Editorial Commentary

eIF4A dependency: the hidden key to unlock KRAS mutant non-small cell lung cancer's vulnerability

Silvia Casacuberta-Serra[1]^, Iñigo Gonzalez-Larreategui[2]^, Laura Soucek[1,2,3,4]^

[1]Peptomyc S.L., Barcelona, Spain; [2]Models of Cancer Therapies Laboratory, Vall d'Hebron Institute of Oncology, Cellex Centre, Hospital University Vall d'Hebron Campus, Barcelona, Spain; [3]Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain; [4]Department of Biochemistry and Molecular Biology, Universitat Autonoma de Barcelona, Bellaterra, Spain

Correspondence to: Laura Soucek, PhD. Models of Cancer Therapies Laboratory, Vall d'Hebron Institute of Oncology, Cellex Centre, Hospital University Vall d'Hebron Campus, c/ Natzaret 115-117, 08035 Barcelona, Spain; Peptomyc S.L., Barcelona, Spain; Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain; Department of Biochemistry and Molecular Biology, Universitat Autonoma de Barcelona, Bellaterra, Spain. Email: lsoucek@vhio.net.

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Lung cancer is the leading cause of cancer-related deaths worldwide. The most common type of lung cancer (~85%) is represented by non-small cell lung cancer (NSCLC) (1). In the past few years, treatment options for advanced NSCLC have undergone a remarkable improvement, especially thanks to the development of potent targeted therapies directed against major genomic cancer drivers like EGFR, HER2, BRAF, MET, ALK, and ROS1, among others. However, despite this recent progress, survival rates for patients with NSCLC, particularly those with the KRAS mutation, continue to be disheartening. Even immunotherapy, which appears to have somewhat improved the overall survival (OS) and progression free survival (PFS) of patients compared to platinum-containing chemotherapy (2,3), has not made sufficient difference and the prognosis remains dire, as the majority of KRAS-mutated (KRASmut) patients do not respond to treatment due to innate or acquired resistance, highlighting the importance of developing new therapeutic approaches for this underserved patient population. To improve treatment responses and considering the significance of the RAF-MEK-ERK pathway in KRAS-driven lung cancer, several attempts have been made to use MEK1/2 inhibitors (MEKi) in combination with either chemotherapy or targeted agents, but they have shown limited efficacy (4). Indeed, trials combining chemotherapy with MEKi have shown trends of improved PFS, OS, and response rates but with no significant differences (5). Thus, further research is needed to refine MEKi treatment and define effective clinical strategies in this oncological setting.

Recently, covalent KRAS G12C inhibitors (KRASi), namely sotorasib (AMG510) and adagrasib (MRTX849), have been approved for the treatment of patients with advanced NSCLC carrying KRAS G12C mutations who have progressed after at least one prior line of treatment based on the CodeBreaK 100 and the KRYSTAL-1 phase I/II trials, respectively (6). NSCLC has been, so far, the most successful application of these KRASis, but somewhat also their worst disappointment. Indeed, KRAS mutation is found in one third of NSCLC and the G12C mutation

^ ORCID: Silvia Casacuberta-Serra, 0000-0002-2595-1115; Iñigo Gonzalez-Larreategui, 0000-0002-0959-8497; Laura Soucek, 0000-0002-4750-7971.

occurs in 40% of the cases, offering the perfect validation model for KRASi (7). However, less than 50% of patients benefit from this therapeutic option and the duration of response is very limited, with patients rapidly developing resistance (8,9). Understanding resistance mechanisms to G12Ci and identifying biomarkers that can predict patients' responsiveness to these agents are crucial steps to develop new strategic combination of treatments to achieve better and long-lasting responses for KRASmut NSCLC patients. Growing evidence suggests that resistance mechanisms to G12Ci exhibit an heterogenous nature (6,10). The main primary and acquired resistance mechanisms described up to date include, but are not limited to, loss of function mutations in tumor suppressor genes, rewiring through alternative signaling pathways, appearance of secondary KRAS mutations or upregulation of the wild-type RAS isoforms and acquisition of new pathogenic mutations in other RTK-RAS-MAPK pathways members (6,7). While numerous resistance mechanisms have been identified, the intricate nature of the G12Ci resistance landscape remains largely unexplored. In addition, KRASi for other KRAS mutations (like G12D, G12A, G12S, among others) have not been approved yet, leaving the majority of NSCLC still underserved.

Numerous efforts have been made to discover vulnerabilities in KRAS-driven tumors, but synthetic-lethal approaches have not pinpointed a universal target yet. This could be because of the different tissues of origin, other mutations in downstream effectors, among other reasons. In an attempt to define a better strategy to maximize the success of KRASi and alternative inhibitors of the RAS pathway (namely, the MEKi trametinib), Nardi and colleagues underwent a thorough and excellent study focused on cap-dependent translation (11). This mechanism is commonly hyperactivated in tumors through genetic changes in elements of the eukaryotic initiation factor 4F complex (eIF4F), or as a result of abnormal activation of oncogenic pathways like RAS/ERK, PI3K/mTOR, and MYC, all of which intersect at this complex (12). Of note, eIF4F controls the translation of mRNAs that encode proteins that induce proliferation, survival, metastasis, and immune evasion (13,14). The eIF4F complex is of significant interest in cancer research and treatment, due to its pivotal role in tumorigenesis and cancer progression (15,16), which points at its targeting as an exciting avenue for developing more effective and personalized cancer therapies. Notably, numerous studies underscore the potential of targeting the eIF4F complex in lung cancer. For instance, inhibiting the interaction between eIF4E and eIF4G, two key components of the eIF4F complex, has shown therapeutic promise across various cancer types, including NSCLC (17,18). Furthermore, small-molecule inhibitors of EIF4G1 have exhibited potent repression of NSCLC growth in both *in vitro* and *in vivo* settings (19). Additionally, several natural compounds have been identified for their ability to hinder cap-dependent translation by selectively targeting and inhibiting the activity of eukaryotic initiation factor-4A (eIF4A) (20). Rocaglate analogs are the most studied eIF4A inhibitors in the field, with eFT226 (zotatifin), a structure-guided rocaglamide-inspired inhibitor, currently being evaluated in clinical trials (21).

In this study, Nardi *et al.* focused on one of the eIF4F components, the RNA helicase eIF4A, which is essential for cap-dependent transcripts unwinding (11). Their publication in *JCI* shows that a KRASi, adagrasib (MRTX849), and genetic or pharmacologic inhibition of eIF4A cooperate and induce dramatic cell killing of RAS mutant NSCLC *in vitro* and *in vivo*, in cell-derived xenograft (CDX) and patient-derived xenograft (PDX) (11). This appears particularly interesting considering that either compound alone is mostly cytostatic or just modestly cytotoxic, while their combination induces significant apoptosis, revealing a promising therapeutic strategy for KRAS G12Cmut NSCLC (11). Perhaps even more interesting is that the durability of response to the combinatorial treatment *in vivo* seems to be quite long and promising compared to the one exerted by KRASi alone. Importantly, the inhibition of eIF4A alone did not promote a deeper suppression of the RAS signaling pathway, suggesting that additional factors or cooperative mechanisms may be at play in regulating the therapeutic effect of its inhibition (11).

The authors complement this finding with KRAS mutant experimental models different from G12C, making use of the MEKi trametinib, which also turns out to strongly cooperate with the eIF4Ai eFT226, both *in vitro* and *in vivo*, reinforcing the notion that eIF4A dependency is a common vulnerability in most KRAS mutant contexts (11). Hence, this newly found vulnerability could not only benefit those patients that do not respond to current KRAS G12Ci, but also those harboring other KRAS mutations, for whom treatment options are limited to highly toxic and often ineffective chemotherapies.

Importantly, the authors also succeeded in identifying the underlying molecular mechanism of action of the cooperation, pinpointing the suppression of key pro-survival BCL-2 family proteins, MCL1, B-cell lymphoma-

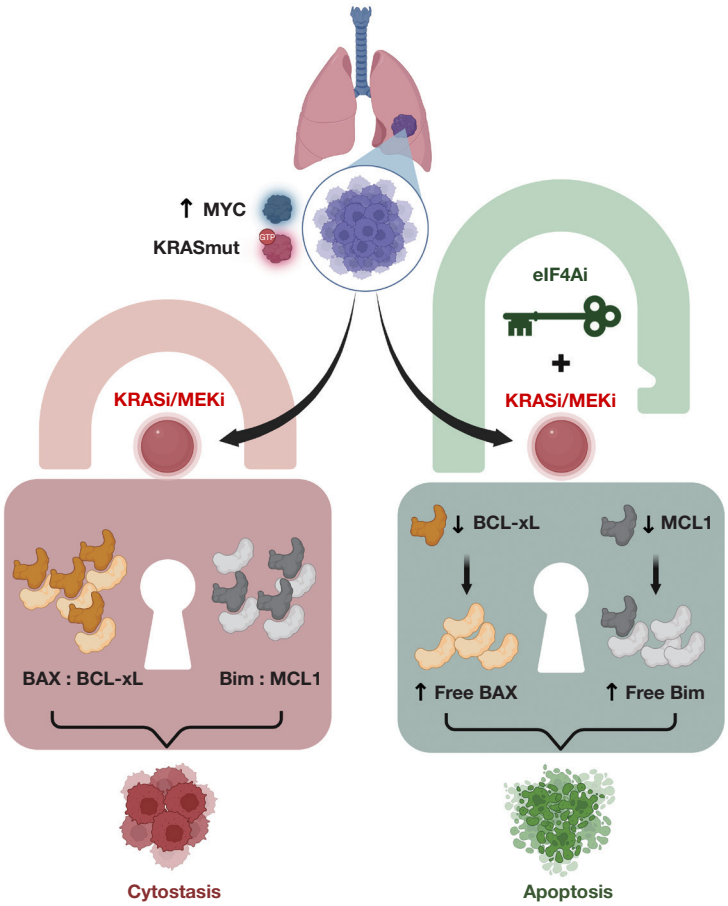

Figure 1 The eIF4A is a relevant vulnerability in KRAS mutant NSCLC. In KRAS-driven tumors with high MYC levels, treatment with KRASi or MEKi induces a cytostatic response. This response is dependent on the balanced ratio between the apoptosis regulator BAX protein and the BCL-xL, as well as between the Bcl-2 homology 3-only protein Bim and the induced myeloid leukemia cell differentiation protein MCL1. However, combination therapy involving any of these inhibitors with an eIF4A inhibitor leads to reduced levels of BCL-xL and MCL1, which result in increased free BAX and Bim levels that trigger tumor apoptosis. Made with Biorender.com. KRASmut, KRAS-mutated; KRASi, KRAS inhibitor; MEKi, MEK inhibitor; eIF4A, eukaryotic initiation factor-4A; BCL-xL, B-cell lymphoma-extra-large molecule; NSCLC, non-small cell lung cancer.

extra-large molecule (BCL-xL) and BCL-2, as the reason for the improved tumor killing of the combinatorial treatment (*Figure 1*). The suppression of these pro-survival proteins was sufficient to promote cell death when eIF4Ai was combined with either KRASi or MEKi. Conversely, the suppression of other known targets as cyclin D1 and CDK4 enhanced the cytostatic effect but not cell killing. The expression of these family proteins was indeed the crucial factor differentiating sensitive cell lines from resistant ones where the combined treatment induced only cytostatic effects (11).

Finally, in line with the notion that MYC overexpressing tumors have consistently elevated cap-dependent translation (22), this beautiful study also reveals that sensitivity to eIF4A and KRAS pathway inhibitors is associated to high MYC levels (11) (*Figure 1*), which could then be considered a good selective biomarker for this combinatorial treatment. This finding is particularly interesting since the MYC oncoprotein has been described to be overexpressed in about 75% of NSCLC and be critical for their pathogenesis and development of resistance (23,24). Thus, having an efficacious treatment against these highly aggressive tumors holds significant promise for effectively targeting a substantial percentage of KRASmut NSCLC cases.

In summary, there are several interesting considerations associated to this study:

(I) A common strategy used to strengthen the effect of a pathway inhibitor has been so far to combine it with other inhibitors impinging on the same pathway. This is no exception for KRASi, which are good candidates for combination with, for example, MEKi or RTKi, aiming at bringing the RAS pathway to its minimum activity. These approaches, although biologically valid, often come with unsustainable toxicity for normal tissues, which also rely on those pathways to some extent. This study by the Cichowski's Laboratory suggests that targeting a completely different dependency function in KRAS mutant cancer cells could offer a viable alternative and improve the therapeutic window of these therapies.

(II) On the same line, the same dual approach could be more effective in extending durability of response, forcing cancer cells to develop resistance to two completely different key functions instead of one.

(III) Since different NSCLCs seem to have different addiction to BCL-2 family proteins MCL1, BCL-xL or BCL-2 (25), it seems more convenient to target a common modulator of all of them at once, eIF4A, than inhibit them separately through BH3 mimetics. In this regard, the authors observed that the most potent cytotoxic effects were produced by the triple combination of eIF4A, BCL-xL/BCL-2, and KRAS G12Ci, underscoring the significance of these proteins (11). However, they objectively noted that this triple combination would probably be poorly tolerated in patients.

In conclusion, by showcasing the potential of combining eIF4A and RAS pathway inhibitors, this study provides a steppingstone towards rational and effective combination therapies. The work by Nardi and colleagues is a beautiful example of scientific rigor and critical insight in cancer key pathways, which, importantly, could instruct the choice of new clinically viable treatment protocols that could benefit patients in the near future, but, while this study offers promising insights, the full extent of its applicability to other MEK or KRAS inhibitors and oncological indications is an avenue that will have to be explored.

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Footnote

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