Review

Cancer Research

Uncoupling the Oncogenic Engine

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Abstract

Inhibition of oncogenic signaling and correction of aberrant metabolic processes may be key paradigms to eliminate cancer cells. The high incidence of activating *RAS* mutations and hyperactivated ERK1/2 signaling observed in many human tumors and the lack of effective targeted therapies to elicit long-term inhibition of the RAS-ERK1/2 signaling pathway add to the importance of discovering novel strategies to treat malignancies characterized by elevated RAS-ERK1/2 signaling. In this review, we describe connections between oncogenic signaling and cancer cell metabolism and how these links may be exploited for novel modern molecular medicine approaches. *Cancer Res; 77(22); 6060–4. ©2017 AACR.*

Introduction

Interrogation of the human genome, transcriptome, and proteome is becoming increasingly precise as a direct result of technologic advances. The wealth of information generated in recent years has been used to further drive the field of molecular medicine to develop new approaches to treat human illnesses, including cancer. Although numerous hypothesis-driven strategies have allowed significant progress in our comprehension of the complexity of malignancies, implementation of this knowledge to achieve durable complete responses remains an unfulfilled aspiration for many cancer patients and their caregivers.

One particularly difficult to treat solid tumor is pancreatic ductal adenocarcinoma (PDAC), a diagnosis of which carries with it a 5-year survival rate of only 7% (1). Over 90% of PDAC cases harbor activating mutations in the *KRAS* gene (2) and mutant *KRAS* is a negative prognostic factor for overall survival in unresectable pancreatic cancer patients (3). KRAS is a member of the RAS family of monomeric G-proteins, which act as a signaling switch to transduce signals from the cell membrane to modulate cell activity. RAS proteins cycle between inactive GDP-bound and activated GTP-bound states. In the GTP-bound state, RAS binds to and activates downstream effectors. Activating RAS mutations occur most frequently in amino acids 12, 13, and 61, with $KRAS^{G12D}$ mutations as the most common in pancreatic cancer, and result in prolonged activation of the RAS–RAF–MEK–MAPK/ERK signal transduction cascade due to decreased rates of GTP hydrolysis. In pancreatic cancer, $KRAS^{G12D}$ promotes tumor invasiveness, drug resistance, and metabolic reprogramming (4–6). Cancer cells are often characterized by their enhanced capacity to produce energy (i.e., ATP) via aerobic glycolysis, through which metabolism of one glucose molecule generates approximately four ATP molecules and a large amount of lactate (7, 8). This process of aerobic glycolysis is referred to as the "Warburg effect." In contrast, healthy differentiated tissues generate energy mainly via mitochondrial oxidative phosphorylation, which generates about 36 ATP molecules per glucose molecule with only limited lactate production, and undergo glycolysis only under oxygen-limiting conditions (anaerobic glycolysis).

The RAS Pathway as a Molecular Target in Cancer

The prominent role of hyperactivated RAS-to-MAPK/ERK signaling in multiple types of human tumors was a decisive factor that led to expenditure of vast resources to develop anticancer strategies based upon inhibition of this signal transduction cascade. Activation of the RAS signal transduction cascade can occur through inactivation of proteins that promote RAS-GTP hydrolysis to RAS-GDP (e.g., neurofibromin), activating mutations in receptor or non-receptor tyrosine kinases that stimulate RAS signaling (e.g., EGFR, BCR-ABL) or via activating *RAS* mutations, which occur in about 10% of acute myelogenous leukemia cases (9), 30% of chronic myelomonocytic leukemia cases (10), 18% of non–small cell lung cancer (NSCLC) cases (11), 40% of colorectal cancer cases (12, 13), and >90% of PDAC (2).

The observation that farnesylation, addition of a 15-carbon isoprenyl group by farnesyltransferase, strongly affects association of RAS proteins with the inner leaflet of the cell membrane, and is critical for RAS function, led to the development of farnesyltransferase inhibitors (FTI) as an anticancer strategy to block oncogenic RAS activity (14). Although widely successful in preclinical studies, this approach largely failed in clinical studies to treat cancer, including advanced pancreatic cancer (15). The discovery that NRAS and KRAS can also be modified by geranylgeranylation via geranylgeranyl transferase-I (GGTase-I) may partially explain the clinical failure of FTI, especially considering that the majority of pancreatic tumors harbor mutated KRAS. Although combination of inhibitors to simultaneously block both FTase and GGTase-I activities can more completely block KRAS prenylation and signaling, systemic delivery of both drug types is too toxic (16). A recent approach to overcome the limitation of nonspecific toxicity

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employed pH-sensitive liposomes to deliver GGTase-I inhibitors (GGTI) to pancreatic tumor cell lines *in vitro* and the liposomes could be equipped with molecules to target cancer cells, such as attachment of transferrin to bind the transferrin receptor that is overexpressed in cancer cells (17). However, it remains to be shown how an anticancer strategy based upon blocking enzymatic processes that influence a multitude of proteins can be tailored to specifically inhibit the activity of oncogenic RAS proteins.

A preclinical study showed that the antisense oligonucleotide AZD4785, which was designed to target wild-type and mutant *KRAS*, decreased KRAS expression, and preferentially inhibited proliferation of KRAS-mutant tumor cell lines (e.g., NSCLC and pancreatic cancer cells), and patient-derived lung cancer xenografts in immunocompromised mouse models (18). Efficacy of AZD4785 is currently tested in a phase I dose-escalation study in adult patients whose solid tumors were demonstrated to contain mutated *KRAS* (ClinicalTrials.gov Identifier: NCT03101839).

A phase I/IIa dose-escalation study to test single administration of the RNA interference (RNAi)-based drug *siG12D-LODER* (Local Drug EluteR) in three different dose cohorts of patients with nonoperable locally advanced adenocarcinoma of the pancreas was recently completed in 15 patients (ClinicalTrials.gov Identifier: NCT01188785; ref. 19). This study demonstrated that *siG12D-LODER* administration with chemotherapy was safe and well tolerated. Partial responses were achieved in 60% of patients for whom computed tomography data were available and no disease progression was reported for the other 40% of patients. A phase II study that combines *siG12D-LODER* with chemotherapy in patients with unresectable locally advanced pancreatic cancer is planned (ClinicalTrials.gov Identifier: NCT01676259).

Downstream effectors of RAS signaling represent logical targets for treatment of pancreatic cancer. Several inhibitors designed to target RAF, MEK1/2, and ERK1/2 were generated and clinically tested in patients with various cancers (reviewed in ref. 20). Although RAF and MEK1/2 inhibitors often achieve initial tumor responses, these drugs are limited by the rapid development of resistance. This resistance may be overcome or at least delayed by simultaneous inhibition of both RAF and MEK1/2 or concomitant inhibition of the PI3K–AKT signaling axis, but toxicities may limit treatment efficacy (21). Notably, *in vitro* experiments with KRAS-mutant PDAC cell lines demonstrated that resistance to MEK inhibitors may be overcome in some models with the ERK inhibitor SCH772984, which suppressed growth upon short-term application (1–3 days) and caused a senescence-like growth-suppressive phenotype upon long-term treatment (several weeks; ref. 22).

One of the currently allowed drugs to treat pancreatic cancer is the nucleoside analogue gemcitabine, which replaces cytidine during DNA replication to arrest tumor growth and cause apoptosis. Pancreatic cancer cell resistance to gemcitabine may be due to ERK-1/2 signaling as combined treatment of gemcitabine with the MEK-1/2 inhibitor U0126, which in turn blocks ERK-1/2 activation, inhibited tumor growth, and increased apoptosis in xenograft tumors derived from human pancreatic cell lines (23). Furthermore, the enhanced gemcitabine activity in orthotopic pancreatic cancer models upon coadministration of the MEK-1/2 inhibitor pimasertib was at least partially due to downregulation of ribonucleotide reductase catalytic subunit M1 (RRM1; ref. 24). Importantly, oncogenic $Kras^{G12D}$ orchestrated use of glycolysis intermediates to promote ribose biogenesis, and thus supported DNA and RNA biosynthesis in an inducible $Kras^{G12D}$ PDAC mouse model (4). Thus, oncogenic RAS can influence cell metabolism and improved strategies to mitigate ERK signaling are likely to increase effectiveness of cancer treatment.

Targeting scaffold protein IQGAP1 as a molecular anticancer approach

Another strategy to block oncogenic activation of the RAS-to-MAPK/ERK signaling cascade is to inhibit association of MAPK/ERK with IQGAP1, a scaffold protein that contains binding sites for many signaling proteins, including members of the downstream signal cascade for RAS: RAF, MEK, and MAPK (25, 26). The feasibility of this approach was demonstrated by Jameson and colleagues (27) who showed that a peptide derived from the WW domain sequence of IQGAP1 blocked MAPK/ERK activation and caused tumor cell death. A recent study conflicts with earlier work regarding ERK2 binding to the WW domain of IQGAP1 and instead suggests that ERK2 actually binds to the IQ domain, like MEK and RAF (28). This raises the question as to how a WW-based peptide could elicit the anticancer effects reported in earlier studies. Bardwell and colleagues (28) propose that ERK2 is unlikely to associate with the IQGAP1 WW domain because ERK2 contains no PPxY sequences, a common motif recognized by some WW domains. However, another group screened peptide recognition properties of 42 WW domains and characterized six groups of WW domains based upon preferred ligand recognition motifs (29). The WW domain of IQGAP1 was classified into the group that associates with ligands that possess a phosphorylated serine or threonine directly followed by a proline ((*po*S/*po*T)P), as the ERK proteins contain. Bardwell and colleagues (28) posit that the anticancer activity of the WW peptide used by Jameson and colleagues (27) may cause conformational changes in IQGAP1, and thus interfere with ERK binding and activation. Furthermore, they called for renewed efforts to determine the "true" WW-binding partner(s) of IQGAP1. Although identification of the actual sites (e.g., WW versus IQ domains) involved in ERK–IQGAP1 association may help us to better understand the mechanism through which the WW-based peptide disrupts ERK–IQGAP1 interaction (e.g., competitive sequestration of the WW domain or induction of conformational change to displace or prevent ERK binding to the IQ domain) and is expected to aid development of more potent inhibitors with greater bioavailability (e.g., small compound peptidomimetics), the end results of the different mechanisms proposed by Jameson and colleagues and Bardwell and colleagues are similar: inhibition of ERK–IQGAP1 interaction and elimination of tumor cells (Fig. 1).

The recent work of Jin and colleagues (30) extends the paradigm of blocking the ERK–IQGAP1 interaction to combat cancer by the novel discovery of fructose-1,6-bisphosphatase (FBP1) as a binding partner for IQGAP1. FBP1 is a rate-limiting enzyme in gluconeogenesis and FBP1 expression is downregulated in many types of tumors, including cancers of the lung, kidneys, liver, and pancreas (31–34). Gluconeogenesis and aerobic glycolysis can be viewed as competing processes as they use some of the same substrates (e.g., fructose 1,6-bisphosphate, fructose 6-phosphate) but for different purposes: glucose anabolism versus catabolism, respectively.

FBP1 was observed to be transcriptionally repressed in PDAC by nucleophosmin (NPM1, B23), which directly bound the *FBP1*

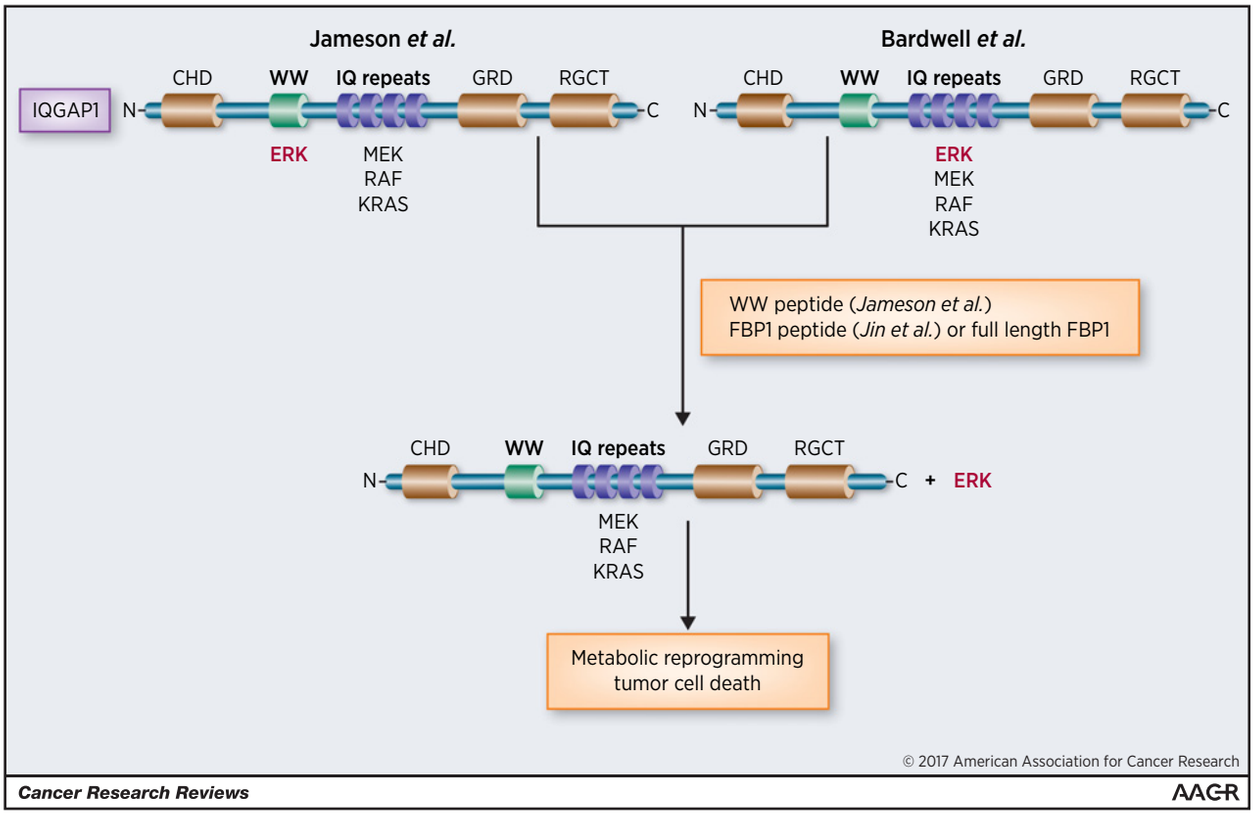

Figure 1.

Schematic of the scaffold protein IQGAP1 structural domains and comparison of the interaction sites for KRAS, RAF, MEK, and ERK proteins as proposed by Jameson and colleagues (27) and Bardwell and colleagues (28). IQGAP1 promotes RAS-RAF-MEK-MAPK/ERK signal transduction via assembly of kinases and thus may be an interesting therapeutic target for malignancies that exhibit elevated RAS-MAPK/ERK activity. Note that Jameson and colleagues determined the ERK–IQGAP1 interaction to occur in the IQGAP1 WW domain, whereas Bardwell and colleagues located ERK binding to the IQGAP1 IQ region. Introduction of peptides based upon the IQGAP1 WW domain (27) or FBP1 (30) disrupted IQGAP1–ERK interactions, resulting in loss of ERK activation and decreased tumor cell growth. IQGAP1, IQ motif-containing GTPase-activating protein 1; CHD, calponin homology domain; WW, tryptophan-containing protein domain; IQ, protein sequence containing Iso/Leu and Gln; GRD, GAP-related domain; RGCT, RasGAP C-terminus domain.

promoter, and high NPM1 expression was associated with worse outcome in PDAC patients (19 low- vs. 46 high-expressing patients determined by IHC staining; 80-month percent survival $P < 0.05$; ref. 34). Ectopic NPM1 expression in pancreatic cancer cell lines caused increased glucose uptake and lactate production, both indicative of aerobic glycolysis, whereas NPM1 inhibition or ectopic FBP1 expression reversed these processes. Thus, the NPM1–FBP1 signaling axis appears to have an important role in controlling pancreatic cancer cell metabolism (34). Accordingly, low FBP1 expression in hepatocellular carcinoma patients was associated with a highly malignant phenotype, impaired gluconeogenesis, and higher rate of aerobic glycolysis (32).

Following identification of IQGAP1–FBP1 interaction via an IP-mass spectrometry approach, Jin and colleagues (30) demonstrated that FBP1 and an FBP1-derived peptide (FBP1-E4) inhibit ERK–IQGAP1 association, suppress IQGAP1-mediated activation of ERK, suppress tumor proliferation, enhance cellular sensitivity to the anticancer drug gemcitabine in PDAC and cause PDAC tumor cell death via binding to the IQGAP1 WW domain (30). This represents an exciting explanation and insight into the mechanism of RAS–MAPK/ERK signaling in tumor cell metabolism. As described above, FBP1 downregulation and ERK activation are common features in many types of tumor cells and downregulation of FBP1 expression may be vital to tumor cells as forced expression of FBP1 causes tumor cell death (30–34). Tumor cells may evolve mechanisms to limit FBP1 expression (e.g., like NPM1 overexpression in pancreatic cancer cells) to direct metabolic activity away from gluconeogenesis and toward aerobic glycolysis for tumor maintenance and expansion. Along this line, specific deletion of the H3K9 methyltransferase Setdb1 in murine hematopoietic cells led to depletion of hematopoietic stem and progenitor cells and leukemic stem cells due to antagonization of glycolysis via activation of gluconeogenic enzymes Fbp1/2 (35). Thus, FBP1 seems to function as a sentinel via modulation of activities critical for transformation of many cell types: activation of ERK/MAPK-1/2 signaling and the metabolic shift from oxidative phosphorylation to aerobic glycolysis.

Delivery of novel molecular therapeutics

To exploit this novel mechanism of oncogenic signal transduction inhibition for therapeutic use, it will likely be necessary to develop suitable small-molecule drug peptidomimetics (36) or to further develop methods for targeted delivery of the FBP1-E4

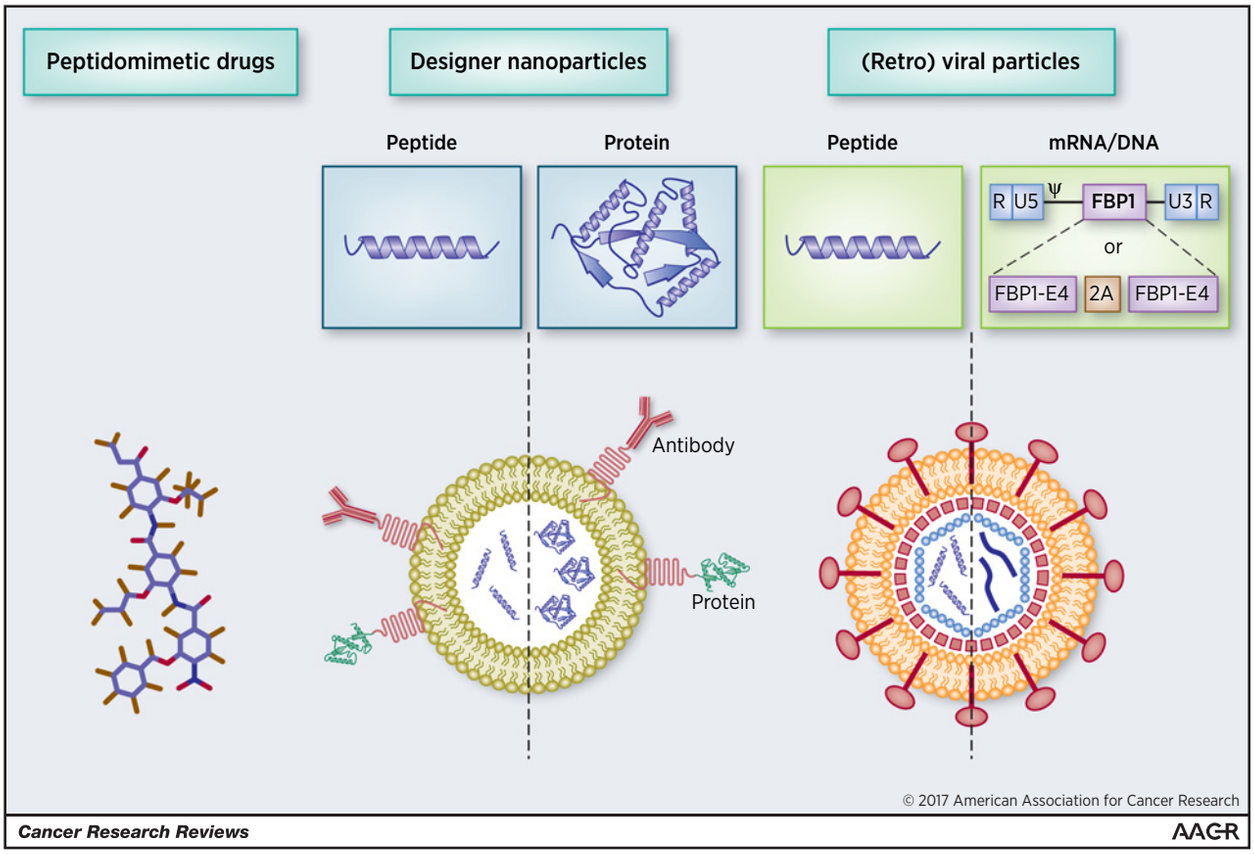

Figure 2.
Potential methods for tumor-specific delivery of therapeutic peptides and peptidomimetics. Similar to the chimeric antigen approaches in immunotherapy, nanoparticles can be outfitted with antibodies or protein ligands (e.g., Transferrin) to deliver the peptide drug to malignant cells. Therapeutic approaches using retroviral gene transfer technologies to deliver therapeutic peptides (e.g., FBP1-E4) can also be envisioned. For example, retrovirus-mediated protein transfer could be adapted for peptide delivery. Alternatively, DNA or mRNA encoding the peptide or full-length protein (e.g., FBP1) could be delivered by retrovirus-mediated episome transfer or mRNA transfer.

peptide as systemic peptide application would result in too low tumor bioavailability. Possible peptide application methods include local tumor injection or use of nanoparticles (37, 38) that incorporate tumor-specific antibodies to direct the peptide-drug to cancer cells (Fig. 2). Alternatively, retroviral transduction could be used to deliver vectors engineered to express full-length FBP1 or multiple copies of the FBP1-derived peptide (e.g., by 2A domains) to overwhelm the oncogenic signal transduction and restore normal metabolic activity. In addition, retrovirus-mediated protein transfer, episome transfer, or mRNA transfer could be used for transient delivery of FBP1/peptide-encoding vectors as previously described for Flp DNA recombinase, transcription factors, and zinc finger nucleases (39–42).

Summary

Perhaps one of the most surprising bits of information that modern genetic analyses have delivered is a more detailed glimpse into the great heterogeneity of tumor cells, even within the same patient. This discovery has wide-reaching clinical implications as different genetic backgrounds may affect tumor responses and resistance to particular therapeutic strategies. However, the development of targeted therapies as precision medicine approaches to treat cancer without harming healthy tissue remains a largely unmet goal. In addition to developing drugs based on individual oncogenic mutations, strategies that combine oncogene targeting with modification of cellular functions, such as metabolism, might prove to be more efficacious in our endeavor to cure cancer. Thus, Jin and colleagues (30) may have identified a vital mechanistic link that connects RAS–ERK signaling and tumor cell metabolism, and with that a *bona fide* Achilles heel of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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