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TUMORIGENESIS

Pushing pancreatic cancer to take off

In the pancreas, injury and inflammation, or oncogenic mutation of KRAS, lead to a phenomenon called acinar-to-ductal metaplasia (ADM). Although ADM is reversible once injuries are resolved, oncogenic KRAS prevents this, and such lesions can progress to pancreatic intraepithelial neoplasia (PanIN), and, following additional oncogenic changes, to pancreatic ductal adenocarcinoma (PDA). The secondary events involved in progression to PDA are less well defined; two papers in *Cancer Cell* now indicate a role for epidermal growth factor receptor (EGFR) signalling early in tumorigenesis.

Ardito *et al.* observed activation of the EGFR pathway in areas of ADM and PanIN in a mouse model with pancreatic-specific expression of oncogenic *Kras* (*Kras*$^{LSL\text{-}G12D/+}$;*Ptf1a*$^{Cre/+}$ mice; hereafter referred to as *Kras*^{G12D} mice). In this model, *Egfr* knockout (*Kras*^{G12D};*Egfr*^{KO}) almost completely abrogated tumorigenesis. Furthermore, *Kras*^{G12D} mice had upregulation of endogenous *Egfr* and of two of its ligands (transforming growth factor-α (*Tgfa*) and amphiregulin (*Areg*)), indicating that EGFR activation in this context might require ligand shedding. To investigate this, the authors examined *Kras*^{G12D} mice that lacked the TGFα and AREG sheddase ADAM17; these mice phenocopied the *Kras*^{G12D};*Egfr*^{KO} mice. In addition, *Kras*^{G12D} mice lacking either *Egfr* or *Adam17* were resistant to ADM and PanIN induced by pancreatitis, and EGFR, ADAM17, TGFα and AREG were upregulated in human chronic pancreatitis.

> “requirement for EGFR in KRAS-driven pancreatic tumorigenesis”

PHOTODISC

Navas *et al.* also investigated the role of EGFR in KRAS-induced pancreatic cancer, using a slightly different mouse model in which pancreatic acinar cells specifically expressed oncogenic *Kras*^{G12V} (*Kras*$^{LSL\text{-}G12Vgeo/+}$; *Elas-tTA/tetO-Cre* mice; hereafter referred to as *Kras*^{G12V} mice). In pancreatic cell explants from these mice, ADM was enhanced by the addition of exogenous TGFα or EGF, and knockout of *Egfr* reduced ADM. PanIN lesions from *Kras*^{G12V} mice and from humans, as well as human pancreatitis samples, had high EGFR expression. Similar to Ardito *et al.*, these authors knocked out *Egfr* in the *Kras*^{G12V} mice and found that loss of EGFR completely abrogated PanIN development. Together, both studies support a requirement for EGFR in KRAS-driven pancreatic tumorigenesis.

The tumour suppressor p53 is often mutated in human PDA, so both groups investigated the role of EGFR in KRAS-mutant mice lacking p53. Ardito *et al.* observed delayed tumour initiation in response to blocking EGFR signalling by pharmacological and genetic methods in *Kras*^{G12D} mice with conditional p53 knockout (*Trp53*^{KO}). However, treatment with the EGFR inhibitor erlotinib (plus gemcitabine) did not improve the survival of *Kras*^{G12D};*Trp53*^{KO} mice with detectable PDA (compared with gemcitabine alone), indicating that later stages of PDA progression might be EGFR-independent. Navas *et al.* examined *Kras*^{G12V} mice with conditional *Egfr* and *Trp53* knockout, as well as *Kras*^{G12V};*Trp53*^{KO} mice treated with erlotinib, and found that in both models EGFR loss delayed PDA formation, but did not eliminate it.

Both groups also examined the activation of pathways downstream of EGFR. Ardito *et al.* found that a threshold level of ERK activation, achieved by activation of both KRAS and EGFR, was required for PanIN formation. Navas *et al.* noted increased activation of the PI3K–AKT pathway and signal transducer and activator of transcription 3 (STAT3). Futher studies should determine the relevance of these pathways to human PDA progression.

It is intriguing that, as demonstrated in mouse models by Navas *et al.* and by clinical data, KRAS and EGFR activation seem to be mutually exclusive in lung or colon tumours, indicating a pancreatic-specific role for KRAS and EGFR cooperation. Furthermore, a limited benefit of erlotinib in advanced PDA was observed in a clinical trial, but these studies now support further research to assess the therapeutic value of EGFR inhibition in more defined patient subgroups, such as those that retain p53 function, or for prevention in those at a high risk of PDA.

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ORIGINAL RESEARCH PAPERS Ardito, C. M. *et al.* EGF receptor is required for KRAS-induced pancreatic tumorigenesis. *Cancer Cell* **22**, 304–317 (2012) | Navas, C. *et al.* EGF receptor signaling is essential for K-*Ras* oncogene-driven pancreatic ductal adenocarcinoma. *Cancer Cell* **22**, 318–330 (2012)