Sapienza University of Rome, SAPIENZA, UNIROMA1, IT

Alessandro Fatica

“Investigating the role of m^{6}A RNA modification in chronic and acute myeloid leukemia”

Defects in cell differentiation and uncontrolled proliferation are a hallmark of several cancers. Chronic Myeloid Leukaemia (CML) and Acute Myeloid Leukaemia (AML) represent a remarkable example of malignancy with these features. They are characterized by an accumulation of immature leukemic cells in the bone marrow and blood that arises from a failure of myeloid progenitors to mature and respond to normal regulators of proliferation. Over the past decades, epigenetic modifications have been shown to play a significant role in this process and are now recognized as targets of therapy for different types of leukaemia. More recently, researchers have identified a new layer of gene expression regulation at the RNA levels that consists of reversible chemical modification of messenger RNAs (mRNAs), which led to the birth of the emerging field of “epitranscriptomics”. Among more than 100 chemical modifications that can occur within various type of RNA molecules, N^6-methyladenosine (m^{6}A) is the most abundant internal chemical modification of mRNA in eukaryotes. The m^{6}A modification is installed by "writers" and removed by "erasers", in addition, it can recruit specific "reader” proteins. m^{6}A modification and the associated regulatory proteins play a critical role in gene expression by affecting different steps of the mRNA life, including splicing, nuclear export, stability and translation (1).

In mammals, the major writer of m^{6}A is a nuclear multicomponent complex composed of two *methyltransferase-like proteins*, METTL3 and METTL14, which specifically methylate the adenosine within the DRACH motif (where D =A/G/U, R=A/G; H=A/C/U). More recently, the *U6 snRNA m6A methyltransferase-like protein 16* (METTL16) has been also shown to target mRNAs. METTL16 binding sites do not overlap with that one of the METTL3/METTL14 methylation complex, indicating independent functions in m^{6}A modification. Notably, METTL3, METTL14 and METTL16 were found overexpressed in AML cells are critical for their survival (2). The overall remit of the project is to provide a comprehensive understanding of the role of m^{6}A in AML and CML cells and to identify novel targets for drug development.

In particular, we want to: I) investigate the precise role of m^{6}A modification in leukemia by knocking down writers, erasers and readers and by identifying targets RNAs; II) purify the METTL complexes in order to identify, if any, specific regulatory proteins; and III) develop lead compounds for interfering with the m^{6}A activity.

References:

1. Zhao BS, Roundtree IA and He C. Post-transcriptional gene regulation by mRNA modifications. Nat. Rev. Mol. Cell. Biol. 2017; 1: 31-42.
2. Ianniello Z, Fatica A. N^6-Methyladenosine Role in Acute Myeloid Leukaemia. Int J Mol Sci. 2018; 19: pii: E2345.