IN THE SPOTLIGHT

Climbing RAS, the Everest of Oncogenes

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Summary: Mutations that activate the small GTP-binding protein KRAS are the most common oncogenic event in human tumors. Thirty years after its discovery, mutant KRAS has yet to be therapeutically conquered. Cancer Discov. 4(1), 19–21. © 2014 AACR.

See related article by Faber et al., p. 42 (1).

The genomic landscape of human cancers contains few mountains (genes mutated at high frequency) and thousands of small hills (genes mutated at low frequency). In this landscape, KRAS is by far the tallest oncogenic peak. With its overwhelming 8,848 meters, Everest is the highest mountain on the earth’s surface. The challenges of tackling mutant KRAS and climbing Everest display noteworthy analogies. For decades, even the most experienced hikers thought that Everest was impossible to conquer. Subsequent generations of climbers challenged this assumption. Several expeditions then started to besiege (literally) Everest from its flanks. The competition was fierce and the initial attempts failed, some with fatal consequences. Eventually, however, Everest was successfully conquered in 1953. Key factors to this landmark success were meticulous planning, technological resources, teamwork, bravery, and resilience, but above all, the lessons learned from previous failed attempts. Similar elements are needed to develop anti-KRAS treatments. Although we have yet to “therapeutically conquer” mutant KRAS, research carried out in recent years, including the study by Faber and colleagues (1) described in this issue of Cancer Discovery, has brought us closer to the summit.

Mutations of the GTPase protein KRAS, the principal of the three isoforms of RAS, occur in approximately 20% of all cancers and are particularly prevalent in malignancies with the highest mortality rates, such as pancreatic (90%), colorectal (40%), and lung (25%) tumors (http://cancer.sanger.ac.uk/cancer-genome/projects/cosmic/). By impairing the intrinsic GTPase activity, KRAS mutations are responsible for maintaining the protein in a constitutively active GTP-bound state (2).

Mutations in KRAS were first reported in 1982 and are associated with poor prognosis and resistance to therapy. Thirty years after its discovery, mutant KRAS still poses a formidable challenge to researchers and clinicians alike as attempts to directly target this small (21 kDa) protein have, so far, failed (2). For this reason, direct pharmacologic blockade of KRAS is often viewed as an impossible mission. As for Everest, a few scientists have started to challenge this assumption and innovative approaches appear to be promising (3, 4).

Although direct assaults on KRAS itself are being refined, many groups approached the problem from a different perspective and decided to besiege mutant KRAS at its flanks. The latter are downstream effectors in the cellular pathways initiated by KRAS, which act as a master switch in the proliferation of mammalian cells. Divergent tactics have been deployed to identify factors essential for the survival and growth of cells harboring KRAS mutations, including synthetic lethality approaches, pharmacologic strategies, or the combination of both.

Genetic-based screens spawned a list of genes, including TBK1, STK33, PLK1, and more recently TAK1, whose suppression was found to be synthetically lethal with KRAS mutations (Fig. 1; refs. 2, 5). Notably, overlaps among candidates identified by these studies are modest and, so far, none of these hits has translated into effective therapies in the clinical setting.

Preliminary attempts at targeting single effectors downstream of KRAS (e.g., PI3K and MEK) showed modest or no efficacy, especially in colorectal tumors (6, 7), likely because KRAS activates multiple parallel networks, such as the MEK–ERK, PI3K–AKT, and NF-κB pathways (refs. 2, 8, 9; Fig. 1).

Combinatorial strategies embracing concomitant inhibition of KRAS effectors were then proposed. Among these, the blockade of MEK and PI3K induced regression in a KRAS-driven mouse model of lung cancer (10). Unfortunately, the toxicity of this combination appears to limit its clinical applicability. Alternative strategies involve targeting MEK together with receptor tyrosine kinases, including IGF-IR (11) or HER3 (Fig. 1; ref. 8).

In this issue of Cancer Discovery, Faber and colleagues (1) propose an alternative combinatorial approach to inhibit KRAS-mutant colorectal cancer cells. Leveraging previous high-throughput screenings that assessed the sensitivity of a collection of more than 600 tumor-cell lines to 130 drugs, they found that KRAS-mutated colorectal cancer cells were selectively affected (as compared with wild-type) by co-inhibition of three members of the antiapoptotic family: BCL-2, BCL-XL, and MCL-1.

Previous work by the same authors showed that targeting BCL-2 and BCL-XL with a BH3 mimetic molecule, named...
ABT-263, is not sufficient to induce apoptosis in KRAS-mutated cells (12). The current study indicates that concomitant suppression of MCL-1 is required to sensitize KRAS-mutant colorectal cancer cells to ABT-263. They report that a single compound, obatoclax, could achieve the triple inhibition of MCL1, BCL2, and BCL-XL. However, the clinical toxicity of this molecule (likely associated with off-target effects) limits its exploitation. To suppress MCL-1 more selectively, Faber and colleagues (1) therefore employed AZD8055, a TORC1/2 inhibitor, which was found to reduce the translation of MCL1 mRNA in a genotype-selective fashion. When targeting of BCL-2/BCL-XL (with ABT-263) and suppression of MCL-1 (by AZD8055) were combined, KRAS-mutant cells, differently from their wild-type counterparts, underwent apoptosis. Remarkably, this combinatorial regimen was equally effective in mouse xenografts and in a genetically engineered mouse model of colorectal cancer driven by mutant KRAS (1).

Although this study is a step forward toward the “therapeutic conquering” of mutant KRAS, it also raises several questions.

As discussed above, this is not the first report to pinpoint a cocktail of drugs that selectively target cells carrying mutant KRAS. Some of the previous findings in this area proved to be less broadly applicable than initially thought. We propose that the intrinsic heterogeneity of KRAS-mutant tumors could account for the modest success achieved so far.

First, heterogeneity can result from oncogenic variants that affect distinct codons of KRAS (12, 13, 61, 117, and 146) or that translate in different amino-acid changes on the same codon. All these mutations might engage with different signaling assets, some of which have just emerged (13). Second, KRAS mutations occur within the given mutational architecture of the genome; how diverse genetic backgrounds can affect the biochemical and biologic behavior of activated KRAS is largely unexplored. Third, depending on the tissue of origin, different feedback loops can be activated in response to inhibition of effectors of the KRAS pathway (8, 14). Finally, it is often believed that all KRAS-mutant tumors are uniformly “addicted” to this genetic alteration. Indeed, a recent report noted that the presence of KRAS-activating
mutations does not necessary imply KRAS dependency of the tumor to maintain viability (15), which suggests that KRAS-mutant cancers could be further subclassified according to their addiction.

All these factors are likely to contribute to the biochemical, biologic, and clinical heterogeneity of KRAS-mutant cancers, thus explaining why a specific drug mix may be effective only in a subset of KRAS-mutated tumors. Related to this is the authors’ finding that the ABT-263–AZD8055 combinatorial treatment is much less effective on KRAS-mutant lung cancer cells (1). Clearly, additional work is warranted to establish the efficacy of TORC–BCL combined inhibition on KRAS-mutant tumors of different histologic origins. If KRAS-mutated tumors are indeed, as we believe, a heterogeneous population, it will be of utmost importance to define biomarkers that can guide their (sub)classification. As genetics is unlikely to be of further help, transcriptional and biochemical signatures may become decisive to predict the subsets of KRAS-mutant cancers that will preferentially benefit from a given combinatorial therapy.

Finally, it remains undefined whether the preclinical activity of ABT-263 in combination with TORC inhibitors is superior to other combinatorial strategies previously devised to target lung, pancreatic, or colorectal KRAS-mutated tumors. Comparative studies are needed to test side by side the most effective drug cocktails. Ideally, these studies should be performed in large collections of cell lines and/or patient-derived xenografts.

Notwithstanding the above issues, the results presented in this issue of Cancer Discovery represent an important step forward, as they reveal a nonconventional drug regimen for some of the most recalcitrant tumors. As both ABT-263 and AZD8055 have entered clinical development as single agents, their combination could then be tested in KRAS-mutant colorectal cancers. As these compounds (especially ABT-263) display prominent intrinsic toxicities, clinical experimentation will be challenging.

So, where do we stand on the climb of mutant KRAS, the Everest of oncogenes? Multiple expeditions performed in cells and mouse models led us encouragingly forward. As a result, several drug combinations, allegedly KRAS-mutant selective, are now undergoing clinical validations, which will eventually determine their merit. Experienced climbers know that the most evident track, devised from base camp, can often be deceiving; once one gets closer to the summit, the solution then becomes apparent, sometimes even obvious. Therapeutic conquering of mutant KRAS will require further nonconventional thinking and daring. As with all journeys that are originally considered impossible, success will be highly gratifying.

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