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RASA1/NF1 mutant lung cancer: Racing to the clinic?

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Summary

Although mutation of *NF1* has been described in non-small cell lung cancer (NSCLC), co-mutation with *RASA1*, another Ras-GTPase activating protein (RasGAP), defines a novel genetically defined subclass of NSCLC. *RASA1/NF1* mutant cell lines are highly sensitive to MEK inhibitors, warranting clinical evaluation of MAPK inhibition in this subclass of patients.

In this issue of *Clinical Cancer Research*, Hayashi and colleagues report that loss-of-function mutation of *RASA1*, a Ras-GTPase activating protein (RasGAP), is significantly enriched in *NF1* mutated non-small cell lung cancer (NSCLC) patients (1). Co-occurring mutation of *RASA1* and *NF1* shows mutual exclusivity with other oncogenic drivers such as *KRAS* and *EGFR*, unveiling *RASA1/NF1* co-mutation as new potentially targetable subclass of NSCLC.

Approximately two-thirds of NSCLC patients harbor genetic alterations that activate receptor tyrosine kinase/RAS pathway mediated downstream mitogenic signaling, including the MAPK and PI3K pathways. The clinical importance of genomically subclassifying lung adenocarcinoma based upon these drivers has been proven by the development of effective targeted therapies directed against *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET* and *NTRK*, although limited by acquired resistance. Notably, *KRAS*, the most frequently mutated oncogene in NSCLC patients, has remained a refractory target despite extensive efforts. While targeting downstream mitogenic signaling effectors such as MAPK and PI3K has been one approach to subvert oncogenic KRAS, clinical trials combining inhibitors of these pathways have been ineffective. Since KRAS activates multiple other effector pathways, including those that co-opt innate immune signaling, it is possible that alternate approaches to combination therapy will yield better results. Direct targeting of specific *KRAS* mutations (e.g. the common smoking associated G12C mutation) and anti-PD-1 directed or adoptive cell immunotherapy strategies have also shown recent promise, though clearly more work is needed to benefit the majority of KRAS mutant patients in the clinic (2).

With broad application of next-generation sequencing data analysis, and increased power as sample sizes grow, the spectrum of clinically relevant novel lung adenocarcinoma alterations continues to expand, shrinking the group previously classified as lacking major oncogenic

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drivers. Loss-of-function mutation of *NF1* gene, a canonical member of RasGAP family, has been well described in lung cancer. Inactivation of NF1 function results in hyperactivation of wild-type RAS proteins through rendering them stuck in the GTP-bound form. Although the detailed mechanistic consequences following NF1 depletion are not fully understood, for example which of wild-type RAS isoforms including KRAS, NRAS and HRAS mainly contribute to oncogenic activity, *NF1* inactivating mutation by itself shows only partial mutual exclusivity with *KRAS* and *EGFR* mutations, suggesting additional tumor suppressive functions of NF1. In addition, how mutation in other members of the RasGAP family impacts RAS signaling, alone or in concert with NF1 mutation, has been incompletely characterized.

In the accompanying manuscript, Hayashi and colleagues demonstrate that *RASA1* inactivating mutation is observed in 1–3% of NSCLC patients through analysis of genomic data from the MSK-IMPACT clinical cohort and the Cancer Genome Atlas (TCGA). Interestingly, *RASA1* mutation was highly enriched in *NF1* mutant NSCLC patients, and co-mutation of *RASA1/NF1* exhibited complete mutual exclusivity with *KRAS* and *EGFR* mutations compared with single mutation of either *RASA1* or *NF1* gene. Moreover, while *NF1*-only mutation was found in lung adenocarcinoma (81%) with higher frequency, *RASA1/NF1* co-mutation was distributed evenly in adenocarcinoma and squamous cell carcinoma. Similar to KRAS mutation itself, and in contrast to alterations in other oncogenic drivers such as EGFR and ALK, *RASA1/NF1* co-mutation was enriched in patients that were smokers. Importantly, the authors further demonstrated that targeting downstream MAPK signaling with MEK inhibition *in vitro* was significantly more potent in NSCLC cells with *RASA1/NF1* co-mutation compared to with single mutation of either *RASA1* or *NF1* gene, or with cells that harbor oncogenic *KRAS* or *EGFR* mutations. Together these findings provide a novel druggable subset of NSCLC, including both lung adenocarcinoma and squamous cell carcinoma patients.

Several questions remain regarding the translation of these findings to the clinic. First, while targeting the MAPK pathway directly downstream of oncogenic *BRAF* mutation in lung adenocarcinoma has been effective clinically (3), MEK inhibition in *KRAS* mutant NSCLC has negligible activity (4) (Figure 1). Most likely this is due to the fact that, as mentioned, KRAS activates multiple parallel downstream signaling pathways. While *RASA1/NF1* mutation should theoretically activate the RAS pathway upstream and behave similarly to oncogenic KRAS, might co-mutation of these GAP proteins indeed create a unique dependency on MAPK pathway signaling, as the authors demonstrate *in vitro*? Furthermore, if this is the case, would combined RAF/MEK inhibition with dabrafenib and trametinib, which shows greater efficacy in BRAF mutant lung adenocarcinoma and amelioration of some toxicities (3), also be more effective in *RASA1/NF1* mutated NSCLC? Another possibility is that the behavior of *RASA1/NF1* mutated NSCLC may differ from KRAS mutant NSCLC due different co-mutated tumor suppressors. For example, the authors show that the *RASA1/NF1* alterations are significantly associated with *TP53* mutation, but not *STK11*, which is commonly inactivated together with KRAS and portends poor outcome. Regardless, the discovery of this subclass and the profound sensitivity *in vitro* to MEK inhibition warrants clinical evaluation of this hypothesis in treatment refractory patients.

Another interesting issue raised by this study involves the potential to repurpose FDA approved drugs for off-label usage in scenarios with strong pre-clinical data. Since dabrafenib and trametinib are FDA approved for BRAF mutant lung adenocarcinoma, in the absence of an available clinical trial is it reasonable for a clinician to seek off-label approval and treat a *RASA1/NF1* mutated lung cancer patient who has no other viable therapeutic options with this combination therapy? There is a precedent for doing this with crizotinib, originally designed as a potent MET inhibitor. While at the time only FDA approved for ALK rearranged lung adenocarcinoma, based upon strong pre-clinical data supporting sensitivity of the MET exon skipping mutation to MET inhibition *in vitro*, we treated such a patient off-label with crizotinib and observed clinical response (5), later validated by larger case series and clinical trials. Although treating patients in the context of a clinical trial is clearly the preferred route, documenting results of off-label therapy and publishing case reports or case series of results are likely to catalyze industry efforts to invest in larger scale clinical trials. Furthermore, access to clinical trials geographically and based upon slot availability remains a major barrier for the majority patients. In the era of expanded genomic testing, as these low frequency subclasses of NSCLC and other cancers continue to be identified, what is the best route to ensure early access to potentially effective targeted therapies, but also to collect the data?

Regardless, this initial description of *RASA1/NF1* co-mutated NSCLC and the strong pre-clinical data warrants clinical evaluation of strategies that incorporate MAPK pathway inhibition. Hopefully, the results observed will side with the efficacy observed in *BRAF* mutated lung adenocarcinoma, and not with those seen with oncogenic *KRAS*, which remains a major hurdle.

Acknowledgments

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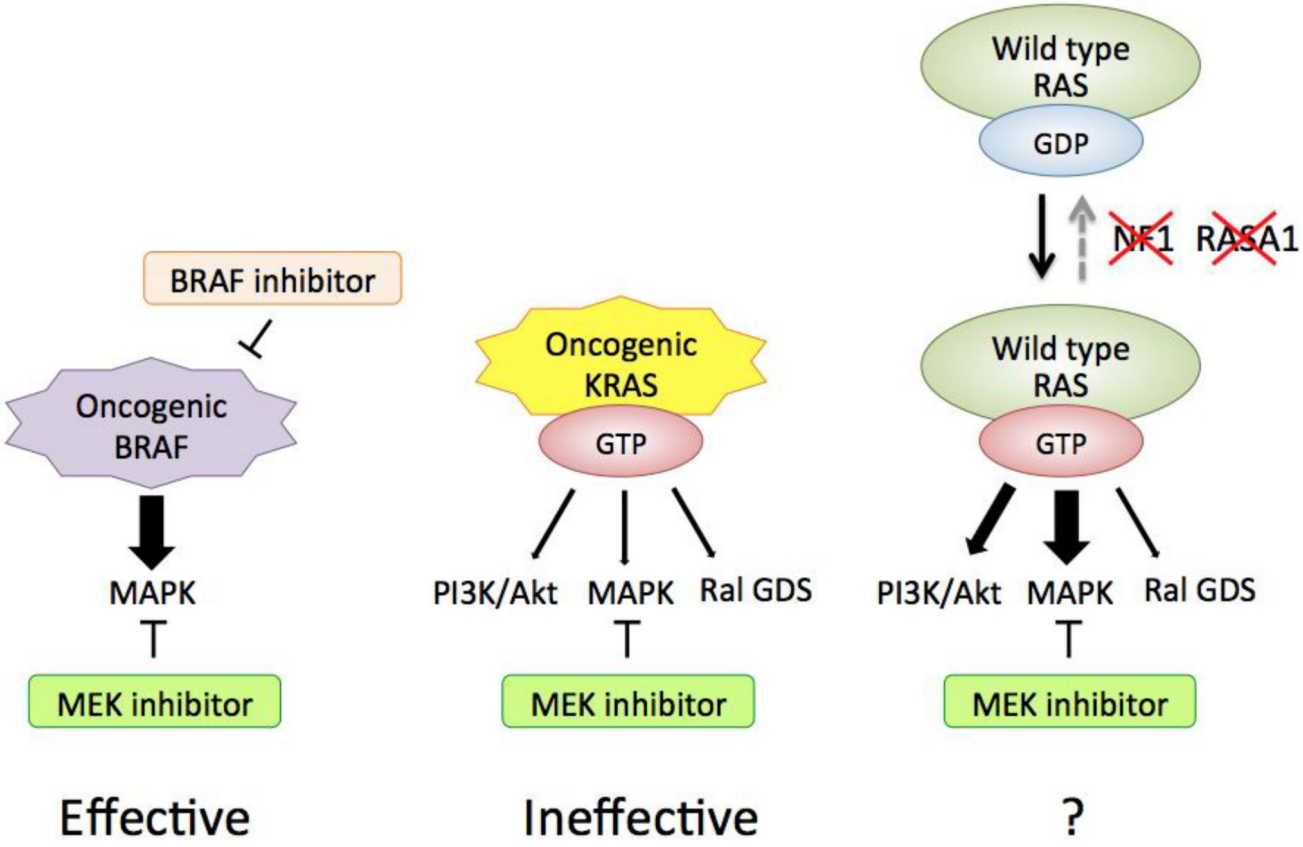

Figure 1.

NSCLC cells harboring *BRAF* mutation show hyperactivation of MAPK signaling, and are effectively treated by combined BRAF and MEK inhibition. Oncogenic mutation in *KRAS* results in disruption of GTPase catalysis. Co-occurring loss-of-function mutations of *RASA1/NF1* also cause dysfunction of GTP hydrolysis. Both mutations result in accumulation of GTP-bound “active” RAS protein that has a high affinity for numerous other effectors such as PI3K and Ral GDS, which activate oncogenic cell growth and survival signaling. Whether treatment with MEK inhibition (+/− BRAF inhibitor) is clinically more effective than with *KRAS*-mutated NSCLC patients remains to be determined.