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# Synthetic Lethality in Anticancer Drug Discovery and Target Identification

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**Abstract: Background:** The concept of synthetic lethality (which arises when simultaneous mutations in two or more genes lead to cell death but a mutation in only one of the genes does not) has been exploited to develop new genotype-selective anticancer agents, identify novel therapeutic targets and characterize genes associated with treatment responses. This review discusses recent advances in anticancer drug discovery and target identification with synthetic lethal approaches. **Results:** We first discuss about the concept and mechanisms of synthetic lethality to facilitate the understanding of using this concept as a research platform in various areas of anticancer studies. We then focused on recent advance in the discovery of novel anticancer agents, identification of genetic lethal partners of oncogenes and characterization of genes associated with treatment responses based on the principle of synthetic lethality. **Conclusion:** Information obtained about synthetic lethal interactions among genes and/or between genes and therapeutic agents provides insights into the molecular mechanisms of some anticancer agents and biological processes and has potential implications for targeted therapy, personalized therapy and the rational design of combinatorial treatment for cancers.

**Key words:** Lethal genes, neoplasms, drug discovery, genetic interaction, ras genes, mutation

## INTRODUCTION

Functional deregulation of several key signaling pathways as a result of genetic and epigenetic alterations is believed to be the driving force behind carcinogenesis and progression of cancers (Ding *et al*., 2008; Wood *et al*., 2007). This functional deregulation provides an opportunity for targeted cancer therapies. Small molecules and antibodies that directly inhibit critical nodes in oncogenic signaling networks-such as trastuzumab against human epidermal growth factor receptor 2 (HER2) (Leyland-Jones, 2002); erlotinib, gefitinib and cetuximab against epidermal growth factor receptor (EGFR) (Lynch *et al*., 2004; Adams and Weiner, 2005); imatinib against the BCR-ABL fusion protein (Druker *et al*., 1996) and sorafenib against Raf kinase and vascular endothelial growth factor receptor (Wilhelm *et al*., 2004) have already been used to treat various cancers in humans. Nevertheless, many critical nodes in oncogenic signaling networks may not be targeted by small molecules. For example, functional loss in tumor suppressor genes caused by gene deletions may not be restored through small molecules. Moreover, the functions of some oncogene products, such as Ras and c-Myc, have been found to be difficult to modulate directly through small molecules (Hartwell *et al*., 1997). The concept of synthetic lethality may provide a new platform for anticancer drug development and an opportunity to eliminate malignant cells by indirectly targeting cancer-driving molecules that otherwise cannot be targeted by small molecules (Hartwell *et al*., 1997; Kaelin, 2005; Chan and Giaccia, 2011). This synthetic lethality strategy should yield agents with high selectivity against cancer cells with the altered genotype and is expected to minimize treatment-induced toxicity to normal cells, thereby improving the safety of therapeutics.

## THE CONCEPT OF SYNTHETIC LETHALITY

The term "synthetic lethality" was originally used to refer to a lethal phenotype caused by mutations in two genes; two genes are synthetic lethal when cells or living organisms with mutations in only one of the two genes are viable but the combination of both mutations is lethal (Dobzhansky, 1946). By evaluating the effects of homozygous mutations on viability in *Drosophila*, Dobzhansky noticed that some homozygous mutations resulted in organisms with normal viability when they

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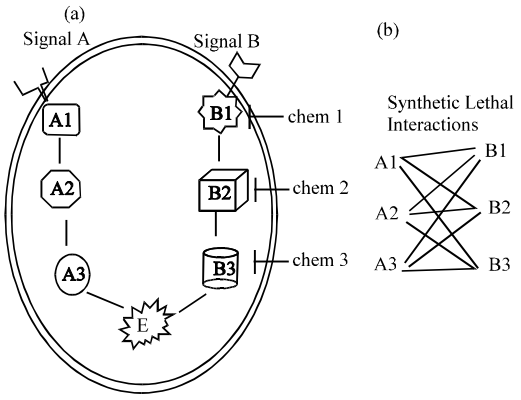


Fig. 1: Diagram of synthetic lethality. (a) The essential biological function E relies on signaling pathways A and B. A functional change in either of these pathways, such as a mutation in A1 or a disruption of B1, B2 or B3 by the compounds Chem1, Chem2 or Chem3, respectively, is insufficient to cause cell death. However, the simultaneous presence of an A1 mutation and a compound disrupting B1, B2 or B3 induces dysfunction of E and results in cell death. (b) Synthetic lethal interactions between components of signals A and B

existed separately but became lethal or semilethal (viability reduced but not completely abolished) when combined with a second homozygous mutation (Dobzhansky, 1946). Dobzhansky called this lethal or semilethal phenotype of double homozygotes "synthetic lethal" or "synthetic semilethal" (Dobzhansky, 1946).

Subsequently, synthetic lethality and semi-lethality were used to determine functional interaction and compensation among genes (Lucchesi, 1968). Several models of interactions of genes or proteins have been proposed to account for synthetic lethality (Kaelin, 2005; Meur and Gentleman, 2008; Ooi *et al*., 2006), including the presence of homologous genes or protein isomers derived from the same ancestral gene (paralogs), subunits of an essential multiprotein complex, components of a single linear essential pathway and components of parallel pathways that together regulate an essential biological function. Figure 1 illustrates synthetic lethality induced by components in parallel pathways. Assume that the biological function of protein E which is essential for cell survival, relies on signals A and B. Signal A is transduced via proteins A1, A2 and A3, whereas signal B is transduced via proteins B1, B2 and B3 and then to E. An abnormality occurring in either signal pathway is insufficient to cause dysfunction of E; therefore, the cell is viable. However, simultaneous abnormalities in both signal pathways lead to the dysfunction of E and thus to cell death. In this case, A1 is synthetic lethal with B1, B2 or B3 but not with A2 or A3 and vice versa.

Studies in yeast revealed that synthetic lethal interactions occurred significantly more frequently between genes with the same mutant phenotype, between genes encoding proteins with the same subcellular localization and between genes involved in similar biological processes or bridging bioprocesses (Tong *et al*., 2001; Tong *et al*., 2004; Ye *et al*., 2005; Costanzo *et al*., 2010). On average, each gene might have more than 30 synthetic lethal interactions (Tong *et al*., 2004; Pan *et al*., 2006; Lin *et al*., 2008). Moreover, synthetic lethality may also occur as a result of gain-of-function mutations and is then called synthetic dosage lethality (Kroll *et al*., 1996; Measday *et al*., 2005). Indeed, *RAS* oncogene can induce either cell transformation or apoptosis, depending on cell type and context (Tanaka *et al*., 1994; Serrano *et al*., 1997). Expression of oncogenic *RAS* in primary human or rodent cells often results in apoptosis or senescence, whereas expression of oncogenic *RAS* in immortal cells or cells with inactivation of p53, p16 or the transcriptional activator interferon regulatory factor 1 leads to transformation and tumorigenesis (Tanaka *et al*., 1994; Serrano *et al*., 1997). Oncogene-induced apoptosis and/or senescence were also observed for *MYC* (Hoffman and Liebermann, 2008; Hemann *et al*., 2005), *STAT5* and *E2F1* (Mallette *et al*., 2007), suggesting that normal cells have barriers to safeguard against malignant transformation. When cancer cells become dependent on elevated activity of an oncogene for survival, oncogene addiction occurs (Ehrenreiter *et al*., 2009; Wise *et al*., 2008). Then, inhibiting downstream molecules in a single linear pathway of the oncogene to which the cells are addicted may also induce synthetic lethality.

## ANTICANCER DRUG DISCOVERY AND DEVELOPMENT

The selective killing of *BRAF* mutant cancer cells by Mitogen-activated Protein (MAP) kinase kinase (MEK) inhibitors (Solit *et al*., 2006; Corcoran *et al*., 2010) could be explained as a synthetic lethality caused by inhibition of the downstream component in a single linear essential pathway because of oncogene addiction. Various constitutively active mutations of the *BRAF* gene have been identified in human cancers (Davies *et al*., 2002). The exquisite dependence of *BRAF* mutant or other RAF isoform active tumors on MEK activity may provide a personalized therapeutic strategy for patients with this type of cancer (Solit *et al*., 2006; Villanueva *et al*., 2010).

On the other hand, knowledge of parallel molecular pathways can also facilitate the development of anticancer drugs based on synthetic lethality. An example is selective killing of *BRCA1* and *BRCA2* mutant cancer cells by poly(ADP-ribose) polymerase 1 (PARP1) inhibitors. *BRCA1* and *BRCA2* are tumor suppressor genes important for DNA Double-Strand Break (DSB) repair by homologous recombination, possibly by interacting with and recruiting RAD51 to the DNA DSBs (Chen *et al*., 1998; Patel *et al*., 1998). Loss-of-function mutations in these genes predispose carriers to breast, ovarian and other types of cancers (Antoniou *et al*., 2003; Thompson *et al*., 2002). In contrast, PARP1 is required for the assembly or stability of nuclear foci of the Single-Strand Break (SSB) repair protein XRCC1 (El-Khamisy *et al*., 2003) and to facilitate repair of DNA SSBs. PARP1 may not be directly involved in DSB repair and homologous recombination as $PARP1^{-/-}$ embryonic stem cells and embryonic fibroblasts exhibited normal repair of DNA DSBs and RAD51 foci formation (Yang *et al*., 2004). Nevertheless, $PARP1^{-/-}$ mice have defective DNA SSB repair and increased homologous recombination, sister chromatid exchange and chromosome instability (Yang *et al*., 2004; De Murcia *et al*., 1997).

Two groups simultaneously reported that defects in *BRCA1* and *BRCA2* genes in some breast and ovarian cancer cells make them highly sensitive to small-molecule PARP inhibitors (Bryant *et al*., 2005; Farmer *et al*., 2005). *BRCA* mutant cells are 1000 times more sensitive to PARP1 than are *BRCA* wild-type cells (Farmer *et al*., 2005). Moreover, nanoparticle mediated delivery of PARP1 specific siRNA resulted in induction of apoptosis in Brca1-deficient ovarian tumor cells both in vitro and in vivo and prolonged the survival of mice bearing tumors derived from Brca1-deficient ovarian cancer cells but not from Brca1 wild-type cells (Goldberg *et al*., 2011). This proof-of-concept result led to phase I clinical trials of an orally active PARP1 inhibitor, olaparib (AZD2281), in cancer patients with or without *BRCA1* or *BRCA2* mutations (Fong *et al*., 2009, 2010). The results showed that durable objective antitumor activity was observed only in confirmed carriers of *BRCA1* or *BRCA2* mutations. The follow-up multicenter phase II clinical trials in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer or recurrent ovarian cancer also showed promising results (Tutt *et al*., 2010).

Nevertheless, genetic interactions remain unknown for most cancer related genes. Thus, synthetic lethality screening is an approach to identify cytotoxic agents targeted to cancer cells with mutations in a particular oncogene or tumor suppressor gene. Using the human colon cancer cell line DLD-1 which contains the mutant K-Ras allele and its isogenic derivative in which the mutant K-Ras allele has been deleted by homologous recombination, Torrance *et al*. (2001) performed synthetic lethality screening on 30,000 compounds and identified 2 compounds, triphenyl tetrazolium and a sulfinyl cytidine derivative which demonstrated approximately sixfold selectivity for cell lines containing mutant *KRAS* (Torrance *et al*., 2001). Similarly, using immortalized human fibroblasts with or without the mutant *HRAS* gene, Stockwell's group performed synthetic lethality screening on 23, 550 compounds and found that camptothecin and a new compound named erastin were more effective in killing *HRAS*-expressing cells than their isogenic counterparts (Dolma *et al*., 2003). Subsequently, erastin was found to exhibit lethal selectivity in human tumor cells harboring mutations in the *HRAS*, *KRAS* or *BRAF* oncogenes by acting on mitochondrial voltage-dependent anion channels and inducing oxidative cell death (Yagoda *et al*., 2007). STF-62247, a small molecule that is synthetic lethal for the von Hippel-Lindau tumor suppressor gene (*VHL*), was identified by Turcotte *et al*. ( 2008) after screening 64, 000 compounds on renal cancer cells with mutant or wild-type *VHL*. STF-62247 selectively suppresses *VHL* mutant tumor cell growth through autophagy induction, possibly by acting on Golgi trafficking pathways (Turcotte *et al*., 2008).

We used immortalized human ovarian epithelial cells (designated T29) and their tumorigenic derivatives transformed with either mutant *HRAS* (T29Ht1) or mutant *KRAS* (T29Kt1) (Liu *et al*., 2004) to screen a chemical library consisting of 10,000 compounds. We identified a compound, designated oncrasin-1 that was not toxic to T29 or T29Ht1 cells at any of the doses tested but induced apoptosis in T29Kt1 cells at a wide range of doses (Guo *et al*., 2008). Oncrasin-1 was also effective against several human lung cancer cells that harbor *KRAS* mutations (Guo *et al*., 2008). Molecular characterization revealed that oncrasin-1 suppressed phosphorylation of the C-terminal domain (CTD) of the largest subunit of RNA polymerase II (RNAP II) and induced co-aggregation of protein kinase C iota (PKCι) and splicing factors into megaspliceosomes in sensitive cells (Guo *et al*., 2009). Interestingly, a Ras-dependent pathway that regulates CTD phosphorylation or function was reported in cardiac myocytes (Abdellatif *et al*., 1998) and in yeast (Chang *et al*., 2004). Mutations compromising the function of the CTD were synthetic lethal in yeast with elevated levels of Ras activity (Howard *et al*., 2002). Evidence also indicates that oncogene-transformed cells, such as *c-Myc*-transformed cells, were more sensitive than their normal counterparts to RNAP II inhibitors,

suggesting that RNAP II may serve as a therapeutic target for anticancer therapy (Koumenis and Giaccia, 1997).

Compound optimization through synthesis and analysis of analogues led to the identification of several compounds that are more effective than oncrasin-1 in inducing apoptosis in a subset of cancer cells. One of these, NSC-741909, was found to suppress the growth of a subset of NCI-60 cancer cell lines, including those with mutations in *KRAS* and *PIK3CA*. Mechanistic studies by reverse-phase protein microarray revealed that NSC-741909 treatment led to sustained activation of c-Jun N-terminal Kinase (JNK) by suppressing their dephosphorylation, possibly by inducing oxidative stress and inactivating MAP kinase phosphatases (Wei *et al*., 2009; Wei *et al*., 2010). It is also interesting that cancer cells with increased Akt (Nogueira *et al*., 2008) or Ras (Trachootham *et al*., 2006) oncoprotein activity can be selectively killed through oxidative apoptosis.

## TARGET IDENTIFICATION

Using the human colon cancer *KRAS* mutant cell line DLD-1 and its isogenic derivative with the mutant *KRAS* gene disrupted, Elledge's group screened a library of about 75,000 retroviral shRNAs targeting 32,293 unique human transcripts and identified 368 *KRAS* synthetic lethal candidate genes with a stringent cutoff and 1613 genes with relaxed statistical criteria (Luo *et al*., 2009). Genes involved in the regulation of several biological processes or pathways, including nucleic acid metabolism, ribosome biogenesis, protein neddylation or sumoylation, RNA splicing, the cell cycle, mitosis and proteasome complexes, were found to be required as additional support to maintain the Ras oncogenic state (Luo *et al*., 2009). In particular, *KRAS* mutant cells are hypersensitive to inhibition of PLK1, a serine/threonine protein kinase that has important functions throughout the M phase of the cell cycle, including the regulation of centrosome maturation, spindle assembly, mitotic exit and cytokinesis (Petronczki *et al*., 2008). Small-molecule inhibitors that disrupt mitosis, including paclitaxel and the PLK1 inhibitor BI-2536 (Steegmaier *et al*., 2007), were found to be synthetic lethal in Ras mutant cells (Luo *et al*., 2009).

Using the murine *K-ras*-induced lung cancer cell lines LKR10 and LKR13 (Johnson *et al*., 2001), Vicent *et al*. ( 2010) performed an *in vitro* proliferation screen and an *in vivo* tumorigenesis screen on a shRNA library containing genes associated with the *KRAS* gene expression signature (Sweet-Cordero *et al*., 2004), genes previously implicated as K-Ras effectors and potential transcriptional regulators and they identified 23 genes required for *K-ras*-mediated tumorigenesis (Vicent *et al*., 2010). The transcription factor Wilms' tumor 1 (Wt1), one of the genes identified, was found to be a critical regulator of senescence and proliferation in cells expressing oncogenic *K-ras*. Silencing of Wt1 in cells expressing activated *K-ras* triggered senescence *in vitro* and suppressed tumor growth *in vivo* (Vicent *et al*., 2010). In *K-ras* mutant mouse tumor cells, senescence was also induced by ablation of CDK4 but not by ablation of CDK2 or CDK6 (Puyol *et al*., 2010).

Scholl *et al*. (2009) performed synthetic lethality screening with shRNA constructs targeting 1011 human genes, including most known and putative protein kinase genes and a selection of protein phosphatase genes and known cancer-related genes, on 8 human cancer cell lines with mutant or wild-type *KRAS* and on normal human fibroblasts and immortalized human mammary epithelial cells. The results showed that *STK33* which encodes a putative member of the calcium/calmodulin-dependent protein kinase subfamily of serine/threonine protein kinases, is required for the survival of several *KRAS* mutant and *KRAS*-dependent (i.e., with impaired viability after *KRAS* knockdown) cancer cell lines. The viability of *KRAS* wild-type, *NRAS* mutant or *KRAS* mutant but *KRAS*-independent (i.e., *KRAS* knockdown did not impair viability) cancer cells was not affected by *STK33* knockdown (Scholl *et al*., 2009). Mechanistic characterization showed that the catalytic activity of *STK33* is essential for maintaining S6K1 activity in mutant *KRAS*-dependent cells (Scholl *et al*., 2009). S6K1 suppresses mitochondrial apoptosis by phosphorylation and inactivation of the BH3-only pro-apoptotic protein BAD (Harada *et al*., 2001; Zha *et al*., 1996). Suppression of *STK33* decreased BAD phosphorylation and promoted mitochondria-mediated apoptosis (Scholl *et al*., 2009).

TBK1, a noncanonical IκB kinase that regulates the stability of IκB (Chien *et al*., 2006), was another synthetic lethal partner for muatnt *KRAS* identified by shRNA screening (Barbie *et al*., 2009). Using a similar shRNA library to that used by Scholl *et al*. (2009), Barbie *et al*. (2009) screened 19 cell lines with or without mutant *KRAS* allele and identified 45 synthetic lethal partners for mutant *KRAS*, one of which was *TBK1*. Suppression of *TBK1* induced apoptosis in *KRAS*-dependent cancer cells but not in *KRAS*-independent cancer cells (Barbie *et al*., 2009). Analysis of expression profiles of human lung adenocarcinomas revealed that most *KRAS* mutant tumors showed RAS signature activation and co-expression of the NF-κB signature. Interestingly, 30 of 109 *KRAS* wild-type tumors also showed RAS and NF-κB signature co-activation (Barbie *et al*., 2009). *In vitro* study revealed

that *KRAS* wild-type and *KRAS*-dependent (*KRAS* si RNA susceptible) cancer cells were also susceptible to TBK1 inhibition, suggesting that a subset of *KRAS* wild-type tumors depend on TBK1 and NF-κB signaling for survival. Suppression of *TBK1* in *KRAS* mutant cancer cells restored cytoplasmic levels of IκB, reduced the total and nuclear c-Rel levels and downregulated *BCL-XL* (Barbie *et al*., 2009).

Indeed, a study of susceptibility to shRNA-mediated KRAS depletion in lung and pancreatic cancer cell lines showed that cancer cell lines harboring *KRAS* mutations can be broadly classified into *KRAS*-dependent and *KRAS*-independent groups (Singh *et al*., 2009). Gene expression profiling analysis revealed that a 46-gene signature could be used to segregate the two groups. Levels of genes encoding Syk tyrosine kinase (*SYK*), integrin b6 subunit (*ITGB6*) and the RON receptor tyrosine kinase (*MST1R*) and a gene named *ANKRD22*, with unknown function, were relatively high in *KRAS*-dependent lung and pancreatic cancer cell lines (Singh *et al*., 2009). Knockdown of those four genes induced growth inhibition in *KRAS*-dependent cell lines but not in *KRAS*-independent cell lines. Moreover, *KRAS*-dependent cell lines showed substantially greater sensitivity to a small-molecule inhibitor of Syk (R406) (Braselmann *et al*., 2006) than did *KRAS*-independent cell lines.

## GENES ASSOCIATED WITH TREATMENT RESPONSE

The tumor suppressor gene p53 is inactivated in about 50% of human cancers because of genetic mutations (Vogelstein *et al*., 2000). A recent study showed that Ataxia Telangiectasia Mutated (ATM) kinase directly modulated p53-mediated apoptosis or cell cycle arrest (Jiang *et al*., 2009). In cells and tumors that lacked a functional p53 pathway, inactivation of ATM or its downstream molecule CHK2 was sufficient to globally sensitize the cells to genotoxic chemotherapy with cisplatin or doxorubicin (Jiang *et al*., 2009). In contrast, in p53 wild-type cells, inhibition of ATM or CHK2 resulted in a substantial survival benefit, suggesting that a combination of cisplatin and doxorubicin with inhibitors of ATM and CHK2 could benefit patients with p53 mutant tumors. Several clinical trials of CHK1/CHK2 inhibitors in combination with genotoxic agents for cancer treatment are currently under way (Bolderson *et al*., 2009).

A study to investigate TRAIL-induced apoptosis in HeLa cells after knockdown of 510 genes encoding known and predicted kinases, proteins with known functions in TRAIL-mediated signaling pathways or proteins with unknown functions led to the identification of several genes whose knockdown either enhanced or inhibited TRAIL-mediated apoptosis (Aza-Blanc *et al*., 2003). siRNA against PAK1 and AKT1 strongly enhanced TRAIL activity, whereas siRNA against MYC or the WNT transducer TCF4 inhibited TRAIL-induced apoptosis, suggesting that PAK1 and AKT1 overexpression may cause TRAIL resistance and that the MYC and WNT pathways are required for TRAIL-mediated apoptosis (Aza-Blanc *et al*., 2003). RNAi screening also identified topoisomerase levels as critical factors in determining response to doxorubicin or camptothecin treatment *in vitro* and *in vivo* (Burgess *et al*., 2008).

Whitehurst *et al*. (2007) performed synthetic lethality screening for gene targets that specifically reduce cell viability in the presence of an otherwise sublethal dose of paclitaxel in the human non-small-cell lung cancer line NCI-H1155. They used a library of more than 84, 000 chemically synthesized siRNAs targeting 21, 127 unique human genes and applied highly stringent statistical criteria to identify a set of 87 candidate genes whose knockdown sensitizes cells to paclitaxel. Several of those targets sensitized lung cancer cells to paclitaxel more than 1000 fold. The candidates included multiple genes encoding core components of the proteasome and proteins involved in the function of microtubules, posttranslational modification, cell adhesion and cancer/testis antigens (Whitehurst *et al*., 2007). This observation indicates the possible benefit of combinatorial therapeutic regimens of paclitaxel plus the proteasome inhibitor bortezomib and the possible resistance of tumors with high levels of cancer/testis antigens to paclitaxel treatment. Nevertheless, clinical trials of paclitaxel plus bortezomib showed that such a combination may also increase toxicity (Croghan *et al*., 2010; Cresta *et al*., 2008).

Astsaturov *et al*., 2010 used a siRNA library targeting 638 genes encoding proteins with evidence of functional interaction with the EGFR signaling network, including those transcriptionally responsive to inhibition or stimulation of EGFR, to screen for genes associated with response to EGFR inhibitors; their study identified 61 genes whose knockdown sensitized the A431 cervical adenocarcinoma cell line to the EGFR inhibitors erlotinib or cetuximab (Astsaturov *et al*., 2010). Most of those genes encode proteins connected in a physically interacting network, including kinases and phosphatases. Nevertheless, when 45 of those genes were tested in 7 other cell lines for sensitization to erlotinib or cetuximab, none of them sensitized all tested cell lines, although several of them sensitized 3-5 of the cell lines (Astsaturov *et al*., 2010), suggesting that synthetic lethality is highly dependent on cell context.

## CHALLENGES AND PERSPECTIVES

The biological functions of compounds identified through cell-based synthetic lethality screening are likely to be unknown. Identifying the cellular targets of these compounds is challenging and time-consuming. To identify targets of those compounds, some chemical biology approaches may be used, including conjugating compounds to biotin or resin beads and performing affinity-based target precipitation and subsequent protein identification by mass spectrometry analysis (Godl *et al*., 2003; Yagoda *et al*., 2007; Bantscheff *et al*., 2007). However, conjugating and immobilizing a small compound may change its biological function and protein binding specificity. Alternatively, target proteins may be enriched by protecting the targets from protease-mediated degradation through binding of unmodified compounds to their targets (Lomenick *et al*., 2009). The results may depend on the efficiency and specificity of the protection.

Note that synthetic lethal interaction may be highly dependent on cell context. Cell lines harboring the same mutant oncogene or tumor suppressor gene may not have the same synthetic lethal partner, as exemplified by *KRAS* mutant cancer cell lines which have *KRAS*-dependent and *KRAS*-independent subgroups (Singh *et al*., 2009). Different genetic and epigenetic alterations in other gene loci may account for this variation. Moreover, some *KRAS* wild-type cancer cells may be susceptible to a synthetic lethal partner of mutant *KRAS* as about 30% of *KRAS* wild-type tumors may have a molecular signature similar to that of *KRAS*-mutant tumors (Barbie *et al*., 2009). A possible explanation is that, even in the absence of a Ras mutation, increased Ras activity in human cancers frequently results from gene amplification (Hoa *et al*., 2002; Filmus and Buick, 1985); overexpression (Coleman *et al*., 1994); an increase in upstream signals from tyrosine kinase growth factor receptors, such as HER2 (Ehrhardt *et al*., 2004); overexpression of other oncogenes, such as *c-Myc* (Bild *et al*., 2006); or a decrease in microRNA, such as let-7 miRNA family members (Johnson *et al*., 2005). Therefore, once a synthetic lethal agent or gene partner is identified through screening, further characterization in more cell lines is warranted to delineate mechanisms and other factors that may contribute to the observed synthetic lethality.

## CONCLUSION

Synthetic lethality has been emplored as research tools to identify genetic interaction among genes in yeast. In combination with siRNA technology, synthetic lethality is a useful research platform for identification of lethal partners of oncogenes and tumor suppressor genes in mammalian cells. Such synthetic lethal partners may serve as potential therapeutic targets for future drug development. Moreover, synthetic lethality screen is becoming a useful approach in identifying genes that sensitize cells to chemotherapy or radiotherapy or small molecules that selectively induce cell death in a subset of mutant cancer cells. The development of genotype-selective anticancer agents and advances of our knowledge about networks of genetic interactions is expected to impact on personalized anticancer therapy and facilitate the rational design of combinatorial therapy to enhance therapeutic efficacy.

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