Jackson SP. The DNA-dependent protein kinase. Genes Dev 1999;13:916–34. [PubMed: 10215620]

89. Gurley KE, Kemp CJ. Synthetic lethality between mutation in Atm and DNA-PK(cs) during murine embryogenesis. Curr Biol 2001;11:191–4. [PubMed: 11231155]

90. Gao Y, Chaudhuri J, Zhu C, Davidson L, Weaver DT, Alt FW. A targeted DNA-PKcs-null mutation reveals DNA-PK-independent functions for KU in V(D)J recombination. Immunity 1998;9:367–76. [PubMed: 9768756]

91. Callen E, Jankovic M, Wong N, Zha S, Chen HT, Difilippantonio S, et al. Essential role for DNA-PKcs in DNA double-strand break repair and apoptosis in ATM-deficient lymphocytes. Mol Cell 2009;34:285–97. [PubMed: 19450527]

92. Luo J, Emanuele MJ, Li D, Creighton CJ, Schlabach MR, Westbrook TF, et al. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 2009;137:835–48. [PubMed: 19490893]

93. Scholl C, Frohling S, Dunn IF, Schinzel AC, Barbie DA, Kim SY, et al. Synthetic lethal interaction between oncogenic KRAS dependency and STK33 suppression in human cancer cells. Cell 2009;137:821–34. [PubMed: 19490892]

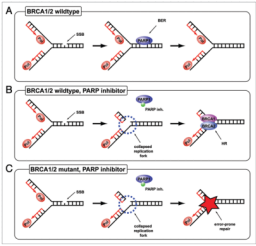

Figure 1.

Exploiting the synthetic lethal relationship between PArP1 and BrCA1/2 for the targeted treatment of HR-deficient human tumors. HR can serve as a backup DNA repair pathway to resolve DSBs resulting from replication fork collapse. (A) In normal cells, base modifications are repaired using base excision repair prior to S-phase entry. (B) Pharmacological inhibition of the base excision repair component PARP1 results in unrepaired SSBs, which collapse replication forks into DSBs during S-phase. The newly synthesized sister chromatid can serve as a template for HR-mediated repair in BRCA1/2-proficient cells. In BRCA1/2-deficient cancer cells HR-mediated repair of PARP inhibitor-induced DSBs in not available. Instead, error-prone repair pathways, such as NHEJ and SSA are utilized, which results in progressive genomic instability and ultimately cell death.

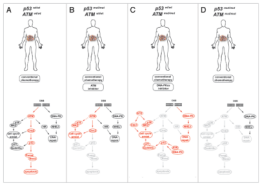

Figure 2.

Exploiting synthetic lethal interactions for the treatment of human cancer. DNA damage signaling networks commonly show extensive rewiring incancercells.(A)Inp53andATM-proficient cancer cells primarily promotes apoptosis. Due to a functional proapoptotic ATM-Chk2-p53- Puma/Noxa signaling axis conventional DNA-damaging chemotherapeutics should be recommended. (B) Loss of p53 in cancer cells largely abrogates DNA damage-induced apoptosis. in these cells ATM signaling is re-directed to induce a robust cell cycle arrest following genotoxic stress. ATM-mediated homologous recombination repair remains intact in p53-deficient cancer cells. Rewiring of DNA damage-induced ATM signaling promotes cellular survival in response to DNA damage. Treatment of p53-deficient tumors should include a combination of conventional DNA-damaging chemotherapy and ATM inhibitors. (C) Loss of ATM selectively reduces the induction of the pro-apoptotic p53 target genes *Puma* and *Noxa* following genotoxic stress. induction of the cell cycle-regulatory p53 target genes *p21* and *Gadd45α* remains intact allowing ATM-depleted cancer cells to arrest the cell cycle after DNA damage. ATM-deficient cancer cells with retained p53 expression depend on the DNA-PKcs-mediated NHEJ pathway to repair chemotherapy-induced DSBs and maintain genomic stability. Abolishing DNA-PKcs signaling in these cells results in a dramatically increased sensitivity to DNA-damaging chemotherapy. Treatment of ATM-deficient tumors with retained p53 expression should include a combination of conventional DNA-damaging chemotherapy and DNA-PKcs inhibitors. (D) The combined loss of ATM and p53 precludes the execution of functional cell cycle checkpoints in cancer cells that are exposed to DNA-damaging agents. This inability to halt progression through the cell cycle despite the presence of DNA damage ultimately results in mitotic catastrophe. p53 and ATM-deficient cancer cells should be exquisitely sensitive to treatment with conventional DNA-damaging chemotherapy.