Editorial Commentary

Divide and conquer: towards isoform-specific diagnosis and therapy of *KRAS*-mutant lung cancer

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The identification of oncogenes in animal cells by experiments with retroviruses, and the discovery that similar genetic alterations can cause tumours in humans, laid the foundation for modern cancer research. From that pioneering work to the current genomic era, *RAS* genes marked the beginning of molecular oncology, and remained at the forefront of cancer research ever since.

In humans, the three genes *HRAS*, *NRAS* and *KRAS* encode four proteins: H-Ras (Harvey-Ras), N-Ras (Neuroblastoma-Ras) and two isoforms of K-Ras (Kirsten-Ras), K-Ras4A and K-Ras4B, which in turn derive from alternative splicing isoforms (1). These oncoproteins are members of a larger superfamily of small guanosine triphosphatase (GTPase), containing over 170 proteins, which are divided into five main branches on the basis of protein structure, function or both: Ras, Rho, Rab, Ran and Arf (2,3). All Ras isoforms are characterised by two main domains: a highly conserved catalytic domain, and a farnesylated hypervariable region that modulates membrane interaction for distinctive localizations. The catalytic domain contains the guanosine triphosphate (GTP)-guanosine diphostate (GDP) binding site and interaction sites with effector proteins: because it is identical in all Ras isoforms, all the proteins can interact with the same set of downstream effectors (4). Similar to all the RAS proteins, Kras functions as binary molecular switch in the regulation of pathways responsible for cell proliferation and survival. When stimulated by mitogenic signals, Kras binds to GTP, and activates downstream molecules and effectors. When the stimulation is terminated, Kras-GTP switches to Kras-GDP. Given the slow intrinsic hydrolysis rate of Kras, deactivation of the signal depends critically on GTPase activating protein (GAP), that enhances the GTPase activity and leads Kras to an inactive state (1,4).

Due to differences in post-translational modifications of Ras, including farnesylation, geranylgeranylation and palmitoylation, and because of different intracellular localizations at the plasma membrane and the endomembranes, Ras proteins have access to different effector pools, and are thus able to generate distinct signals (1,5). More than 20 downstream effector signalling pathways responsible for basic cellular process have been identified, including the serine/threonine protein kinase Raf, MAPK and ERK kinase (MEK), extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway, and the phosphatidylinositol-3-kinase (PI3K)-protein kinase B (PKB/AKT) pathway.

Mutations in RAS proto-oncogenes are present in about 20% of all human cancers. *KRAS* mutations are responsible for 75% of adenocarcinomas, while *NRAS* and *HRAS* are mutated more often in melanomas and squamous epithelial carcinomas, respectively. The highest prevalence of *KRAS* mutations are found in pancreatic adenocarcinomas (90%), appendiceal adenocarcinomas (60%), small bowel adenocarcinomas (50%), and colorectal carcinomas (50%) (6,7). *KRAS* mutated lung adenocarcinomas represent about

25% to 30% of all lung cancers, but cannot be considered as a homogeneous entity anymore. Indeed, different isoforms are known: 80% of *KRAS* mutations occur at codon 12 and 13 of exon 2, with G12C the most common form (40%), followed by G12V (about 20%) and G12D (about 15%). Very few mutations are observed at codon 61 of exon 3, which instead is common in *NRAS* mutated cancer. Mutational heterogeneity can be in part explained by tissue exposure to mutagenic agents and specific molecular regulatory mechanisms. For example, exposure to tobacco smoke shows a distinctive coupling to *KRAS*-driven non-small cell lung cancer (NSCLC), especially to G12C variants. This specific mutation is common in former and current smokers, and rarely exists in never-smokers (4,8,9). *KRAS*-mutated lung cancers are characterised by high tumor mutation burden (TMB), a genetic signature of direct tobacco smoke exposure with predominant C>A (G>T) transversion mutations and elevated markers of immune evasion (high PD-L1 expression) (8,10,11). Patients are predominantly female (58%), median age is 65 years, and with history of smoking (93%) (8,12). *KRAS* mutations have been linked to a poor prognosis compared to epidermal growth factor receptor (*EGFR*)-mutated and *KRAS*-wild type lung cancer. Isoform specific outcomes are not consistent across studies. Patients with *KRAS* codon 13 mutations appear to have shorter overall survival compared with patients with codon 12 mutations, G12C and G12V are associated with worse progression-free survival compared with other G12X mutations or wild-type *KRAS* (13-16).

Although no significant differences in survival and demographic data were observed according to the different *KRAS* G12X variants, distinct genomic and transcriptomic features, location and variant type are important factors for oncogenic potential, activation of distinct signalling pathways, and allele-specific genomic landscapes (10,12).

In their article "*Comparative Analysis and Isoform-Specific Therapeutic Vulnerabilities of KRAS Mutations in Non-Small Cell Lung Cancer*", Ricciuti *et al.* show that *KRAS* mutational isoforms correlate with distinct biological and genomic profiles, clinical phenotypes and therapeutic outcomes (17). Based on *in vitro* and *in vivo* analysis the authors demonstrate that *KRAS* G12D has the highest oncogenic potential of all the variants analysed. Although no difference in PD-L1 expression was observed between the isoforms, *KRAS* G12D was associated with the lowest tumour mutational burden. These results are important and consistent with previous data published recently (10).

KRAS mutations may confer insensitivity to inhibitors of upstream and downstream signalling pathways. Ricciuti *et al.* observe that the MEK-inhibitor trametinib presents similar anti-proliferative effects in all *KRAS*-isoforms, whereas sensitivity to selumetinib, another MEK-inhibitor, is different across the isoforms, with 12C and Q61H being the most responsive. Selumetinib *in vivo* exerts a better response in G12C than sotorasib. The authors postulate delayed feedback mechanisms for MEK inhibitors compared with *KRAS* G12C inhibitors as a single agent. Interestingly, the combined treatment with selumetinib and sotorasib is more effective than either drug alone, leading to significant size reduction of *KRAS* mutated tumours in mice. Also, the combined SH2 containing protein tyrosine phosphatase-2 (SHP2)/MEK inhibition is efficacious, principally in G12C, G12D and G12V mutants compared with other *KRAS* mutants. This observation is consistent with previous experiments and is relevant because SHP2 play an important role in several types of cancer (18). Numerous combination trials with *KRAS* and other MAPK pathway (SHP2/MEK/ERK) inhibitors are in progress (NCT04185883, NCT05480865).

In the analysis of the co-mutational landscape and gene-expression profiles, Ricciuti *et al.* demonstrate that each genomic variant presents specific patterns: mutations in serine/threonine kinase 11 (*STK11*) and ataxia telangiectasia mutated (*ATM*) genes were significantly enriched in tumours harbouring G12C, G12A, or G12V, while G13X mutations were associated with the highest rate of concomitant *STK11* and Kelch-like ECH-associated protein 1 (*KEAP1*)-mutations. *STK11/KEAP1* co-mutations downregulate pathways of innate and adaptive immunity, which in turn are associated with reduced response to PD(L)-blockade (19,20). These results are in accordance with previous observations, suggesting a link between *KRAS*, the genomic landscape, and the immune system (20,21).

The recent approval by Food and Drug Administration (FDA) of sotorasib and adagrasib, two selective and irreversible inhibitors of *KRAS* G12C, is an important milestone in the treatment of patients with metastatic lung cancer (22,23). Further advances in the field of *KRAS* mutant cancers can be expected from combination therapies, as evidenced by recently published results about the combination of adagrasib and cetuximab in colorectal carcinoma (24). In consonance with the results by Ricciuti *et al.*, broader genomic and transcriptomic characterisation of *KRAS* mutant tumours is an important basis for the

research of further combination therapies. This, and the development of compounds targeting *KRAS* mutations other than G12C, necessitates an accurate molecular sub-classification and a broader view on the genomic landscape in *KRAS* mutated cancers.

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Footnote

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