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Review Article

Not just gRASping at flaws: Finding vulnerabilities to develop novel therapies for treating *KRAS* mutant cancers

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Mutations in Kirsten rat-sarcoma (KRAS) are well appreciated to be major drivers of human cancers through dysregulation of multiple growth and survival pathways. Similar to many other non-kinase oncogenes and tumor suppressors, efforts to directly target KRAS pharmaceutically have not yet materialized. As a result, there is broad interest in an alternative approach to develop therapies that induce synthetic lethality in cancers with mutant KRAS, therefore exposing the particular vulnerabilities of these cancers. Fueling these efforts is our increased understanding into the biology driving *KRAS* mutant cancers, in particular the important pathways that mutant KRAS governs to promote survival. In this mini-review, we summarize the latest approaches to treat *KRAS* mutant cancers and the rationale behind them.

Oncogenic mutations in Kirsten rat-sarcoma (*KRAS*) occur in up to 25% of human cancers, positioning them as the most common gain-of-function mutations in human cancer.[1–3] Despite the development of small-molecule inhibitors that interfere with the localization of KRAS or inhibit the activity of mutant KRAS,[4,5] oncogenic KRAS remains a largely elusive target of drug development. Thus, blocking mutant KRAS may require a strategy more akin to one designed to counter the loss of a tumor suppressor – via targeting of vital downstream effector pathways. Along these lines, a number of studies in *KRAS* mutant cancers have led to strategies to target these pathways. Below, we will discuss the main effector pathways of KRAS and current approaches to develop combination therapies targeting these KRAS-effector pathways. Also, other approaches targeting KRAS, including synthetic lethal screening, will be summarized.

Downstream Effectors of KRAS

Kirsten rat-sarcoma protein cycles between an inactive GDP-bound state and an active GTP-bound state. A number of stimuli, including ligands that activate growth factor receptors and G-protein coupled receptors on the cell membrane, lead to the activation of RAS guanine exchange factors (GEFs).[6] This, in turn, results in the formation of active GTP-bound KRAS. In wild-type KRAS cells, KRAS is subsequently inactivated by Ras-GTPase activating proteins (RasGAPs). However, oncogenic *KRAS* mutations, which occur most frequently at amino acids 12, 13, and 61, render KRAS proteins resistant to RasGAP-mediated GTP-hydrolysis. This leads to constitutive activation of KRAS protein. Mutant KRAS activates multiple downstream effector pathways, resulting in the uncontrolled growth, proliferation, and survival of cancer cells (Fig. 1). Amongst these, three major effector pathways have emerged as being critical to mutant *KRAS*-mediated transformation and will be discussed in greater detail: the RAF-MEK-ERK pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and the Ral-NF-kB pathway.

RAF-MEK-ERK pathway. The RAF serine/threonine kinases bind KRAS via their RAS Binding Domain (RBD). RAF activation in turn activates the serine/threonine kinases MEK1 and MEK2, which in turn activate ERK. The requirement for the RAF-MEK-ERK (MAPK) pathway in *KRAS*-mediated transformation and tumorigenesis has been well established.[7] However, inhibition of the MAPK pathway alone is not sufficient to eradicate *KRAS* mutant tumors. MEK inhibitors exhibit cytostatic rather than cytotoxic activity, inhibiting proliferation but not inducing significant apoptosis.[8,9] In accordance with these preclinical studies, the MEK inhibitor selumetinib (Astra-

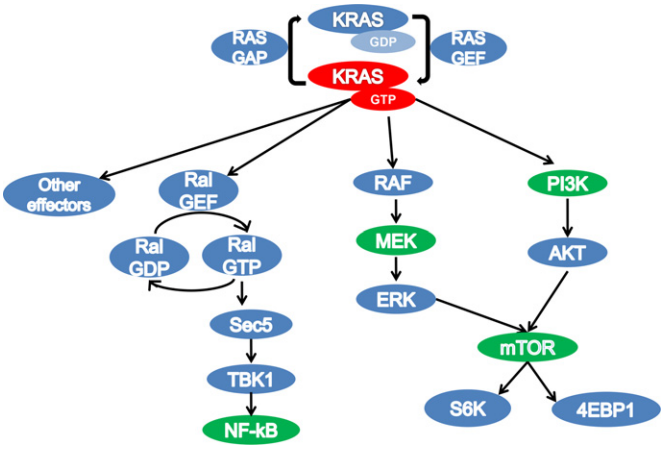

Fig. 1. Effector pathways of Kirsten rat-sarcoma (KRAS). Proteins highlighted green are pharmacologically targetable.

Zeneca, Macclesfield, UK) failed to show clinical activity in an unselected pretreated patient population with a high-rate of *KRAS* mutations.[10–12]

PI3K pathway. The precise role of KRAS in regulating PI3K has been difficult to elucidate because PI3K can be activated by multiple upstream signals, not all of which integrate KRAS to promote downstream signaling. Several lines of evidence suggest PI3K associates with, and is activated by KRAS, thus serving as a principal mechanism of PI3K regulation. The binding of KRAS to p110α induces a conformational change in p110α, which opens and orients the active site of KRAS toward its substrate. Although RBD mutants of p110α fail to bind KRAS, they still maintain enzymatic activity. Interestingly, mice engineered to express RBD-mutant p110α cannot develop mutant *Kras*-driven lung tumors.[13] Furthermore, by using an inducible mouse model of mutant *Kras*-driven lung cancer, Downward and colleagues showed that loss of Kras-p110α binding leads to long-term tumor stasis and partial regression.[14] These elegant studies showed that the interaction between mutant KRAS and p110α is not only required for tumorigenesis but also for tumor maintenance.

In addition to direct activation by KRAS, PI3K can also be activated by receptor tyrosine kinases (RTKs) in *KRAS* mutant cancers. We have reported in colorectal cancers that insulin-like growth factor 1 receptor (IGF-IR) exerts dominant control over PI3K signaling through binding to insulin receptor substrate (IRS) adaptor proteins even in the presence of mutant *KRAS*.[15] PI3K activity is also dependent on basal IGF-IR activity in *KRAS* mutant lung cancer, although in this context mutant KRAS is still thought to be involved in PI3K activation. It has been shown that IGF-IR activation causes IRS-1:p85 complex formation, which in turn relieves an inhibitory effect of p85 on PI3K signaling.[16] Additionally, a recent study showed the *KRAS* mutant NCI-H358 non-small cell lung cancer (NSCLC) cell line still remains dependent on ERBB3 for PI3K signaling.[17] Altogether, these studies suggest numerous contributors, including mutant KRAS and RTKs, activate PI3K signaling in *KRAS* mutant cancers. Another confounding issue is that the role of mutant KRAS may further differ depending on other mutations that may be more or less prevalent among the different tissue types of origin. For example, oncogenic mutations in *KRAS* and *PIK3CA* often coexist in colorectal cancer but less often in pancreatic cancer.[18] The coexistence of *KRAS* and *PIK3CA* mutations in colorectal cancers suggests that mutant KRAS is not sufficient for robust PI3K activity. Similar to MEK inhibitors, single agent PI3K inhibitors are also ineffective for treatment of *KRAS* mutant cancers; murine lung cancers driven by oncogenic *Kras* do not respond to the PI3K/mammalian target of rapamycin (mTOR) inhibitor, NVP-BEZ235.[19] Furthermore, *KRAS* mutations predict resistance to PI3K inhibitors in cell culture experiments.[20,21]

Ral-NF-κB pathway. While the RAF-MEK-ERK and PI3K pathways have been established as key KRAS-effector pathways, KRAS has a number of additional effectors. Among them, the guanine exchange factors of the Ras-like (Ral) GTPases (RalGEFs) have emerged as important effectors of KRAS. Ras-like GTPases directly interact with RAS, and subsequently activates Ral small GTPases.[22,23] Two Ral small GTPases, RalA and RalB, appear to have distinct biological roles in *KRAS* mutant cancers. For instance, inhibition of RalA alone is enough to inhibit tumor initiation, while RalB is vital for tumor invasion and metastasis.[24–26] Similar to KRAS, activated Ral-GTP interacts with multiple downstream effector proteins including RalBP1, which promotes membrane ruffling and filopodia formation through Rac1 and CDC42, as well as receptor trafficking via endocytic regulation.[27] Additional effectors of Ral are the octometric exocyst subunits Sec5 and Exo84, important for secretory vesicle delivery to different membrane compartments.[28,29] Lastly, active RalB signaling causes the association of Sec5 complex with the atypical IkB-related protein kinase TBK1 to promote cell survival through activation of the oncogenic transcription factor NF-κB.[30]

Targeting PI3K-AKT and MEK-ERK Signaling by Combinatorial Approaches

The lack of efficacy seen following suppression of single effector pathway (e.g. use of MEK inhibitors or PI3K inhibitors) in *KRAS* mutant cancers suggests that a combinatorial approach targeting multiple effector pathways is needed. When cancer cells exhibit dependency on a single oncogene ("oncogene addiction"), inhibition of the oncogene leads to downregulation of both PI3K/AKT and MEK/ERK signaling in most instances. Importantly, combination of both a PI3K inhibitor and a MEK inhibitor is sufficient to recapitulate much of the apoptosis and suppression of tumor growth induced by EGFR inhibitors in *EGFR* mutant NSCLC.[31] Moreover, *HER2* amplified and/or *PIK3CA* mutant breast cancers are particularly sensitive to single agent PI3K inhibitors, which surprisingly downregulate both PI3K and MEK/ERK signaling in these cancers, resulting in apoptosis.[32] These results suggest that concomitant disruption of PI3K/AKT and MEK/ERK signaling may underlie much of the antitumor effects observed with targeted therapies in oncogene-addicted models. Consistent with this concept, pharmaceutical inhibition of both the MEK and PI3K pathways has shown durable responses in *KRAS* mutant cancers *in vivo*.[8,19]

Currently, a large number of clinical trials to assess the combination of PI3K inhibitors and MEK inhibitors are ongoing (Table 1). A recent dose-escalation trial tested the combination of the dual PI3K/mTOR inhibitor SAR245409 (Sanofi, Paris, France) with the MEK1/2 inhibitor pimasertib (Merck KGAA, Darmstadt, Germany) in 46 cancer patients. Among the patients, two partial responses were observed: one in a patient with *KRAS* mutant colorectal cancer whose tumor exhibited neuroendocrine features, and a low-grade ovarian cancer patient with simultaneous *KRAS* and *PI3KCA* muta-

Table 1. Currently ongoing trials combining phosphatidylinositol 3-kinase (PI3K) inhibitor and MEK inhibitor

NCT no.	Phase	Company	PI3K inhibitor	MEK inhibitor	Patient selection
01347866	I	Pfizer (New York, NY, USA)	PF-05212384 (PI3K/mTOR inhibitor)	PD-0325901	At the MTD dose, further assessment of these combinations will be done in patients with KRAS mutated colorectal cancer
01363232	Ib	Novartis	BKM120 (pan PI3K inhibitor)	MEK162	At the MTD dose, this combination is explored in patients with EGFR mutant NSCLC, whom have progressed on EGFR inhibitors and triple negative breast cancer, as well as other advanced solid tumors with KRAS, NRAS, and/or BRAF mutations
01390818	I	EMD Serono (Rockland, MA, USA)	SAR245409 (PI3K/mTOR inhibitor)	Pimasertib	Locally advanced or metastatic solid tumors
01155453	Ib	Novartis	BKM120 (pan PI3K inhibitor)	Trametinib	At the MTD dose, further assessment will be done in patients with KRAS or BRAF mutated NSCLC, ovarian, and pancreatic cancer
01859351	I	Wilex (München, Germany)	WX-037 (pan PI3K inhibitor)	WX-554	Solid tumor
01337765	Ib	Novartis	BEZ235 (PI3K/mTOR inhibitor)	MEK162	At the MTD dose, this combination was assessed in patients with EGFR mutant NSCLC, whom have progressed on EGFR inhibitors and triple negative breast cancer, as well as other advanced solid tumors with KRAS, NRAS, and/or BRAF mutations
01392521	Ib	Bayer (Leverkusen, Germany)	BAY80-6946 (pan class I PI3K inhibitor)	BAY86-9766	Advanced cancer
00996892	Ib	Genentech (San Francisco, CA, USA)	GDC-0941 (Pan PI3K inhibitor)	GDC-0973	Locally advanced or metastatic solid tumors
01449058	Ib	Novartis	BYL719 (PI3K alpha-specific inhibitor)	MEK162	Advanced solid tumors or AML or high risk and very high risk MDS, with documented RAS or BRAF mutations
01248858	I	GlaxoSmithKline	GSK2126458 (pan PI3K/mTOR inhibitor)	Trametinib	Advanced solid tumors

AML, acute myeloid leukemia; EGFR, epidermal growth factor receptor; MDS, myelodysplastic syndromes; MEK, mitogen-activated protein kinase kinase; MTD, Maximum Tolerated Dose; mTOR, mammalian target of rapamycin; NCT, national clinical trial that is given to each registered clinical trial; NSCLC, non–small-cell lung cancer; PI3K, phosphatidylinositol 3-kinase.

tions. Grade 3 and 4 toxicities were infrequent, with the most common grade 3 event being skin rash in 14% of patients.[33] In a separate trial combining the PI3K inhibitor BKM120 (Novartis, Basel, Switzerland) and the MEK inhibitor trametinib (GlaxoSmithKline, Brentford, UK), three patients with *KRAS* mutant ovarian cancer achieved partial responses among 66 patients in an unselected population.[34] Based on these three responses, this trial is expanding cohorts to specifically include patients with *KRAS* or *BRAF* mutant tumors. These results suggest that the combination of PI3K and MEK inhibitors has activity, but the activity appears relatively limited. This lack of robust activity seems to be attributed to the difficulty of sufficiently suppressing both pathways without toxicities in a given patient. For example, a trial combining MK-2206 (Merck), an AKT inhibitor, and selumetinib, four of eight patients demonstrated biologically significant inhibition in one marker; however, at the maximum tolerated dose no patient had ≥70% inhibition of both targets.[35]

Alternative therapeutic strategies targeting RTKs that indirectly suppress the PI3K pathway in combination with MEK inhibition may be more tolerable, and as a consequence more effective. As mentioned, the IGF-IR is largely responsible for PI3K activation in *KRAS* mutant colorectal and lung cancer cell lines, and the combination of IGF-IR and MEK inhibitors results in tumor regressions in these xenografts.[15,16] This approach is currently being evaluated in a phase I/II trial of IGF-IR antibody ganitumab (Amgen, Thousand Oaks, CA, USA) combined with the MEK inhibitor MEK162 (Novartis) in *KRAS* mutant colorectal and pancreatic cancer and *BRAF* mutant melanoma (ClinicalTrilas.gov registry number, NCT01562899).

Targeting the Apoptotic Machinery

As mentioned above, in cancers addicted to a single oncogene, effective target inhibition generally results in apoptosis. This process involves the downstream BCL-2 family of proteins, which act as guardians of mitochondria-mediated apoptosis. For example, in *EGFR* mutant NSCLCs, treatment with an EGFR inhibitor shifts the balance of pro- and anti-apoptotic BCL-2 family members, reducing the expression of anti-apoptotic MCL-1 as a result of PI3K/mTORC1 inhibition,[31] and increasing the expression of pro-apoptotic BIM as a result of MEK/ERK suppression, leading to apoptosis.[31,36] In addition,

a recent study using engineered mice deficient for the pro-apoptotic BCL-2 family members BIM or PUMA provided evidence that BIM and PUMA are both key apoptotic effectors of tyrosine kinase inhibitors in *EGFR* mutant NSCLC and *HER2* amplified breast cancer.[37]

The TBK1/BCL-XL pathway. In addition to the PI3K and MEK/ERK pathway, mutant KRAS maintains proliferation and evades apoptosis through other pathways. For instance, shRNA screening using *KRAS* mutant cancer cell lines identified TBK1 as a synthetic lethal partner of oncogenic KRAS. Interestingly, BCL-XL, a known NF-κB target, was identified as a TBK1-regulated gene. Overexpression of BCL-XL rescued apoptosis induced by KRAS or TBK1 knockdown in the NCI-H23 KRAS mutant cell line.[38]

Combination of MEK inhibitor with BCL-XL inhibitor. Pharmacological inhibition of the MEK/ERK pathway is relatively more achievable compared with the PI3K pathway.[39,40] Therefore, MEK inhibitor therapy could be a backbone for combinatorial approaches for *KRAS* mutant cancers. To this point, shRNA screening was performed to identify genes that, when inhibited, cooperate with MEK inhibitors to reduce cell survival in *KRAS* mutant cell lines.[41] BCL-XL emerged as a top hit through this approach. That is, BIM induction following MEK inhibition is not enough to cause apoptosis, but BCL-XL knockdown disrupts an inhibitory complex between BIM and BCL-XL, leading to apoptosis in the presence of MEK inhibitor. Induction of apoptosis is recapitulated by combining the BCL-2/BCL-XL inhibitor navitoclax (ABT-263) with a MEK inhibitor. Two additional studies have also shown the efficacy of this combination.[42,43]

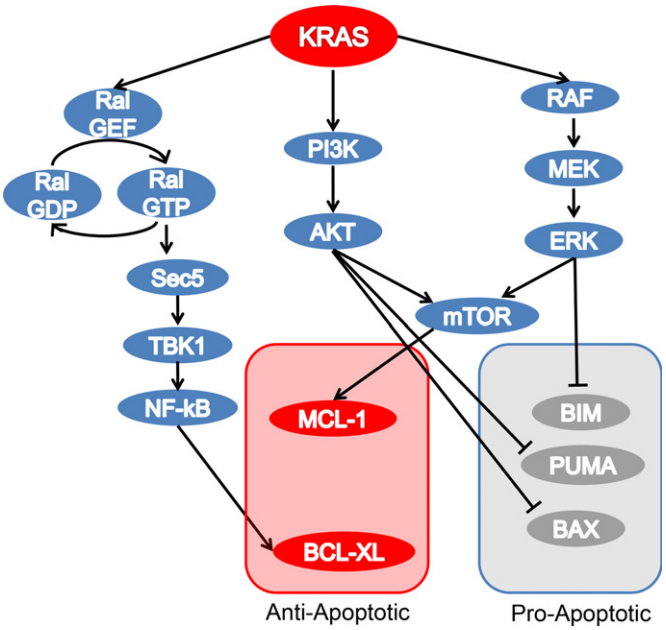

Fig. 2. Effector proteins of Kirsten rat-sarcoma (KRAS) and apoptosis. The BCL-2 family of proteins regulates mitochondrial-driven apoptosis in KRAS mutant cancers. The BCL-2 family consists of three subfamilies: the pro-survival members such as BCL-2 or MCL1, the pro-apoptotic BCL-2 homology domain 3 (BH3)-only proteins such as BIM and PUMA, and the pro-apoptotic BAX and BCL-2 antagonist/killer (BAK; not shown in this figure). The anti-apoptotic function of oncogenic KRAS is mediated by several effector pathways that converge on the BCL-2 family of proteins. The PI3K effector pathway suppresses pro-apoptotic protein PUMA and BAX, the RAS–RAF pathway downregulates the pro-apoptotic protein BIM, and the mTORC1 pathway regulates MCL-1. In addition, the Ral-NF-κB pathway has been implicated in the regulation of BCL-XL. Thus, KRAS suppresses cell death responses through regulation of both pro-apoptotic and anti-apoptotic BCL-2 family proteins.

Combination of mTORC1/2 inhibitor and BCL-2/BCL-XL inhibitor. We have recently showed *KRAS* mutant colorectal cancers are particularly vulnerable to simultaneous inhibition of the BCL-2 anti-apoptotic proteins BCL-2, BCL-XL and MCL-1.[44] Pure mTORC catalytic site inhibitors downregulated MCL-1 in *KRAS* mutant colorectal cancers, and targeting *KRAS* with shRNA similarly reduced mTORC1 signaling and MCL-1 levels, suggesting MCL-1 to be a vital KRAS-effector molecule in these cancers. When combined with the BCL-2/BCL-XL inhibitor navitoclax, the mTORC1/2 inhibitor AZD8055 induced tumor regressions in *KRAS* mutant human colorectal cancer xenografts and *Kras* mutant genetically engineered mouse models of colorectal cancers. In all, this study provides the rationale to use mTORC inhibitors in combination with BCL-2/BCL-XL inhibitors in *KRAS* mutant colorectal cancers. Altogether, these data mark the apoptotic machinery as an attractive target to treat *KRAS* mutant cancers (Fig. 2).

Combination of MEK inhibitor and docetaxel. Several studies have demonstrated that cytotoxic agents, including microtubule stabilizing drugs, stimulate MAPK signaling upon administration. Combining inhibitors of MAPK signaling with one such drug, docetaxel, results in an enhanced anti-tumorigenic phenotype.[45] One of the key mechanisms of this synergy is induction of pro-apoptotic proteins by inhibiting MAPK signaling, which reduces the threshold for apoptosis induction by cytotoxic agents. In fact, prolonged exposure to the MEK inhibitor selumetinib induced BIM expression in the *KRAS* mutant HCT-116 xenograft model. A prospective randomized phase II study assessing the impact of adding selumetinib to docetaxel in previously treated patients with advanced *KRAS* mutant NSCLC was conducted based on these pre-clinical results. Despite no differences in median overall survival, there was significant improvements in both progression-free survival and objective response rate in patients administered selumetinib.[46]

Concurrently with the clinical trials in human subjects, a *Kras* mutant transgenic mouse model was used to optimize treatment modalities, a so-called "co-clinical" trial.[47] This mouse study revealed that adding selumetinib was beneficial for mice with *Kras* or *Kras / p53* mutant lung cancer, but not with *Kras* and *Lkb1* mutations. Interestingly, *Kras/Lkb1* tumors show substantially less phosphorylation of ERK, suggesting that the ERK pathway is less active in these cancers. Furthermore, integrated genomic and proteomic profiles revealed SRC is activated in *Kras/Lkb1* tumors,[48] suggesting that *Kras/Lkb1* mutant tumors are a distinct subset of *KRAS* mutant cancers that may be less dependent on ERK signaling and more dependent on other pathways. Intriguingly, another recent report suggests that NSCLCs harboring mutations both in *KRAS* and *LKB1* are addicted to coatomer complex I (COPI)-dependent lysosome acidification, which participates in retrograde transport, is required for endosome maturation and is a CDC42 effector required for CDC42 transformation.[49]

Identifying Synthetic Lethal Interaction with KRAS

Recent high-throughput screening has provided an expanded list of targets for *KRAS* mutant tumors (Table 2). For example, siRNA screening in *KRAS* mutant NSCLC cell lines identified the transcription factor GATA2 as necessary for the survival

Table 2. Candidate genes showing synthetic lethal interaction with Kirsten rat-sarcoma (KRAS)

Synthetic lethal genes or pathways	Methodology	Pharmacological inhibition	References
TBK1	shRNA screening	Not assessed	38
Coatomer complex I (COPI)	Parallel screening of chemical and genetic perturbations	Saliphenylhalamide A	49
GATA2	siRNA screening	Bortezomib with Fasudil	50
CDC6	siRNA screening	Bortezomib and topotecan	51
STK33	shRNA screening	Specific inhibitor was subsequently developed, but failed to suppress growth of cells	52, 57
TAK1	Expression data based bioinfomatic analysis	5Z-7-oxozeaenol	53
Polo-like kinase (PLK) 1 and 2	shRNA screening and outlier kinase analysis	BI-2536	54, 58
CDK4	Mouse genetic studies	PD0332991	55
Reactive oxygen species	Chemical screening	Lanperisone	56

Fasudil is a Rho signaling inhibitor, approved for the treatment of cerebrovascular spasm in Japan.

of these cancers.[50] GATA2 maintains cell survival via the proteasome machinery, the IL-1/NF-κB signaling pathway, and the Rho-signaling cascade. Combined inhibition of the proteasome and Rho signaling recapitulates the effect of GATA2 loss on *KRAS*-driven tumorigenesis. CDC6, a critical regulator of DNA replication, has also been identified as a synthetic lethal protein with mutant *KRAS*.[51] Bioinformatic analysis suggests proteasome components functionally interact with CDC6, and knockdown of CDC6 showed additional synthetic lethal effects with proteasome inhibitor treatment. Other targets identified by synthetic lethal approaches include, as discussed above, TBK1,[38] as well as COPI,[49] STK33,[52] TAK1,[53] APC/C,[54] CDK4,[55] Polo-like kinase (PLK) 1,[54] and reactive oxygen species (ROS).[56] It should be cautioned that a major caveat associated with RNAi screening is potential off-target effects and the potential disconnect between reduction of total expression and inhibition of kinase function. For example, while STK33 knockdown was synthetic lethal for *KRAS* mutant cancers, inhibition of STK33 kinase activity does not appear to be effective therapy for *KRAS* mutant cancers.[57]

Other Means to Target KRAS

"Outlier kinase" approach. Using an innovative approach of identifying "outlier kinase" expression through analysis of transcriptome sequencing data from a large number of cancers, polo-like kinases (PLKs) were noted to be overexpressed in a subset of *KRAS* mutant pancreatic cancers, and these cancers had specific sensitivity to the PLK-pan inhibitor, BI-6727.[58]

HSP90 inhibitor combinations. Pharmaceutically targeting HSP90 has attracted significant interest. HSP90 inhibitors target HSP90 client proteins resulting in their rapid degradation. Although KRAS is not a client protein of HSP90, *KRAS* mutant NSCLCs are exquisitely sensitive to HSP90 inhibition,[59] most likely through the HSP90-inhibitor-mediated degradation of downstream signaling proteins such as C-RAF[60] as well as the production of ROS.[61] Interestingly, HSP90 inhibitors may have particular activity in combination with the mTOR inhibitor rapamycin in *KRAS/p53* mutant NSCLCs through rapamycin-mediated suppression of glutathione in the presence of HSP90-inhibitor induced ROS.[61]

Targeting posttranslational modification of KRAS. Lastly, targeting mutant *KRAS* by interfering with important KRAS post-translational modifications has recently been explored. The phosphorylation of KRAS on Serine 181, which is mediated by PKC,[62] is indispensable for full KRAS oncogenic activity.[63,64] As such, treatment of *KRAS* mutant cancers with PKC inhibitors has anti-proliferative and pro-apoptotic activity,[63,64] marking PKC as an intriguing therapeutic target.

Conclusion

Targeted therapies that directly disrupt oncogene function have changed the way cancers are treated. While one of the most obvious targets is oncogenic *KRAS*, mutated in roughly one-fourth of all cancers, direct targeting of KRAS has remained largely elusive. Instead, co-targeting pathways downstream of mutant KRAS has emerged in pre-clinical studies as a promising therapeutic strategy. However, validation of these pre-clinical studies has been hindered by unanticipated challenges, such as dose-limiting toxicity of combinatorial inhibition of PI3K and MEK/ERK signaling. Alternatively, blocking upstream activators of PI3K, such as IGF-IR, in combination with MEK inhibition, may be a less toxic and thus more successful strategy. More recently, targeting the apoptotic machinery in *KRAS* mutant cancers has garnered attention. For instance, mTORC inhibitors in combination with BCL-2/BCL-XL inhibitors showed dramatic pre-clinical efficacy in *KRAS* mutant colorectal cancers *in vivo*. Moreover, the identification of novel targets that offer synthetic lethality with mutant *KRAS* has paved the way toward new therapeutic strategies. However, whether effective drugs can be designed to disrupt these targets, and whether these drugs can be administered at doses high enough to inhibit their targets, remains to be seen. Lastly, the identification of already clinically available drugs that show efficacy in subsets of *KRAS* mutant cancers, such as the combination of docetaxel and selumetinib in *KRAS* mutant NSCLC with wild type *LKB1*, may speed up the implementation of much needed novel therapies.

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