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Genetic interactions in translational research on cancer

Bingliang Fang

Bingliang Fang, Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

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Correspondence to: Bingliang Fang, MD, PhD, Professor, Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States. bfang@mdanderson.org
Telephone: +1-713- 5639147 Fax: +1-713-7944901
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Abstract

Genetic interactions are functional crosstalk among different genetic loci that lead to phenotypic changes, such as health or viability alterations. A disease or lethal phenotype that results from the combined effects of gene mutations at different loci is termed a synthetic sickness or synthetic lethality, respectively. Studies of genetic interaction have provided insight on the relationships among biochemical processes or pathways. Cancer results from genetic interactions and is a major focus of current studies in genetic interactions. Various basic and translational cancer studies have explored the concept of genetic interactions, including studies of the mechanistic characterization of genes, drug discovery, biomarker identification and the rational design of combination therapies. This review discusses the implications of genetic interactions in the development of personalized cancer therapies, the identification of treatment-responsive genes, the delineation of mechanisms of chemoresistance and the rational design of combined therapeutic strategies to overcome drug resistance.

INTRODUCTION

Genetic interactions are functional crosstalk among genes of different loci that regulate or compensate for one another in many signaling and/or metabolic pathways, leading to phenotypic changes, including disease status (sickness) or viability alterations (lethality or semilethality). Unlike the dominance caused by interactions between alleles of the same genetic locus, the interactions of different genetic loci may lead to unexpected phenotypic changes that are different from the effects of mutations in each individual gene. An example of a typical phenotypic change caused by genetic interaction is synthetic lethality or synthetic semilethality; in brief, homozygous mutations in two genes result in normal viability in living organisms when the mutations exist separately but become lethal or semilethal (viability reduced but not completely abolished) when they occur simultaneously[1].

Because a lethal phenotype can be easily identified, synthetic lethality has frequently been used as a research tool for identifying interactions among genes. Global gene knockout studies in yeast showed that about 20% of genes in *Saccharomyces cerevisiae* (*S. cerevisiae*) are essential for growth on a rich glucose-containing medium, whereas

about 80% of the approximately 6200 predicted genes are nonessential, suggesting that the genome is buffered from the lethal effects of genetic disorders in more than 4700 genes that may have redundant functions associated with essential processes[2-4]. Thus far, global synthetic lethality analysis in yeast has generated substantial new information on genetic interactions that compensate for one another in biologically essential processes[5]. Information on genetic interactions has been used to predict the function of uncharacterized genes and decipher complex regulatory relationships among biochemical processes or pathways[5]. The principle of genetic interactions is also being exploited by various investigators to identify genes that are crucial to the survival of certain oncogene-transformed cells[6-9] or genes that sensitize cells to chemotherapy[10,11] or to find small molecules that selectively induce cell death in a subset of oncogene-transformed cells[12-14]. Thus, the principles of genetic interaction have become a research platform for characterizing gene functions, discovering novel anticancer agents, identifying molecular biomarkers for personalized therapy and designing effective combination therapies to overcome drug resistance. Applications of genetic interactions in anticancer drug discovery were recently reviewed in several articles[15-17]. This review will discuss potential applications of genetic interaction in personalized therapy and in the rational design of multimodality therapy.

NETWORKS OF GENETIC INTERACTIONS

The functional interactions among genes are more comprehensive than the physical interactions among proteins. Studies in yeast have shown that, on average, each gene may have more than 40 genetic interactions[18-20], whereas yeast proteins may have an average of 8 physical interactions per protein[21]. A study used 74 genes known to be involved in genomic integrity in *S. cerevisiae* to search for genetic interactions with those genes resulted in the identification of a network of 4956 unique pairs of genetic interactions involving 875 genes[19]. Within this network, several novel components and functional modules or minipathways were defined that are important for DNA integrity, including those involved in DNA replication, postreplication repair, homologous recombination and oxidative stress response[19]. More recently, several groups of researchers used a gene knockdown approach to search for genes that are synthetic lethals to the oncogenic *KRAS* gene and identified numerous synthetic lethal partners with mutant *KRAS* gene in various human cancer cells[6-9]. For example, a genome-wide RNAi screening in the isogenic human colon cancer cell line DLD-1 with and without oncogenic *KRAS* led to the identification of 368 lethal interaction candidate genes with a stringent cutoff and 1613 genes with relaxed statistical criteria[8]. 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[8]. Thus, genetic interactions are more complicated and comprehensive than physical interactions.

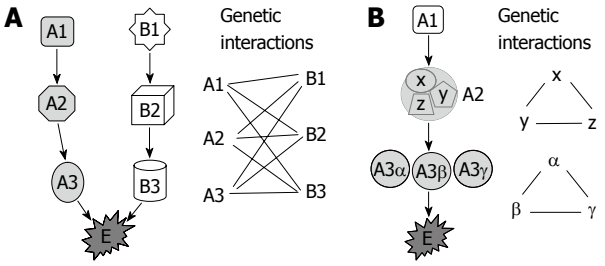

Figure 1 Diagram of genetic interactions. A: The essential biological function E is regulated by pathways A and B. A functional change in either of these pathways, such as a mutation in A1 or B1, is insufficient to induce dysfunction of E. However, the simultaneous presence of a mutation in A1 and a mutation in any of B1, B2 or B3 induces dysfunction of E (or phenotype changes). Thus, A1 has genetic interaction with B1, B2 and B3, and vice versa; B: The essential biological function E is regulated by pathway A alone, in which A2 is a multiprotein complex composed of X, Y and Z, while A3 has homologues of α, β and γ. Genetic interaction may exist among X, Y and Z, and among A3α, β and γ.

Several models have been proposed to account for genetic interactions[21-23], including the components of parallel pathways that together regulate an essential biological function, subunits of an essential multiprotein complex and components of a single linear essential pathway (Figure 1). Synthetic genetic array analysis and synthetic lethality analysis by microarray in yeast revealed that genetic interactions occurred the most 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[5,18]. Although genetic interactions were more frequent than expected between genes encoding proteins within the same protein complex and among gene pairs encoding homologous proteins, relatively few synthetic lethal interactions (only 1%-2%) fall into these two categories[18]. Most of the genetic interactions were identified among functionally related genes or among genes that function in parallel or compensating pathways[2,5,18,24].

STRATEGIES FOR PERSONALIZED CANCER THERAPY

Activating mutations in oncogenes and growth factor receptors are known to play critical roles in tumorigenesis and in the malignant evolution of cancers[25,26]. Several oncogenes or growth factor receptors have been successfully targeted by small molecule inhibitors and/or monoclonal antibodies for cancer treatment. Genetic changes, such as gene amplifications or mutations in the corresponding genes, have been used as predictive biomarkers for identifying patients who would benefit from a particular treatment[27]. Cancers overexpressing HER2 were shown to respond favorably to the monoclonal antibody trastuzumab[28,29]. Similarly, the epidermal growth factor receptor (EGFR) inhibitors erlotinib and gefitinib

were found to be more effective against EGFR mutant cancers[30], whereas imatinib was highly effective against cancer cells with BCR-Abl fusion protein[31].

Therapeutic benefits can also be obtained by targeting oncogenes and tumor suppressor genes indirectly through genetic lethal interactions. Functional alterations in some oncogenes or tumor suppressor genes may render the mutant cells more susceptible to a functional change in another gene. Therefore, the mutant cells can be eliminated through pharmaceutical intervention that leads to synthetic lethality. Selective cytotoxicity of poly (ADP-ribose) polymerase 1 (PARP1) inhibitors in *BRCA1* and *BRCA2* mutant cancer cells is mediated through genetic interaction between *PARP1* and *BRCA*s. *PARP1* is required for DNA single-strand break (SSB) repair because PARP1$^{-/-}$ mice have defective DNA SSB repair and increased homologous recombination, sister chromatid exchange and chromosome instability[32,33]. On the other hand, *BRCA1* and *BRCA2*, whose loss-of-function mutations predispose carriers to breast, ovarian and other types of cancers[34,35], are required for homologous recombination of DNA double-strand break (DSB) repair[36,37]. *PARP1* may not be directly involved in DSB repair and homologous recombination since PARP1$^{-/-}$ embryonic stem cells and embryonic fibroblasts exhibited normal repair of DNA DSBs[32]. Nevertheless, concurrent blockage of DNA DSB repair, resulting from a mutation in *BRCA* genes and DNA SSB repair due to PARP1 inhibition, is fatal to a cell[38,39]. As a result, *BRCA* mutant cells are 1000 times more sensitive to PARP1 than are *BRCA* wild-type cells[39]. Clinical trials also showed that cancer patients with *BRCA1* or *BRCA2* mutations responded favorably to an orally active PARP1 inhibitor, olaparib (AZD2281)[40-43].

Functional changes in several genes involved in DNA DSB repair pathways, such as *ATM*[44], *RAD54*[45] and *BRIT1*[46] genes, have been found to be highly associated with susceptibility to radiotherapy and the DNA cross-linking agent mitomycin C, suggesting that mutations in those genes may be used as biomarkers of susceptibility to radiotherapy or DNA-damaging chemotherapeutic agents. The *ATM* gene encodes the ataxia telangiectasia mutated (ATM) protein kinase that is rapidly activated when DNA DSBs occur in eukaryotic cells[47]. Activated ATM phosphorylates a variety of proteins involved in cell cycle checkpoint control, apoptosis and DNA repair pathways, including p53, CHK2, BRCA1, H2AX and FANCD2[47,48]. A recent study indicated that interactions of ATM and p53, two commonly mutated tumor suppressor genes, should be explored to determine their ability to predict clinical response to genotoxic chemotherapies[49]. In p53-deficient tumor cells, inactivation of ATM or of its downstream molecule CHK2 was sufficient to sensitize the cells to the genotoxic chemotherapeutic agents cisplatin and doxorubicin[49]. Interestingly, inhibition of ATM or of CHK2 resulted in a substantial survival benefit in p53 wild-type cells. Several clinical trials of CHK1/CHK2 inhibitors in combination with genotoxic agents for cancer treatment are currently under way[50]. The p53 inactivation that occurs in about 50% of human cancers because of genetic mutations[51] may serve as a biomarker for the efficacy of combination therapies containing cisplatin and doxorubicin plus inhibitors of ATM and CHK2.

Another indirect approach is targeting a downstream component in a single linear essential pathway. Evidence has shown that *BRAF* mutant cancer cells can be selectively killed by inhibitors of mitogen-activated protein (MAP) kinase (MEK), a substrate of Raf protein kinases[52]. The RAS/RAF/MEK/Erk pathway is one of the critical signal transduction cascades of most growth factor receptors and is pivotal in oncogenesis[53,54]. RAF kinases are activated by RAS upon the stimulation of extracellular ligands, such as growth factors, cytokines and hormones. Activated RAF phosphorylates and activates the dual-specificity protein kinase MEK, which in turn phosphorylates both tyrosine (Tyr185) and threonine (Thr183) residues of extracellular-signal-regulated kinase (ERK) proteins[55], leading to activation of ERK1/ERK2. Various constitutively active mutations of the *BRAF* gene have been identified in human cancers, including 60%-70% of malignant melanomas, 36%-50% of thyroid cancers, 5%-22% of colorectal cancers, 30% of serous ovarian cancers and lower percentages of other cancers[56]. The strong dependence of *BRAF* mutant tumors on MEK activity may provide a personalized therapeutic strategy for patients with this type of cancer[52].

Overexpression of the *MYC* oncogene was reported to upregulate the expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) death receptor DR5, thereby sensitizing tumor cells to TRAIL-induced apoptosis[57]. An analysis of the knockdown of 510 genes encoding known and predicted kinases, proteins with known functions in TRAIL-mediated signaling pathways, or proteins with unknown functions also revealed that siRNA against *PAK1* and *AKT1* strongly enhanced TRAIL activity, whereas siRNA against *MYC* or the WNT transducer *TCF4* inhibited TRAIL-induced apoptosis, indicating that the MYC and WNT pathways are required for TRAIL-mediated apoptosis[58]. On the other hand, deficiency of the tumor suppressor gene adenomatous polyposis coli (APC) was found to cause accumulation of β-catenin in the nucleus, which interacts with TCF4 and promotes TCF4's binding to c-MYC promoter and overexpression of c-MYC[59]. Deletion of the *MYC* gene rescued the phenotypes caused by deletion of the *APC* gene, despite the presence of high levels of nuclear β-catenin[60]. Thus, *MYC* overexpression is a critical component in the malignancy of APC-defective cancers. A recent study showed that the combination of TRAIL and all-trans-retinyl acetate, another death receptors inducer, significantly enhanced apoptosis induction in *APC* gene-defective tumor cells and premalignant cells[61], indicating that this combination can be useful for chemoprevention and personalized therapy in patients with APC-defective cancers.

SYSTEMATIC ANALYSIS OF GENES ASSOCIATED WITH TREATMENT RESPONSE

Genetic interaction has been exploited as a research tool to identify genes or biomarkers associated with treatment responses. Studies of the Food and Drug Administration (FDA)-approved anticancer agents in a panel of yeast mutants revealed that the DNA cross-linking agent cisplatin displayed high specificity for mutants defective in postreplication repair, whereas the topoisomerase II inhibitor mitoxantrone was highly specific for defects in DNA DSB repair[62]. Because many human disease-related genes are conserved with their yeast counterparts[63,64], yeast has been exploited for mechanistic study of clinically relevant compounds[65,66]. A genome-wide screen of yeast heterozygotes with therapeutic compounds could reveal not only the possible targets but also synthetic lethal partners of the tested compounds[67]. For example, heterozygotes of *TRX2*, a nonessential gene involved in antioxidative stress, were found to be sensitive to camptothecin, whereas heterozygotes of genes involved in exosome rRNA processing were identified as possible lethal partners with 5-fluorouracil[67]. An analysis of more than 1000 structurally diverse compounds, including drugs approved by the FDA and the World Health Organization, in yeast whole-genome heterozygous and homozygous deletion collections showed that genes involved in endosomal transport, vacuolar degradation, aromatic amino acid biosynthesis or encoding of some transcription factors may function as multidrug-resistance genes because their deletion renders yeast sensitive to multiple drug treatments[68]. Nevertheless, information obtained from yeast studies needs to be validated in human cell systems before the results can be translated into clinical applications.

The advent of gene knockdown technology allows us to perform systematic analysis of genes associated with treatment response in human cancer cells. Whitehurst *et al*[10] used a library of more than 84 000 chemically synthesized siRNAs targeting 21 127 unique human genes to screen 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. Their study identified a set of 87 candidate genes whose knockdown sensitized cells to paclitaxel and some of the genes increased the sensitization of lung cancer cells to paclitaxel by more than 1000 times. Multiple genes encoding core components of the proteasome, proteins involved in the function of microtubules, post-translational modification and cell adhesion, or cancer/testis antigens were found to be associated with the sensitivity of paclitaxel[10]. A similar approach has been used by Astsaturov *et al*[11] for identification of genes associated with response to EGFR inhibitors. Analysis of 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, led Astsaturov *et al*[11] to identify 61 genes whose knockdown sensitized the A431 cervical adenocarcinoma cell line to the EGFR inhibitors erlotinib or cetuximab[11]. Most of those genes encode proteins connected in a physically interacting network, including kinases and phosphatases. Nevertheless, a further test in 7 other cell lines for sensitization to erlotinib or cetuximab showed that none of the tested genes sensitized all cell lines, although several of them sensitized 3-5 of the cell lines[11], suggesting that genetic interactions are highly dependent on cell context.

MECHANISMS OF RESISTANCE AND RATIONAL DESIGN OF COMBINATION THERAPY

Genetic interactions could be the underlying mechanisms of resistance to targeted cancer therapies. The same concept may allow us to develop strategies to overcome this resistance. Mutation analyses of primary cancers for genes encoding kinases or genes with known associations with cancers have revealed that an individual tumor may harbor 50 or more mutations in such genes[25,69-71]. Several important signaling pathways might cooperatively be involved in the oncogenesis and malignant evolution of cancers[25,69-72]. Thus, cancer itself is a result of genetic interactions. Tumor cells, xenograft tumors and primary tumors may carry multiple concomitantly activated oncogenes or inactivated tumor suppressor genes. As a result, interrupting a single pathway is often insufficient to induce cell death in most cancer cells because redundant input from various pathways drives and maintains downstream signaling; thus, single-agent therapies have limited efficacy[73,74]. Consequently, combinations of targeted agents are frequently required for effective anticancer therapy or for overcoming drug resistance[73]. Numerous combination regimens of targeted agents are currently being investigated at either the preclinical or clinical level[74,75]. The information about networks of genetic interactions may facilitate the rational design of combinatorial therapy to enhance therapeutic efficacy.

The SRC oncogene encodes a nonreceptor tyrosine kinase that interacts with multiple receptor tyrosine kinases (RTKs), including EGFR, vascular endothelial grow factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor, insulin-like growth factor 1 receptor, hepatocyte growth factor receptor and others[76,77]. Recruiting SRC to receptor tyrosine kinases activates SRC and triggers a cascade of downstream signaling promoting cell proliferation, survival and invasion, as well as angiogenesis. Moreover, SRC can interact synergistically with RTKs by phosphorylating RTKS and modulating their activities[78-80]. Increased SRC activity is associated with resistance to conventional anticancer agents, such as cisplatin[81] and gemcitabine[82], and targeted anticancer agents, such as

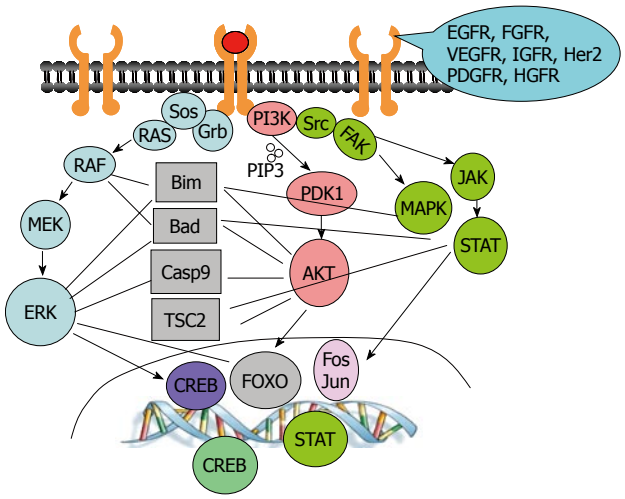

Figure 2 Growth factor activated pathways and their crosstalks. Growth factors, such as epidermal growth factor (EGF), vascular endothelial grow factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF) and platelet derived growth factors (PDGF), interact with their receptors and activate the common downstream pathways, such as PI3K/AKT, RAS/RAF/MAPK and SRC/JAK/STAT pathways. Moreover, there are crosstalks among those pathways in regulating transcription factors and apoptotic/survival proteins. Inhibiting a single target or blocking a single pathway is often not sufficient to induce apoptosis in cancer cells.

gefinitib[83] and trastuzumab[84]. Simultaneous targeting of SRC and Her2 sensitizes multiple trastuzumab-resistant breast cancer cells to trastuzumab *in vitro* and *in vivo*[84]. Inhibiting SRC also sensitized *KRAS* mutant colorectal tumors to cetuximab[85]. Combined inhibition of SRC and EGFR sensitized pancreatic tumor cells to gemcitabine[86]. These results demonstrated that combination therapy consisting of SRC and RTKs inhibitors could be an effective strategy for overcoming resistances to a variety of anticancer agents.

Both EGFR and hepatocyte growth factor receptor (MET)[87,88] play important roles in carcinogenesis[89,90]. Once activated by their ligands, EGF and hepatocyte growth factor, respectively, EGFR and MET activate common downstream pathways, including the PI3K/AKT, RAS/RAF/MAPK and SRC/JAK/STAT pathways (Figure 2). Therefore, elevated activity of MET may negate the effects of anti-EGFR therapeutic agents. Indeed, focal amplification of MET in EGFR-inhibitor-sensitive lung cancer cell lines rendered the cells resistant to anti-EGFR treatment by maintaining ERBB3/PI3K/AKT activity[91]. MET amplification was observed in lung cancer specimens that had developed resistance to gefitinib or erlotinib and in untreated tumors[91,92]. Treatment of resistant cells with a tyrosine kinase inhibitor for either MET or EGFR could not induce cytotoxicity in resistant cells, whereas combined targeting of MET and EGFR resulted in substantial growth inhibition of resistant cells and complete suppression of ERBB3/PI3K/AKT activity[91,92]. Such a therapeutic combination strategy overcame resistance to the EGFR inhibitor erlotinib in an *EGFR* mutant lung cancer tumor model, both *in vitro* and *in vivo*[93].

Crosstalk among downstream pathways of growth factors is also common. The RAS/RAF/MEK/ERK and PI3K/AKT pathways crosstalk and regulate many common downstream targets (Figure 2), such as forkhead transcription factors[94-96], the TSC2/mTOR complex[97-101], BAD[102-104] and caspase-9[105,106]. It is expected that high levels of PI3K/AKT activity can negate antitumor activity induced by MEK/ERK inhibition. Indeed, inhibition of MEK/ERK is sufficient to suppress cell growth or induce apoptosis in cells with low levels of AKT activity but is ineffective in cells with high levels of AKT activity[107]. Combination treatment with MEK and AKT inhibitors was more effective than either single agent alone in human non-small cell lung cancer models *in vitro* and *in vivo*[108].

CONCLUSION

Genetic interaction is likely to be involved in every biological process and has been used as a research platform in various areas of biomedical research. It will continue to be a powerful research tool for both basic and translational studies. Knowledge of the networks of genetic interactions is expected to be translated into clinical applications, in particular for the treatment of cancers.

Note that genetic interactions may be highly dependent on cell context. For a particular gene, genetic interaction may vary in different cell lines. Therefore, it is not unexpected that different candidate genes were obtained when the same oncogenic *KRAS* gene was used to query its genetic lethal interactions in various cell lines[6-9], or that a candidate gene identified in one cell line may not necessarily be applicable to another cell line[11]. Therefore, individualized therapeutic interventions will be required for patients with cancer, even though their cancers may harbor the same oncogene or tumor suppressor gene mutations. Nevertheless, it is possible that certain key nodes may exist in the networks of genetic interactions that will allow us to develop a common strategy to overcome resistance derived from different genetic interactions[84].

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