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CCR Translations

Clinical Cancer Research

Oncogenic NRG1 Fusions: A New Hope for Targeted Therapy in Pancreatic Cancer

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Approximately 8%–10% of pancreatic ductal adenocarcinoma cases are *KRAS* wild type. In a subset of these tumors, *NRG1* gene fusions have been identified as targetable oncogenic drivers, a discovery that highlights the importance of deep molecular characterization for *KRAS* wild-type pancreatic cancers and provides a novel treatment strategy in this disease.

See related article by Jones et al., p. 4674

In this issue of *Clinical Cancer Research*, Jones and colleagues report the identification of oncogenic Neuregulin 1 (NRG1) gene fusions in patients with *KRAS* wild-type pancreatic cancer (1). As part of a prospective clinical trial, the authors performed whole-genome sequencing (WGS) and whole transcriptome analysis on 47 patients with metastatic pancreatic ductal adenocarcinoma and identified *KRAS* mutations in 94% (44/47) of cases. In all 3 patients with *KRAS* wild-type tumors, the authors discovered translocations affecting the *NRG1* gene that were predicted to be in-frame and preserved the EGF-like domain of the NRG1 protein (Fig. 1A). Two patients harbored a recurrent *ATP1B1* fusion partner, and the third patient demonstrated a complex structural rearrangement in which exons 6 and 7 of *NRG1* (harboring the EGF-like domain) were inserted between exons 15 and 16 of the *APP* gene. All three NRG1 fusion partners were predicted to donate trans-membrane domains to the NRG1 fusion protein, and gene expression analysis demonstrated that relevant NRG1 transcripts were upregulated in all three cases. Given that NRG1 is known to bind the ERBB3 receptor which heterodimerizes with ERBB2 to activate downstream signaling pathways, the authors treated 2 patients with the pan-ERBB receptor inhibitor afatinib and observed partial responses to therapy. This report describes NRG1 fusion proteins as an important oncogenic driver in a subset of *KRAS* wild-type pancreatic cancers and suggests a new therapeutic strategy for patients harboring these lesions.

NRG1 belongs to a well described set of ligands for the ERBB family of transmembrane receptor tyrosine kinases (RTKs). NRG1 binds to ERBB3, which is kinase-deficient but heterodimerizes with ERBB2. The ERBB2:ERBB3 heterodimer potently activates wild-type RAS and the MAPK and PI3K mitogenic signaling pathways (2). NRG1 rearrangements were first described in invasive mucinous adenocarcinoma of the lung (3), where they occur in approximately 30% of cases, but these fusions have now been identified in multiple other tumor types, including cancers of the pancreas, bladder, liver, head and neck, kidney, ovary, uterus, and prostate (1, 4, 5). NRG1 rearrangements have been identified with multiple fusion partners, including *CD74*, *ATP1B1*, *APP*, *CDH6*, *SARAF*, ROCK1, and others, with the occurrence of complex structural rearrangements with multiple fusion partners in some tumors (1, 3, 4, 6). The EGF-like domain of the protein is maintained in essentially all fusions that have been identified (1, 4, 6), and is thought to mediate ERBB3 binding and subsequent oncogenic signaling (Fig. 1A). In addition, NRG1 transcript levels have been shown to be elevated in fusion-positive cancers (1, 4). Functional studies of several *NRG1* fusions have supported that these events are oncogenic drivers across a range of *in vitro* and *in vivo* models (3, 4, 6). In addition to NRG1 translocation events, NRG1-mediated autocrine and paracrine signaling loops have also been implicated in cancer (2).

Heining and colleagues have previously described a striking incidence of targetable oncogenic gene fusions in young adults with pancreatic cancer (6). In a small cohort of 17 patients, four tumors were *KRAS* wild type. Three of the *KRAS* wild-type pancreatic cancers harbored a *NRG1* fusion and the tumor from the fourth patient had an NCOA4-RET fusion. Two patients with NRG1 fusions were treated with therapy directed at ERBB signaling (afatinib or erlotinib/pertuzumab) and demonstrated clinical benefit. Thus, combined analysis of available published cases demonstrates that *NRG1* fusions occur in a subset of patients with *KRAS* wild-type pancreatic cancer, with *ATP1B1* and *APP* being recurrent fusion partners, and that ERBB receptor–directed therapy may have clinical efficacy.

The work of Jones and colleagues and Heining and colleagues add important data to the growing appreciation for the relevance of alternative oncogenic driver events that occur in *KRAS* wild-type pancreatic cancer (Fig. 1B). Analyses done by The Cancer Genome Atlas project (7), the International Cancer Genome Consortium (8), and others have suggested that multiple targetable oncogenic events occur in these *KRAS* wild-type pancreatic cancers, including mutations or in-frame deletions in *BRAF* (8, 9), and mutations or amplifications in *ERBB2*, *MET*, *FGFR1*, and other RTKs (7, 8). In addition, other oncogenic rearrangements have been identified in known oncogenes such as *ROS1* (9), *ALK1* (10), and *RET* (6). Notably, in the report by Jones and colleagues (as well as in the prior report by Heining and colleagues), no other alternative drivers were identified in these *KRAS* wild-type tumors, further suggesting that the NRG1 fusion

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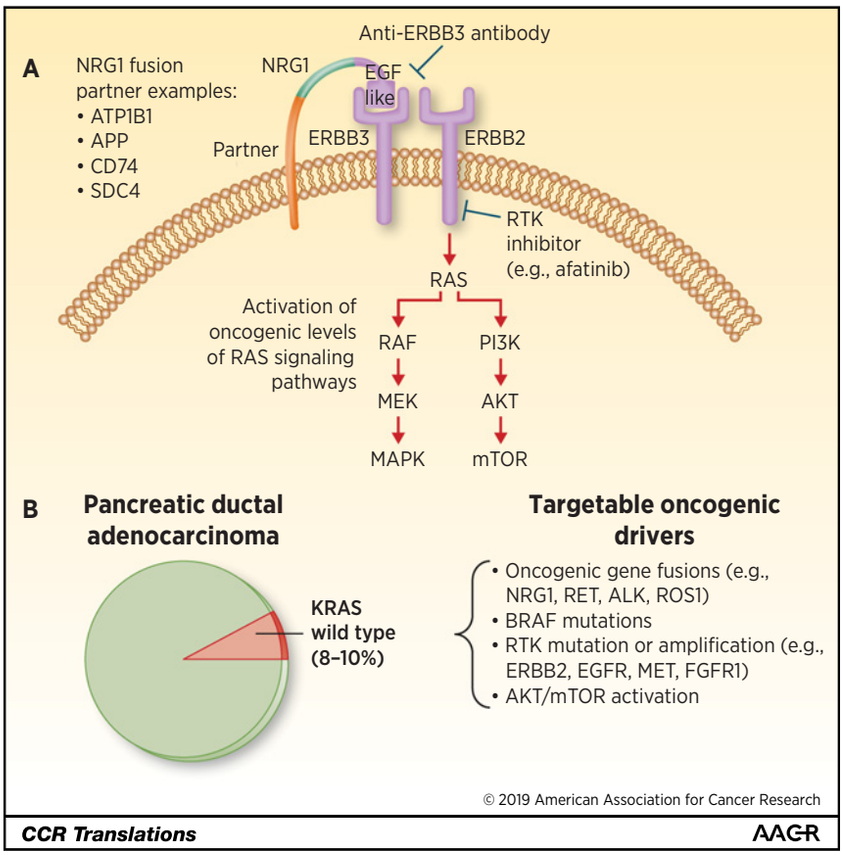

Figure 1.
NRG1 fusions are targetable alterations in *KRAS* wild-type pancreatic ductal adenocarcinoma. **A,** Model for how NRG1 fusion proteins harboring the EGF-like domain bind ERBB3, which heterodimerizes with ERBB2 and activates oncogenic levels of RAS effector signaling pathways (see also ref. 2). RTK, receptor tyrosine kinase; EGF, EGF-like domain of NRG1. **B,** Actionable oncogenic driver events in *KRAS* wild-type pancreatic ductal adenocarcinoma.

proteins are oncogenic drivers of these cancers. Collectively, these studies indicate that *KRAS* wild-type tumors can be driven by multiple different potentially targetable oncogenes, many of which provide an alternative pathway to activate oncogenic levels of RAS signaling. Thus, deep genomic and transcriptomic analyses—preferably utilizing WGS and whole transcriptome approaches to identify fusion events—should be pursued for *KRAS* wild-type tumors in a prospective manner to discover targetable events early in a patient's disease course. Moreover, given the relatively small numbers of patients with *KRAS* wild-type pancreatic cancer with any particular actionable alteration, development of multicenter umbrella trials with treatment arms targeting distinct oncogenic events should be prioritized to test targeted therapy strategies in sufficient numbers of patients.

Given the solid evidence that *NRG1* fusions are oncogenic and targetable, the field must further study these *NRG1* translocated tumors to understand the best approach to therapy. Multiple examples have now been published of patients with pancreatic cancer with *NRG1* fusions demonstrating partial responses to ERBB family receptor–directed therapy with afatinib (1, 6), and these data should fuel further work in relevant patient-derived models to understand how to maximize the efficacy of single-agent and combination therapy approaches with afatinib or other ERBB-directed kinase inhibitors. Drilon and colleagues recently described a small series of patients with lung adenocarcinoma with *NRG1* fusions that did not readily respond to afatinib monotherapy; however, they also reported an exceptional response for one of these patients on a phase I trial of a novel mAb that directly targets ERBB3 (4). Development of additional ERBB3-targeting therapies or combination strategies that target the ERBB–RAS–MAPK signaling pathway also remains an important priority. Given that treatment responses may vary based on the specific NRG1 fusion protein or the type of tumor in which it arises, appropriately powered basket trials that include a variety of lineages and genetic contexts may be useful to investigate the efficacy of novel therapies directed at these *NRG1* fusions.

The discovery of *NRG1* gene fusions in *KRAS* wild-type pancreatic cancers identifies a tractable therapeutic target in a disease that has long been thought to lack such actionable events, thus providing much needed hope for therapeutic benefit in a subset of patients suffering from this difficult disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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