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RNA-modifying enzymes as novel targets for anti-cancer therapies

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EDITORIAL ARTICLE

RNA-MODIFYING ENZYMES AS NOVEL TARGETS FOR ANTI-CANCER THERAPIES

Cancer is a group of diseases whereby a group of cells escape biological mechanisms that control homeostasis and proliferate uncontrollably. Cancer cells have the ability to invade surrounding tissues and to spread through the vasculature to distant organs, a property that distinguishes them from benign tumor cells, the latter being incapable of invasion.¹ The transformation of normal cells to cancer cells requires the presence of genetic mutations. These mutations often occur in DNA sequences that encode genes important for tumor progression (oncogenes) or genes that repress tumorigenic potential (tumor suppressor genes). Thus, a combination of mutations that results in gain of function of oncogenes and loss of function of tumor suppressor genes confers growth advantage to cancer cells over normal cells. Genetic mutations in cancer can be found in the form of gene amplifications or deletions, gene rearrangements or point mutations.² For example, gene amplification lead to high copy number and increased expression levels of oncogenes. On the other hand, gene deletions of tumor suppressor genes prevent their expression and shut down their protective mechanisms against tumor onset. Different types of gene rearrangement result in the formation of gene fusions, consisted of fragments of two different genes. This gives rise to chimeric genes in which one fragment possess the pro-tumorigenic function and the second fragment contributes to the constitutive expression of the first, leading to high expression and activity of an oncogene. Point mutations refer to single nucleotide mutation in DNA, that results in a substitution of an amino acid in the protein generated by this gene. This single amino acid change can confer a gain of function in an oncogene or a loss of function in a tumor suppressor gene.

Apart from genetic mutations, another major factor that contributes to tumorigenesis is the epigenetic landscape in a given cell. In that case, epigenetics refers to changes of gene function that are not associated to alterations in DNA sequences. Epigenetic modifications occur in the form of DNA methylation, as well as methylation or acetylation of histones, the proteins that bind tightly DNA, forming the chromatin. Epigenetic modifications affect chromatin conformation and are capable of creating open and closed chromatin. Open chromatin means that the genomic region is accessible to factors (proteins) that regulate the expression of a gene. In contrast, closed chromatin is compact and not accessible to these factors. For example, in cancer, open chromatin is frequently observed nearby oncogenes, leading to their increased expression levels. On the contrary, many tumor suppressor genes are epigenetically silenced, due to their compact chromatin.³

Another layer of gene expression regulation takes place at the RNA level. RNA molecules are transcribed from DNA and are usually modified at specific bases. These, so called, epitranscriptomic modifications include methylation, pseudouridination, inosine-to-adenine editing and more. The most abundant RNA modification is the N⁶-methyladenosine (m⁶A), as it is estimated that around 25% of RNAs bear the m⁶A marker, genome-wide. The m⁶A regulators are the "writers", enzymes that catalyze m⁶A deposition to RNA, the "erasers", enzymes that remove the modification and the "readers", proteins which recognize and "interpret" the modification.⁴ M⁶A has been detected in several types of RNAs. The molecular

functions of m⁶A RNA methylation has been mainly explored in the case of messenger RNAs (mRNAs), whereby it has been demonstrated that it affects several properties of mRNAs, such as splicing, stability/degradation, nuclear export and translation to proteins.⁵ Thus, by modulating biochemical properties of mRNAs, m⁶A deposition influences gene expression and therefore it is crucial for many physiological processes. In addition, recent studies provide evidence for critical roles of m⁶A in tumorigenesis, by modulating cell proliferation, invasion, metastasis or immune evasion.⁶

During the last years, many studies have unraveled novel roles for m⁶A regulators in cancer progression. The most important m⁶A regulators are the methyltransferases METTL3 and METTL14, which transfer a methyl group to target RNAs, the erasers FTO and ALKBH5, which remove the methyl group from methylated RNAs and numerous proteins (such as YTHDC2, YTHDF1, YTHDF2) that recognize and bind m⁶A-modified RNAs. Interestingly, the expression of the genes encoding these proteins is frequently altered in cancer.⁷ For example, METTL3 is highly expressed in acute myeloid leukaemia (AML), breast and prostate cancers. In these cancers, METTL3 exerts pro-oncogenic functions. In glioblastoma and hepatocellular carcinoma (HCC) both pro- and anti-tumorigenic properties have been attributed to METTL3. On the other hand, in endometrial cancer and in renal cell carcinoma METTL3 is mainly anti-tumorigenic. Similarly, the erasers FTO and ALKBH5 have been found to be over-expressed in some or under-expressed in other types of cancer.⁸ Thus, m⁶A regulators can have dual function, as they can act as oncogenes or tumor suppressors depending on the cancer type. However, these proteins can undoubtedly impact cancer progression and, therefore, can be attractive druggable targets in cancer therapy.

Indeed, the last years small molecule chemical inhibitors have been designed to target mainly FTO. For instance, R-2-hydroxyglutarate (R-2HG) halts proliferation and induces cell death, by inhibiting the function of FTO in AML and glioma cell lines, *in vitro*. In addition, the ethyl ester form of meclofenamic acid (MA2) represses tumor progression in glioblastoma cells and extends survival in xenografted mice. More recently, the use of the novel FTO inhibitors FB23 and FB23-2 in *in vivo* studies for AML treatment show encouraging results, in terms of blocking AML progression in xenotransplanted mice.⁹ Although several FTO inhibitors have been designed and tested for their anti-cancer properties, similar progress has not been achieved concerning the development of inhibitors targeting METTL proteins. In fact, the first pioneer study describing a novel selective inhibitor of METTL3 has been published the current year. According to the results of Yankova et al., treating AML with STM2457, a catalytic inhibitor of METTL3, diminishes tumor growth and induces cell death *in vitro* and prolongs survival of mice *in vivo*.¹⁰

In conclusion, current drug-based anti-cancer therapies include chemotherapy and, more recently, immunotherapy, which are the standard approaches for treating advanced malignancies. Although the use of chemotherapy has greatly improved the survival rates of cancer patients, a significant amount of patients develop resistance to the current treatment regimens. In addition, a large proportion of patients do not benefit from current chemotherapeutic drugs used for treatment. Moreover, a specific drug may exhibit a favorable outcome for only one or a limited number of cancer types. Thus, the identification of novel molecular targets for cancer treatment is absolutely urgent. To this end, the groundbreaking advances in the field of RNA biology, during the last decade have highlighted the crucial role of RNA-modifying enzymes in

cancer, which can now be pharmacologically targeted with encouraging results for some cancer types, such as AML. It remains a challenge to elucidate the efficacy of targeting RNA-modifying enzymes, in a large panel of cancer types, including solid cancers with limited success of treatment, such as pancreatic and liver cancers. Nevertheless, RNA-modifying enzyme inhibitors will be on their way to clinical trials in the near future and the scientific community awaits with great interest the outcome of these trials.

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