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Oncogenic KRAS signalling in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is almost universally fatal. The annual number of deaths equals the number of newly diagnosed cases, despite maximal treatment. The overall 5-year survival rate of <5% has remained stubbornly unchanged over the last 30 years, despite tremendous efforts in preclinical and clinical science. There is unquestionably an urgent need to further improve our understanding of pancreatic cancer biology, treatment response and relapse, and to identify novel therapeutic targets. Rigorous research in the field has uncovered genetic aberrations that occur during PDAC development and progression. In most cases, PDAC is initiated by oncogenic mutant KRAS, which has been shown to drive pancreatic neoplasia. However, all attempts to target KRAS directly have failed in the clinic and KRAS is widely assumed to be undruggable. This has led to intense efforts to identify druggable critical downstream targets and nodes orchestrated by mutationally activated KRAS. This includes context-specific KRAS effector pathways, synthetic lethal interaction partners and KRAS-driven metabolic changes. Here, we review recent advances in oncogenic KRAS signalling and discuss how these might benefit PDAC treatment in the future.

PANCREATIC DUCTAL ADENOCARCINOMA IS DRIVEN BY ONCOGENIC KRAS

Pancreatic ductal adenocarcinoma (PDAC), the predominant form of pancreatic cancer, develops via acinar-ductal metaplasia (ADM) and neoplastic precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasia (IPMN), mucinous cystic neoplasia and atypical flat lesions (AFLs; Morris *et al*, 2010; Aichler *et al*, 2012). Mutationally activated KRAS is present in >90% of PDAC and represents the most frequent (>90%) and the earliest genetic alteration, being found in low-grade PanIN 1A lesions (Morris *et al*, 2010; Kanda *et al*, 2012).

The *KRAS* proto-oncogene encodes an ~21 kDa small GTPase, which cycles between GTP-bound active and GDP-bound inactive states. The switch to the active state is promoted by guanine nucleotide exchange factors (GEFs), which aid exchange of GDP for GTP. KRAS inactivation is mediated by GTPase-activating proteins (GAPs), which induce hydrolysis of GTP. Activating mutations of *KRAS* found in human PDAC (point mutations at codon G12 (98% of all *KRAS* mutations in PDAC), G13 and Q61) impair intrinsic GTPase activity of the KRAS protein and can block the interaction between KRAS and GAPs. This leads to constitutive activation of KRAS and persistent stimulation of downstream signalling pathways that drive many of the hallmarks of cancer, sustained proliferation, metabolic reprogramming, anti-apoptosis, remodelling of the tumour microenvironment, evasion of the immune response, cell migration and metastasis (Pylayeva-Gupta *et al*, 2011).

Targeting of mutant $Kras^{G12D}$ or $Kras^{G12V}$ specifically to the murine pancreas is sufficient to initiate development of ADM, PanINs, IPMNs and AFLs, which progress with long latency to invasive metastatic PDAC, thus recapitulating the human disease (Hingorani *et al*, 2003; Guerra *et al*, 2007; Seidler *et al*, 2008; Morris *et al*, 2010; Pylayeva-Gupta *et al*, 2011). The low frequency of spontaneous progression of precursor lesions to invasive PDAC suggests that additional genetic aberrations are needed for disease progression (Morris *et al*, 2010). Pancreatic intraepithelial neoplasia and PDAC development can indeed be accelerated in Kras-driven mouse models by introducing inactivating mutations in tumour suppressor genes *Cdkn2a*, *Trp53*, or *Dpc4/Smad4*,

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all of which occur frequently in human lesions as they progress to invasive PDAC (Jones *et al*, 2008; Morris *et al*, 2010; Biankin *et al*, 2012).

These mouse studies showed that oncogenic Kras is capable of initiating PDAC, but could not investigate whether continuous Kras activity is required for maintenance of PanINs and PDAC. Recently developed mouse models in which the Kras oncogene can be switched on and off have impressively demonstrated that continuous oncogenic Kras signalling is essential for both progression and maintenance of PDAC (Ying *et al*, 2012; Collins *et al*, 2012a). In addition, it became evident that sustained oncogenic Kras signalling is also necessary for the growth and maintenance of metastatic lesions (Collins *et al*, 2012b). However, individual tumour cells can remain dormant over a long time period after Kras inactivation. Accordingly, reactivation of oncogenic Kras in these dormant cancer cells leads to rapid disease progression (Collins *et al*, 2012b). This accords with studies of human pancreatic cancer cell lines that are addicted to oncogenic KRAS for sustained proliferation and survival (Zimmermann *et al*, 2013).

Together, these findings place oncogenic KRAS squarely at the top of the list of therapeutic targets. However, a subset of human PDAC cells is known to resist KRAS inactivation, a phenotype associated with an epithelial to mesenchymal transition (Singh *et al*, 2009). This highlights the importance of the genetic heterogeneity of human PDAC. Whole-exome and genome sequencing has revealed that human PDAC is an extremely heterogeneous disease with diverse molecular subtypes (Jones *et al*, 2008; Biankin *et al*, 2012; Cowley *et al*, 2013). Such *in vitro* findings therefore suggest that only a subset of pancreatic cancer patients will benefit from KRAS inhibition. This view is supported by an outstanding gene expression profiling study, which revealed three distinct subtypes of pancreatic cancer. One, termed the 'classical subtype', represents 41.2% of the analysed pancreatic cancer cases, has high expression of epithelial genes, and was found to be strongly dependent on constitutive KRAS signalling (Collisson *et al*, 2011). The 'quasi-mesenchymal' and the 'exocrine-like' subtypes were found in 36.5% and 22.3%, respectively (Collisson *et al*, 2011). These distinctions clearly have a broad impact on clinical practice, and it is vital that the molecular determinants be defined.

Because oncogenic KRAS drives PDAC maintenance, at least in a large subset of PDAC patients, there have been considerable efforts to develop direct inhibitors. However, all clinical attempts to directly interfere with KRAS oncoprotein activity have failed, and KRAS is still widely considered undruggable (Berndt *et al*, 2011). A new approach is to identify and characterise druggable crucial downstream effectors of oncogenic KRAS. We now focus on effector pathways of oncogenic KRAS that contribute to PDAC initiation, progression and maintenance and how these pathways can be addressed therapeutically.

EFFECTOR PATHWAYS OF ONCOGENIC KRAS

KRAS signalling is highly complex and dynamic, engaging various downstream effectors, such as canonical Raf/Mek/Erk, phosphatidylinositol 3-kinase (PI3K)/3-phosphoinositide-dependent protein kinase-1 (Pdk1)/Akt, RalGDS/p38MAPK, Rac and Rho, Rassf1, NF1, p120GAP and PLC-ε (Castellano and Downward, 2011; Pylayeva-Gupta *et al*, 2011). It is believed that oncogenic KRAS signalling in PDAC passes through three major pathways: Raf/Mek/Erk, PI3K/Pdk1/Akt and the Ral guanine nucleotide exchange factor pathway (Lim *et al*, 2005; Feldmann *et al*, 2010; Collisson *et al*, 2012; Eser *et al*, 2013).

Recent findings in mice showed that pancreatic cancer initiation, progression and maintenance depend on tumour cell autonomous Kras-PI3K-Pdk1 signalling. Pancreas-specific expression of PIK3CA^{H1047R} (p110α^{H1047R}), a constitutively active oncogenic class IA phosphatidylinositol 3-kinase, in Ptf1a-positive cells enabled selective activation of the PI3K/Pdk1/Akt pathway and phenocopied Kras^{G12D}-driven pancreatic carcinogenesis with striking similarity. In this model, oncogenic signalling flowed through Pdk1 and Akt without cross-activation of Kras, showing that the PI3K-Pdk1 axis represents a pathway capable of inducing cell plasticity, ADM, PanIN and PDAC formation (Eser *et al*, 2013). It is important to mention that contrasting findings have been reported using another murine model. Expression of p110α^{H1047R} in Pdx1-positive cells using a tamoxifen activatable *Pdx1-CreER* mouse line failed to induce PanIN and PDAC formation (Collisson *et al*, 2012). Different target cells of distinct Cre-driver lines, differences in recombination efficacy, or different expression and signalling levels of p110α might explain these opposing results.

Importantly, genetic proof of the importance of PI3K-Pdk1 signalling was shown in the classical Kras^{G12D}-driven PDAC model. Genetic inactivation of *Pdk1 (PDPK1)* completely blocked the development of ADM, PanIN and PDAC (Eser *et al*, 2013). This was evident in several mouse models using different Cre-driver lines, clearly demonstrating that the PI3K/Pdk1 pathway is essentially engaged by oncogenic Kras and needed for PDAC formation.

Collisson and colleagues showed that selective activation of the Raf-Mek-Erk pathway by expression of a conditional mutant oncogenic *Braf^{V600E}* allele in murine pancreas induces PanIN and PDAC development. In this model, activation of the oncogene resulted in a more aggressive phenotype with more PanINs compared with the classical Kras^{G12D} model (Collisson *et al*, 2012). Thus, activation of the canonical MAPK pathway at the level of Raf is sufficient to drive neoplastic changes in pancreas. However, the contribution of Braf to Kras-driven pancreatic carcinogenesis remains unclear. Interestingly, Craf has no role in PDAC development in the *Ptf1a$^{Cre/+}$;LSL-Kras$^{G12D/+}$* PDAC model, although it is known to be important for Kras^{G12D}-driven non-small-cell lung carcinogenesis (Blasco *et al*, 2011; Karreth *et al*, 2011; Eser *et al*, 2013).

The Ral guanine nucleotide exchange factor (RalGEFs) pathway has also been implicated in pancreatic carcinogenesis and progression. RalGEFs, which load GTP to small GTPases of the RAS superfamily, are necessary for RAS-induced transformation of several human cell types (Lim *et al*, 2005). They activate the RAS-like small GTPases RAL-A and RAL-B, which function as mediators of tumour growth and metastasis in human PDAC cell lines, respectively (Lim *et al*, 2006). High levels of active GTP-bound RAL-A and RAL-B have been found in human PDAC (Lim *et al*, 2006). Inhibition of cyclin-dependent kinase 5 (CDK5) had a marked anti-tumourigenic effect on *KRAS* mutant PDAC cell lines *in vitro* and *in vivo*, which was attributed to reduced RAS-RAL signalling (Feldmann *et al*, 2010). CDK5 inhibition also reduced levels of RHO-GTP and RAC-GTP in these cell lines (Feldmann *et al*, 2010). These proteins belong to the RAS superfamily of small GTPases and are deregulated in PDAC. Interestingly, Rac1 is dispensable for pancreas development, but has an important role in regulating the actin cytoskeleton during metaplastic transdifferentiation in the early stages of pancreatic carcinogenesis (Heid *et al*, 2011). However, expression of a constitutively active form of Rac1 without concomitant expression of oncogenic Kras does not induce pancreatic carcinogenesis (Eser *et al*, 2013).

CONTEXT SPECIFICITY OF ONCOGENIC KRAS SIGNALLING

The therapeutic efficacy of inhibitors that target distinct effector pathways of oncogenic KRAS is likely to vary significantly between

KRAS-driven tumour types. Recent data show that different downstream effectors are engaged by the Kras oncoprotein in PDAC and non-small-cell lung cancer (NSCLC) (Eser *et al*, 2013). The concept of tissue- and context-specific oncogenic signalling is illustrated by the need for Craf in $KRAS^{G12D}$-driven NSCLC (Blasco *et al*, 2011; Karreth *et al*, 2011), but not $KRAS^{G12D}$-driven pancreatic carcinogenesis (Eser *et al*, 2013). Furthermore, $KRAS^{G12D}$-driven PDAC depends completely on signalling via the PI3K effector Pdk1, whereas $KRAS^{G12D}$-driven NSCLC is unaffected by loss of *Pdk1* (Eser *et al*, 2013). This has significant implications for clinical therapy. Indeed, previous pharmacological studies in PDAC and NSCLC have suggested tissue-specific differences in KRAS signalling. Engelman *et al* (2008) found no substantial response of $Kras^{G12D}$-driven NSCLC to PI3K-mTOR inhibition by NPV-Bez235 *in vivo*. Although genetic ablation of the RAS/PIK3CA interaction induced regression of Kras-driven NSCLC *in vivo*, treatment with either a class IA PI3K inhibitor or a p110α isoform-specific inhibitor alone showed modest anti-tumour effects (Castellano *et al*, 2013). However, when either one of these agents was combined with a Mek1/2 inhibitor, striking tumour shrinkage was observed (Engelman *et al*, 2008; Castellano *et al*, 2013). In pancreatic cancer, a clinically available inhibitor of class IA PI3Ks efficiently blocked tumour progression in $Kras^{G12D}$-driven PDAC *in vivo* (Eser *et al*, 2013). Input from receptor tyrosine kinases (RTKs) in Kras mutant tumours also seems to be tissue dependent, because elimination of the epidermal growth factor receptor (EGFR) in a mouse model of $Kras^{G12D}$-driven NSCLC failed to recapitulate the inhibitory effect seen on $Kras^{G12D}$-driven PDAC initiation (Navas *et al*, 2012). Kras signalling is tissue specific, with the important implication that efficacy of a treatment cannot be extrapolated from one Kras-driven tumour type to another. Indeed, it is well known that BRAF-driven melanoma and colon cancer differ markedly in their response to targeted therapies (Chapman *et al*, 2011; Prahallad *et al*, 2012). In line with this view, Kras-driven NSCLC depends on coordinated input from the *Ras* oncogene as well as the insulin-like growth factor 1 receptor (IGF1R), but not EGFR (Molina-Arcas *et al*, 2013). Accordingly, EGFR was predominantly activated in *Kras* wild-type NSCLC (Molina-Arcas *et al*, 2013). These data underscore the need to define tissue- and context-specific molecular hubs and vulnerabilities to develop effective treatment strategies.

CROSS-SIGNALLING AND SIGNALLING LOOPS

It has recently been recognised that autocrine and paracrine signalling loops are important amplifiers of oncogenic Kras signalling in several tumour types (Ardito *et al*, 2012; Navas *et al*, 2012; Molina-Arcas *et al*, 2013).

As described above, different RTKs are engaged in Kras-initiated carcinogenesis in different tissue types, which might explain tissue specificity and the differential response to targeted therapies. In mouse models of PDAC, activation of EGFR by a Kras-induced autocrine-positive feedback loop is essential for Kras-induced ADM and initiation of PanIN lesions (Ardito *et al*, 2012; Navas *et al*, 2012). Although not understood in detail, this positive feedback loop is believed to intensify the level of Kras signalling up to a threshold necessary for transformation of pancreatic acinar cells (Ardito *et al*, 2012; Navas *et al*, 2012). However, additional genetic aberrations, such as functional loss of p53, frequently observed in human PDAC, lead to the development of PDAC even without EGFR expression in this model (Navas *et al*, 2012). How loss of p53 function uncouples $Kras^{G12D}$ from EGFR input in the pancreas is currently unknown. It is also unclear whether EGFR signalling is important for PanIN progression and PDAC maintenance. Treatment with the EGFR inhibitor Erlotinib has shown benefit in a subpopulation ($<10\%$) of PDAC patients (Moore *et al*, 2007). This raises the question whether a subset of human PDAC remains addicted to KRAS signalling amplification via EGFR. However, the response to Erlotinib could also be due to inhibition of 'off-target' kinases with a higher affinity for the drug compared with EGFR (Conradt *et al*, 2011).

Negative feedback loops and inhibitory cross-signalling between different KRAS downstream pathways have a role in health and disease. Under physiological conditions, these inhibitory circuits fine-tune the level of signalling in response to growth factors, providing an appropriate response to external stimuli. Interestingly, persistence of negative feedback is found in tumour cells and seems to represent a major selection pressure for mutations in modulators of these feedback programmes (Chandarlapaty, 2012). Furthermore, persistent feedback inhibition provides an explanation of oncogene addiction as hyperdependency on the oncoprotein to sustain a certain strength of pathway output that acts to counter intrinsic inhibition (Pratilas *et al*, 2009; Chandarlapaty, 2012). This has important implications for the design of targeted therapeutic strategies. Inhibition of oncoproteins or certain effector pathways might reduce negative feedback and actually increase signal output, as shown recently in BRAF mutant colon cancer (Prahallad *et al*, 2012). Selective inhibition of the BRAF oncoprotein reduced a negative feedback loop blocking EGFR. EGFR signalling was consequently activated allowing continued proliferation of colon cancer cells via EGFR-mediated PI3K/AKT pathway activation (Prahallad *et al*, 2012). This contrasts with BRAF mutated melanoma, where BRAF inhibition efficiently blocks MAPK activation without affecting EGFR activation (Chapman *et al*, 2011; Prahallad *et al*, 2012). The mechanisms leading to tissue-specific EGFR expression and activation have yet to be uncovered.

It has long been known that there is inhibitory crosstalk between the PI3K/AKT and MAPK pathways at the level of AKT and RAF that modulates proliferation in human cancer cells (Zimmermann and Moelling, 1999). This interaction was found to be highly complex depending on several parameters such as cell type, RTK input and time course of RTK activation (Moelling *et al*, 2002). A novel RTK-independent crosstalk between these two pathways was found in an intriguing study by Zmajkovicova *et al* (2013). They showed that Mek1, phosphorylated by Erk at T292, is essential for the activity of a MAGI1/Mek1/PTEN complex that negatively regulates PI3K signalling (Zmajkovicova *et al*, 2013). Therefore, inhibition of the MAPK pathway is likely to interfere with PTEN tumour suppressor function and might lead to PI3K pathway activation. Loss of PTEN function and subsequent activation of the PI3K pathway has been found in PDAC and shown to accelerate tumour formation in mouse models of pancreatic cancer by amplification of PI3K/Akt pathway activation (Ying *et al*, 2011). This leads to increased signalling of the NFκB survival pathway and pro-tumourigenic changes in the tumour microenvironment (Ying *et al*, 2011). These examples of cross-signalling between KRAS downstream pathways in cancer might provide the basis for understanding primary therapeutic resistance and tissue-specific signalling requirements in different tumour entities driven by identical oncogenes.

KRAS SIGNALLING, INFLAMMATION AND THE TUMOUR MICROENVIRONMENT

The tumour microenvironment has been implicated as a major player in PDAC and could conceivably determine tissue-specific signalling pathways by paracrine activation of specific cytokine receptors or RTKs. A prominent desmoplastic reaction is found in PDAC that distinguishes it from other KRAS-driven tumour

entities such as NSCLC. Continuous KRAS signalling in the pancreas generates a fibro-inflammatory microenvironment that promotes neoplastic progression via paracrine stimulation, with activated fibroblasts, pancreatic stellate cells and immune cells playing a key role (Erkan *et al*, 2012; Collins *et al*, 2012a). Interestingly, this change in the microenvironment is directly tied to oncogenic Kras signalling, because inactivation of oncogenic Kras in early-stage pancreatic neoplasia completely reverses the fibrotic and inflammatory changes (Collins *et al*, 2012a).

Chronic inflammation caused by repeated and/or sustained pancreatic injury through environmental or genetic factors is known to increase pancreatic cancer risk substantially (Yadav and Lowenfels, 2013). Although incompletely understood, the sustained inflammatory micromilieu contributes to a compromised anti-tumour immune response through the infiltration of immunosuppressive regulatory T cells and myeloid-derived suppressor cells (Pylayeva-Gupta *et al*, 2011; Steele *et al*, 2013). In addition, these inflammatory stimuli activate stellate cells and fibroblasts, causing fibrotic remodelling of pancreatic tissue, which in turn enhances oncogenic Kras signalling (Pylayeva-Gupta *et al*, 2011). Indeed, expression of oncogenic Kras in the adult murine pancreas has been shown to cause neoplastic changes only in the context of pancreatic inflammation (Guerra *et al*, 2007). Thus, oncogenic Kras signalling is enhanced by inflammatory stimuli and also itself drives inflammation and desmoplasia in pancreatic neoplasia.

METABOLIC REPROGRAMMING BY ONCOGENIC KRAS

Nearly 100 years ago, Otto Warburg recognised that altered metabolism is a hallmark of cancer. Tumour cells metabolise about 10 times more glucose than lactate than do normal cells, a phenomenon now known as aerobic glycolysis or the Warburg effect (Warburg, 1956). Oncogenic KRAS drives metabolic reprogramming in tumour cells by increasing aerobic glycolysis (e.g., by increasing expression of glycolytic enzymes, such as Hk1, Hk2, Glut1, Pfkl and Ldha), an effect that might be exploited therapeutically (Ying *et al*, 2012). Pancreatic cancer cells also depend on a particular type of glutamine metabolism that differs substantially from normal cells, again offering a promising therapeutic target (Son *et al*, 2013). The identification of tumour-cell-unique and potentially targetable metabolic pathways is a new and exciting field. How soon this can translate into clinically applicable therapeutic strategies is, however, uncertain. Factors such as context specificity and PDAC heterogeneity will certainly be important.

NOVEL TARGETED THERAPEUTIC STRATEGIES

Conventional chemotherapy has limited effect in pancreatic cancer (Moore *et al*, 2007; Conroy *et al*, 2011; Von Hoff *et al*, 2013). The MAPK and PI3K/PDK1/AKT pathways represent exciting new targets for therapeutic intervention, especially because known inhibitors are already clinically available. More than 20 RAF/MEK/ERK and more than 40 PI3K/AKT inhibitors are currently in clinical trials (www.clinicaltrials.gov). Blockade of PI3K signalling in established genetically engineered $Kras^{G12D}$-driven tumours and patient-derived primary PDAC xenotransplantation models efficiently inhibits growth *in vivo* (Eser *et al*, 2013). Collisson *et al* (2012) found a potent cytostatic effect of MEK1/2 inhibition in orthotopically transplanted human and mouse PDAC cell lines. In line with the known crosstalk between the PI3K and MEK pathways in *KRAS* mutant cancer types, compensatory PI3K/AKT pathway activation was observed upon MEK1/2 inhibition in this study (Collisson *et al*, 2012). This could be overcome by combining MEK1/2 with AKT inhibition. Impressive results of such combination therapy have been obtained in preclinical studies in NSCLC (Engelman *et al*, 2008). The first clinical studies to evaluate the efficacy of dual-pathway inhibition in patients with advanced cancers have also shown promising effects on tumour growth. However, dual-pathway inhibition was significantly more toxic than single-agent therapy (Shimizu *et al*, 2012). This might be overcome by inhibition of tissue-specific effectors required for activation of both pathways. Downward and colleagues applied this concept in preclinical treatment studies of NSCLC by inhibiting IGF1R and MEK, achieving dual-pathway inhibition (Molina-Arcas *et al*, 2013). As IGF1R inhibitors showed less impact on KRAS wild-type cells in this study, they might also cause less toxic side effects. Whether dual MAPK/PI3K pathway inhibition is more effective against Kras-driven endogenous PDAC *in vivo* is thus a question of paramount importance.

Direct inhibition of the KRAS oncoprotein in PDAC is another hopeful strategy. So far, all attempts to develop inhibitors of KRAS post-translational modification, such as farnesyl- and geranyltransferase inhibitors that interfere with membrane association and subcellular localisation, have been unsuccessful in the clinic (Berndt *et al*, 2011). Yet, there are some promising new methods, including small molecule inhibitors that block SOS-mediated nucleotide exchange and thus KRAS activation (Maurer *et al*, 2012; Sun *et al*, 2012), and $KRAS^{G12C}$ inhibitors that allosterically shift the affinity of KRAS to favour GDP over GTP (Ostrem *et al*, 2013). Inhibition of the interaction between KRAS and the prenyl-binding protein PDEδ to suppress oncogenic RAS signalling by altering its localisation to endomembranes has also shown interesting results in human PDAC cells *in vitro* and *in vivo* (Zimmermann *et al*, 2013).

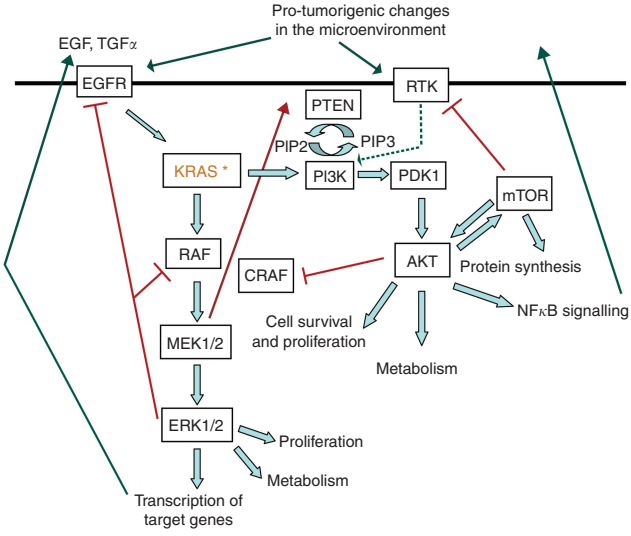

Figure 1. An overview of oncogenic KRAS-driven RAF/MEK/ERK and PI3K/PDK1/AKT signalling networks in pancreatic cancer. Mutationally activated oncogenic KRAS engages the PI3K-PDK1-AKT pathway to drive cancer initiation, progression and maintenance. Additionally, activated KRAS signals through the canonical mitogen-activated protein kinase pathway via RAF-MEK1/2-ERK1/2. KRAS activity is enhanced by positive feedback activation of the epidermal growth factor receptor (EGFR) and possibly by other receptor tyrosine kinases (RTKs) that are engaged by autocrine and paracrine stimuli. Negative feedback loops and inhibitory as well as activating cross-signalling exist at various levels. Activating pro-tumourigenic signalling connections are depicted as arrows in green; inhibitory anti-tumourigenic pathways are shown as solid lines headed by a vertical line in red. Arrows in red depict activating anti-tumourigenic feedback loops. The asterisk (KRAS*) represents the mutational activation of KRAS.

The identification of synthetic lethal interactions of oncogenic KRAS provides another means of targeting mutationally activated KRAS signalling. Defining such interactions depends on comprehensive screening efforts, as recently shown for the synthetic lethal interaction of BCL-XL with MEK inhibition in KRAS-driven cancers (Corcoran *et al*, 2013). However, concerns about the robustness of such screens require that the targets identified are validated independently.

CONCLUDING REMARKS

Oncogenic KRAS signalling is the main driving force behind PDAC. The signalling networks engaged by oncogenic KRAS are highly complex and characterised by the activation of several effector pathways. These are interconnected at various levels by cross-signalling and feedback loops (Figure 1). KRAS-driven signalling networks differ between tumour entities, such as PDAC, NSCLC and colon cancer, and most likely between subtypes of each entity. In different contexts KRAS signalling involves input from different upstream signals and engagement of different downstream effector pathways. Dissection and thorough understanding of these diverse signalling requirements is essential for the development of effective sub-entity-specific targeted strategies. These are urgently needed to improve the poor prognosis for patients suffering from KRAS-driven cancer.

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