Editorial

MicroRNAs: a new tool in the complex biology of *KRAS* mutated non-small cell lung cancer?

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Despite several advances in the last decades in both medical and surgical management, with a 5-year overall survival (OS) not exceeding 15%, non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide (1). The past few years have seen an increased understanding in the molecular alterations of several cancers, helping clinicians to guide medical treatment and offer more accurate prognosis to patients. NSCLC was not left behind (2). Indeed, the recent discovery of oncogenic drivers such as activating mutations in the tyrosine kinase domain of the *Epidermal Growth Factor Receptor* (*EGFR*) has led to a dramatic increase in survival of patients harboring these mutations (3). Meanwhile, the prognostic and predictive values of *EGFR* mutations seem to be largely established in metastatic NSCLC (4), only a fleeting glimpse of clinical implications of many other mutations has been offered so far by the published literature, and might need further researches. One of the most promising molecular markers seems to rely in the mutations of the *V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) gene. *KRAS* encodes for RAS proteins which are small GTPases bounding between inactive guanosine diphosphate (GDP) and active guanosine triphosphate (GTP) forms. RAS proteins are central mediators downstream of growth factor receptor signaling and therefore are critical for cell proliferation, survival, and differentiation. Approximately 15% to 25% of NSCLC adenocarcinomas exhibit *KRAS* mutations (5). In the very large majority of the cases, these mutations are missense mutations introducing an amino-acid substitution at codon 12, 13 or 61 of the exon 2 of the gene (6). This confers a constitutive activation of *KRAS* signaling pathways, including the PI3K-AKT-mTOR pathway, involved in cell survival, and the RAS-RAF-MEK-ERK pathway, involved in cell proliferation. The complexity of *KRAS* mutations is reflected by the difficulty to develop effective therapies for patients with NSCLC harboring such mutations, and so far *KRAS* mutations are related to a poor prognosis in both locally and advanced NSCLC patients (7,8).

A promising area of research seems to be focused on microRNAs (miRNAs). miRNAs are small non-coding RNAs which act as post-translational regulator of genes. Functional studies have confirmed that miRNA dysregulation is causal in many cases of cancer. They are well-known key player in downstream oncogenic pathways, behaving as oncogenes or oncosuppressors in different types of cancer. Their central role in tumorogenesis and their stable and long-lasting presence in tissues and body fluids underlie the increased efforts and interest in defining their role as possible next-generation biomarkers and targets for novel therapeutic approaches (9).

The recently published paper of Langsch and co-workers offers a promising insight of the place of miRNAs in the molecular biology of *KRAS*-driven non-small cell lung cancer, and the possibility to use them as molecular

therapeutic targets (10). Indeed, NSCLC, just like many other cancers, rely in part on the balance between apoptotic and anti-apoptotic signals, with more particularly the over-expression of BCL2 and other members of its anti-apoptotic family. NF-κB, one of its family member, is able to up-regulate BCL2-mediated intrinsic and extrinsic anti-apoptotic action, favoring tumor progression and resistance to chemotherapies. Hence, Langsch and co-workers have shown that miR-29b, member of the miR-29 family, is over-expressed in NSCLC cell lines harboring *KRAS* G12V transversion, and is able to up-regulate NF-κB pathway, leading finally to resistance to extrinsic apoptosis. Interestingly, the silencing of miR-29b led to increased extrinsic apoptosis in *KRAS* G12V cells, making of anti-miR-29b a potential therapeutic target in tumors harboring such mutation. However, miR-29b, just like the very large majority of miRNAs, is known to be a double-sided mirror acting as both oncogene and tumor suppressor gene (11). Hence, in NSCLC cell lines, cisplatine-induced intrinsic apoptosis was favored by miR-29b. Consequently, it seems that according to micro-environmental stimuli, miR-29b can tip the balance towards apoptosis sensitization or resistance. It must be kept in mind that silencing of miR-29b is a double-edged blade which might lead to totally opposite results, with particularly the risk of increasing anti-apoptotic signals. However, because of these promising results, this area of study needs further researches.

Nevertheless, the work of Langsch and co-workers raises once again the notion of heterogeneity of *KRAS* mutations (10). Indeed, even though the worse prognostic value related to *KRAS* mutations in NSCLC seems to be clear (7,8), an increasing number of publications support the idea that *KRAS* mutations consist of a very heterogeneous group of "sub-mutations" according to the amino-acid substitutions, both molecularly and clinically. On a molecular plan, it seems that activated downstream signaling differs according to the amino-acid substitution. Hence, both *KRAS* G12C and G12V exhibited activated Ral signaling and decreased growth factor-dependent Akt activation, although the G12D mutation exhibited activated Pi3K and MEK signaling (12). More, it seems that among exon 2 mutations, codon 12 mutations exhibit higher up-regulation of vascular endothelial growth factor (VEGF) (13) and more robust links with GTP associated to higher resistance to GTPase activity (14), leading to a more persistent activation of RAS downstream signaling. Otherwise, clinical evidences suggest different clinical behaviors according to *KRAS* amino-acid substitution, not only on NSCLC but also in lung metastases of colorectal cancer. Indeed, in colorectal cancer, it seems that codon 13 mutation is associated with better prognosis following lung metastasectomy (15), with different prognosis according to the amino-acid substitution (16). In NSCLC, little evidence suggests that the type amino-acid substitution might impact survival following surgery (17,18). More particularly, in the largest published cohort on the impact of KRAS amino-acid substitution on survival after NSCLC surgery, our team has showed that G12V mutation was associated with worse overall survival and time to recurrence (19). Otherwise, it seems that amino-acid substitution may impact the first site of recurrence following NSCLC surgery. Indeed, our team has published, for example, that *KRAS* G12V mutations developed significantly more pleuro-pericardial metastasis than other mutations (20). This might be explained by different chemo-attractions depending on the type of chemo-attractant produced by the site of metastasis, and over-expression of membrane receptor on the neoplastic cell depending on the amino-acid substitution, and the subsequent downstream signaling activated. Furthermore, it seems that response to radiotherapy (21) and chemotherapy depends also on amino-acid substitution. More particularly, Garassino and colleagues demonstrated the association of *KRAS* G12C with a reduced response to cisplatin and increased sensitivity to taxol and pemetrexed in NSCLC cell lines, whereas the G12V mutations was more resistant to pemetrexed (22). This different response to chemotherapy could be partially explained by different activations of downstream signaling according to the amino-acid substitution, and subsequent miRNAs up-regulation. Indeed, Langsch and co-workers have shown an increased expression of miR-29b in *KRAS* G12V NSLC cell lines only, leading to increase sensitivity to cisplatin (10). One can thereby speculate that in case of other amino-acid substitutions, other miRNAs are up-regulated leading to different chemo-sensitivity.

In conclusion, the increasing knowledge in the molecular biology of NSCLC may probably in the near future improve the management of both surgical and metastatic patients. So far, only a fleeting glimpse of what molecular alterations of cancer can offer in our daily practice has been explored. Particularly, *KRAS* and its different amino-acid substitutions seem to offer a large field of researches. The activation of different downstream signaling according to the amino-acid substitution seems to lead to different clinical behaviors, and might help clinicians in the future to

adapt medical and surgical strategies, as well as follow up. However, published clinical evidences are mainly based on single center retrospective small cohort studies, with a low level and evidence. Consequently, prospective multicenter studies are mandatory to confirm these preliminary observations. Nonetheless, other molecular alterations such as *cMET* mutations or *ALK* translocation should not be forgotten, and need further investigations too. The place of miRNAs seems to be very complex and still needs to be elucidated. Indeed, they seem to be promising therapeutic targets and molecular markers. However, one must keep in mind that they interfere as the same time with several pathways, acting as crosstalk between them. Consequently, acting on miRNAs could lead to the opposite effects than those expected. Nevertheless, molecular biology offers new hope to our patients and deserves further experimental and clinical studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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