Editorial

A novel miR-205-mediated ERRFI1/EGFR regulatory pathway in MET-addicted cancer cells: emerging biomarkers for secondary resistance

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In the last two decades, many efforts have been made towards the development of innovative and targeted therapeutic approaches for cancer treatment. Nonetheless, in contrast to the several hallmarks achieved in recent years, drug resistance to cancer therapies has arisen as the real challenge.

Dysfunction of several receptor tyrosine kinase (RTK)-mediated signaling cascades such as those triggered by tyrosine-protein kinase Met (MET) or epithelial growth factor receptor (EGFR), have been broadly investigated to understand the diverse molecular mechanisms underlying cancer development and progression. Monotherapy as a blockade strategy for these pathways has been broadly used as first-line treatment over the past years. However, different mechanisms have been adapted by tumor cells to skip treatment effects, such as the upregulation of counterpart RTKs to bypass the activation of downstream cascades.

MET, also called hepatocyte growth factor receptor (HGFR), is an RTK normally expressed on epithelial cells that binds to a ligand with mesenchymal origin. MET activation is required for different biological processes, such as organogenesis or embryonic development. Nevertheless, malfunction of this receptor through gene amplification, protein overexpression or different autocrine/paracrine ligand-interactions can lead to cancer development (1).

Several approaches have been based on the use of selective or non-selective RTK inhibitors (TKI) as a first-line therapy for MET-addicted cancer. However, MET has developed different strategies to overcome this therapeutic effect, one of them being the activation of alternative signaling pathways such as the EGFR transduction cascade (2).

Co-activation of RTKs and non-RTKs is a common trait in treatment-naïve EGFR-mutation-positive NSCLC patients (3). Hence, the potential combination of different treatments with interdependent antitumor activity as an alternative to monotherapy seems to be the trend to follow in cancer therapy towards an overall patient survival-rate improvement. Currently, many efforts focus on the combination of immunotherapy with TKI therapies in different types of cancer, such as NSCLC (4).

Not only different TKIs can be synergistically activated during cancer progression, but also as a resistance evasion response upon first-line treatment. The relationship between EGFR and MET has been reported in previous work, where MET amplification and signaling pathway was activated in EGFR-mutated NSCLC cases which developed resistance to approved EGFR TKIs (5). The amplification of EGFR upon MET blockade has been equally reported (2), which suggests the existence of a mechanism mediating molecular communication between both receptors, the one remaining triggered when the other sustains

pharmacological blockade.

In past few years, it has been discovered that microRNAs (miRNAs) play a significant role in cancer, by controlling cell proliferation and apoptosis via regulating expression of different oncogenes. Reprogramming of signaling circuits by miRNAs to avoid pharmacological inhibition of driver oncogenes has been a breakthrough for the study of targeted therapies (6).

In that context, this editorial provides a summarizing view of miR-205-mediated regulatory role of ERBB receptor feedback inhibitor-1 (ERRFI1), triggering the EGFR cascade in a MET blockade-resistant environment (7).

ERRFI1, also known as MIG6, is a cytoplasmic protein that is upregulated during cell growth, and acts as a suppressor of EGFR activity by binding the kinase domains of the stated receptor (8).

The loss of function of ERRFI1 leads to EGFR activation by ligand-induced receptor dimerization and triggering of the subsequent signaling pathways, prompting cell proliferation, migration, and adhesion, along with angiogenesis, leading to tumor development (9).

Consequently, a thorough analysis of the miRNA-mediated mechanism through which ERRFI1 inactivation contributes to the invasive behavior of diverse types of cancer is of paramount importance to understand the intricate regulatory circuits that sustain the resistance to MET-TKIs.

Shedding light on this field, Migliore *et al.* utilized a cellular model to identify miR-205 as a novel mediator of resistance to MET-TKIs via the miR-205/ERRFI1 axis (6).

miR-205 is located in a lung cancer-associated genomic amplification region at 1q32.2 (10,11), and participates in tumorigenesis of lung cancer (12,13). Among multiple tumor-specific miRNAs, miR-205 is one of the most frequently studied (10,14). Overexpression of miR-205 promoted NSCLC cell invasion and metastasis through regulating an epithelial phenotype with increased E-cadherin and reduced fibronectin (15). miR-205 was further developed to identify squamous cell carcinoma (SCC) and adenocarcinoma (ADC) subtypes of NSCLC (16). miR-205 directly repressed PTEN expression and was upregulated in multiple subtypes of NSCLC (17). These and other studies indicated that miR-205 might serve as a potential biomarker for detection of NSCLC, which was confirmed by a recent meta-analysis (14).

It was further shown that epigenetic induction of miR-205 and subsequent inhibition of ERRFI1 was sufficient to cause EGFR activation, yet sustaining resistance to MET-TKIs. Notably, a patient resistant to dual MET/EGFR blockade was found with low expression of ERRFI1, reversely correlated with miR-205 level. This proof of concept adds to the evidence for miR-205 being a potent regulator of signaling cascades in cancer cells, and broadens the perspective of introducing miRNA-based assays into daily practice. Likewise, unveiling the factors that could influence the de-methylation of *miR-205* genomic locus would be of great interest. ERRFI1 was also found an important determinant of cellular response to AKT inhibitors and chemotherapeutics (18). In the light of the aforementioned findings, it could be of significant value to evaluate the role of miR-205 in AKT/EGFR crosstalk in lung cancer cells.

Detailed understanding of the signaling circuitries underpinning resistance must be viewed as an integral component of the clinical development of MET-TKIs. Multiple mechanisms governing MET resistance have already been described. However, little was known about miRNAs reprogramming the MET-addicted tumors. Cell line and *in vivo* studies are still considered a golden standard for evaluation of targeted first-, second-, and third-line combinatory therapies, although the vast majority still focuses on TK-downstream signaling disturbances leading to TKI-resistance (3,19). Notably, other mechanisms appear to be involved in shaping the adaptation of cancer cells to external hindrances. In light of modern technologies, like NGS, it is of utmost interest to broaden our view on cellular regulatory mechanisms to non-coding RNAs, the phenomena of RNA editing, and small RNAs encapsulated in extracellular vesicles (EVs), e.g., exosomes.

The aforementioned questions lead to further concerns about the future implications of these findings. In clinical practice, blood-based liquid biopsies are considered an emanating tool to provide an accurate and comprehensive spatiotemporal snapshot of the tumor and its microenvironment. Plasma-derived EVs were found to be enriched in miRNAs and are therefore considered as useful biomarkers for disease monitoring. miRNA profiling of plasma fractions revealed that miR-205 levels increased in tumor-specific exosomes of patients with SCC, but its levels decreased strikingly after surgery (20). Moreover, levels of miR-205 in plasma of NSCLC patients were also proven to change significantly throughout the treatment (21), thus giving another proof of transmissibility of results between solid tumor and liquid biopsies (14). An ideal strategy to predict and monitor the response to MET-TKIs would be combining EGFR and MET status analysis along with miR-205 expression level in a single-draw liquid biopsy. To

avoid the limitation of analyzing both circulating tumor DNA (ctDNA) and exosomal miRNAs (exo-miRNAs), novel technological strategies have already been addressed (22), and should be prospectively introduced into clinical practice.

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Footnote

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