

The role of m6A mRNA modification during EndMT

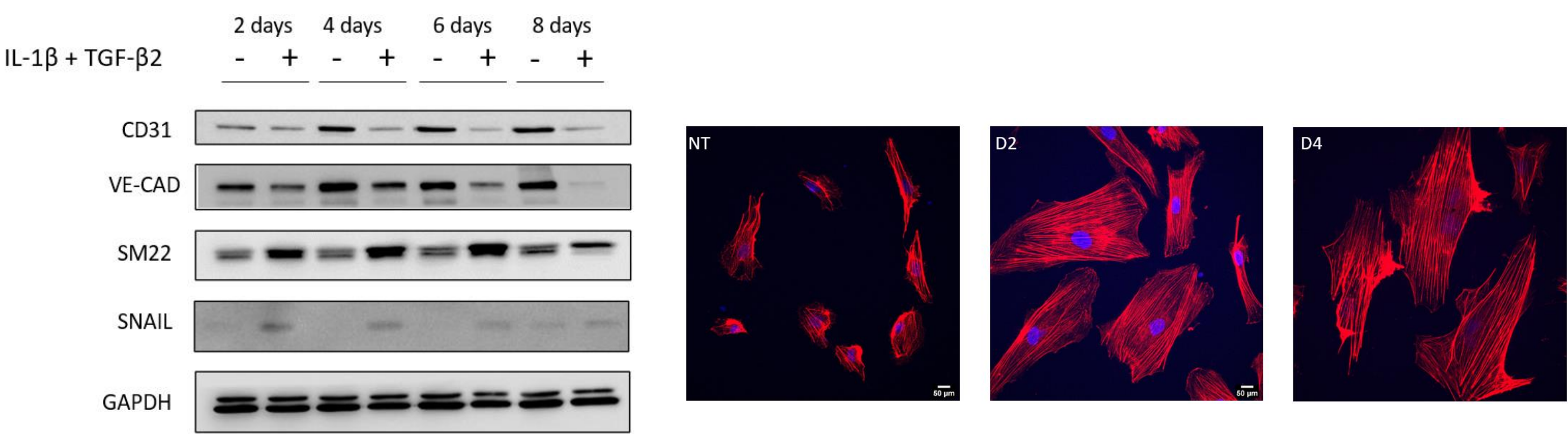
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INTRODUCTION

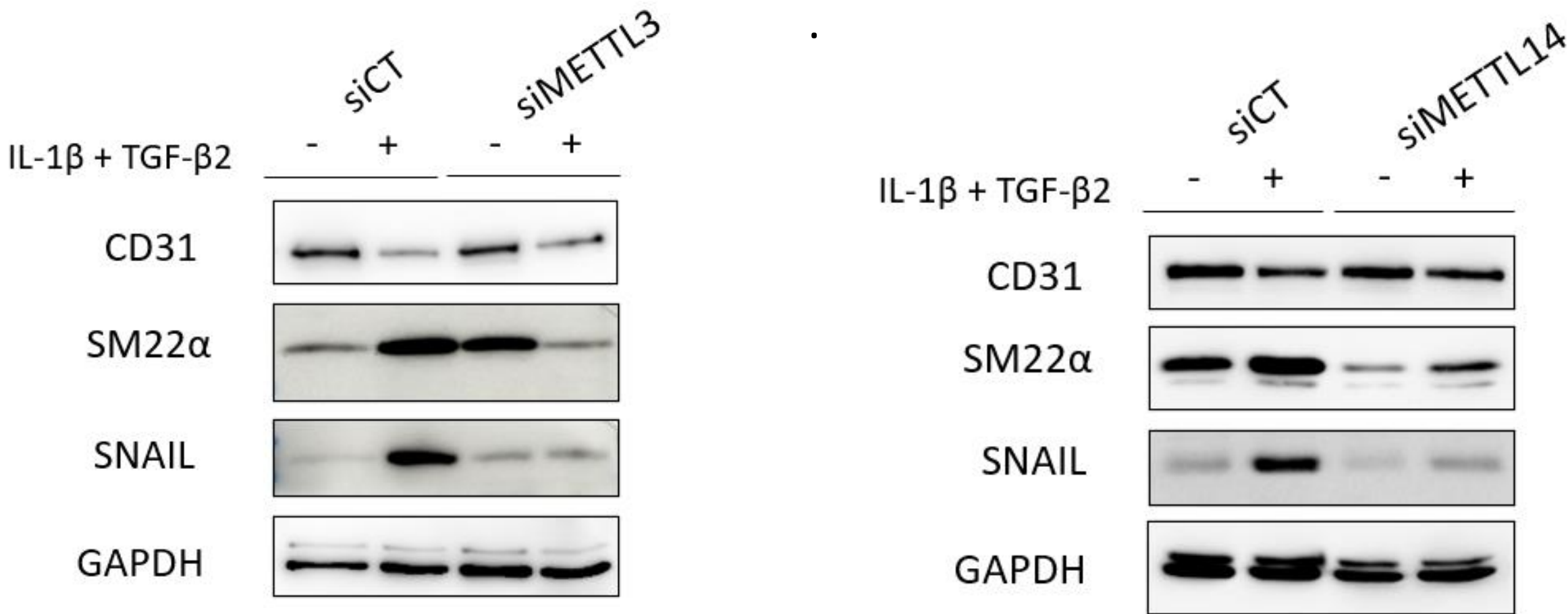
In response to environmental and mechanical stimuli, fully differentiated endothelial cells (ECs) can dedifferentiate into mesenchymal cells. This process is termed endothelial-to-mesenchymal transition (EndMT). The tumor microenvironment is characterized by a pro-inflammatory context, hemodynamic abnormalities and hypoxia, all of which are known to promote EndMT. Recently, several studies have suggested that EndMT might be controlled by epigenetic mechanisms. N6-methyladenosine (m6A) is the most common mRNA internal modification and has been one of the main focuses in the field of epitranscriptomics over recent years. The EndMT m6A epitranscriptome has not been investigated yet. Our objectives are: 1) investigate the role of the m6A epitranscriptomic machinery in EndMT and 2) Identify transcripts whose m6A content is specifically affected during EndMT and 3) test the hypothesis that SNAI1 might be involved in defining the EndMT-associated m6A epitranscriptome

RESULTS

1. Unravelling the role of m6A during EndMT

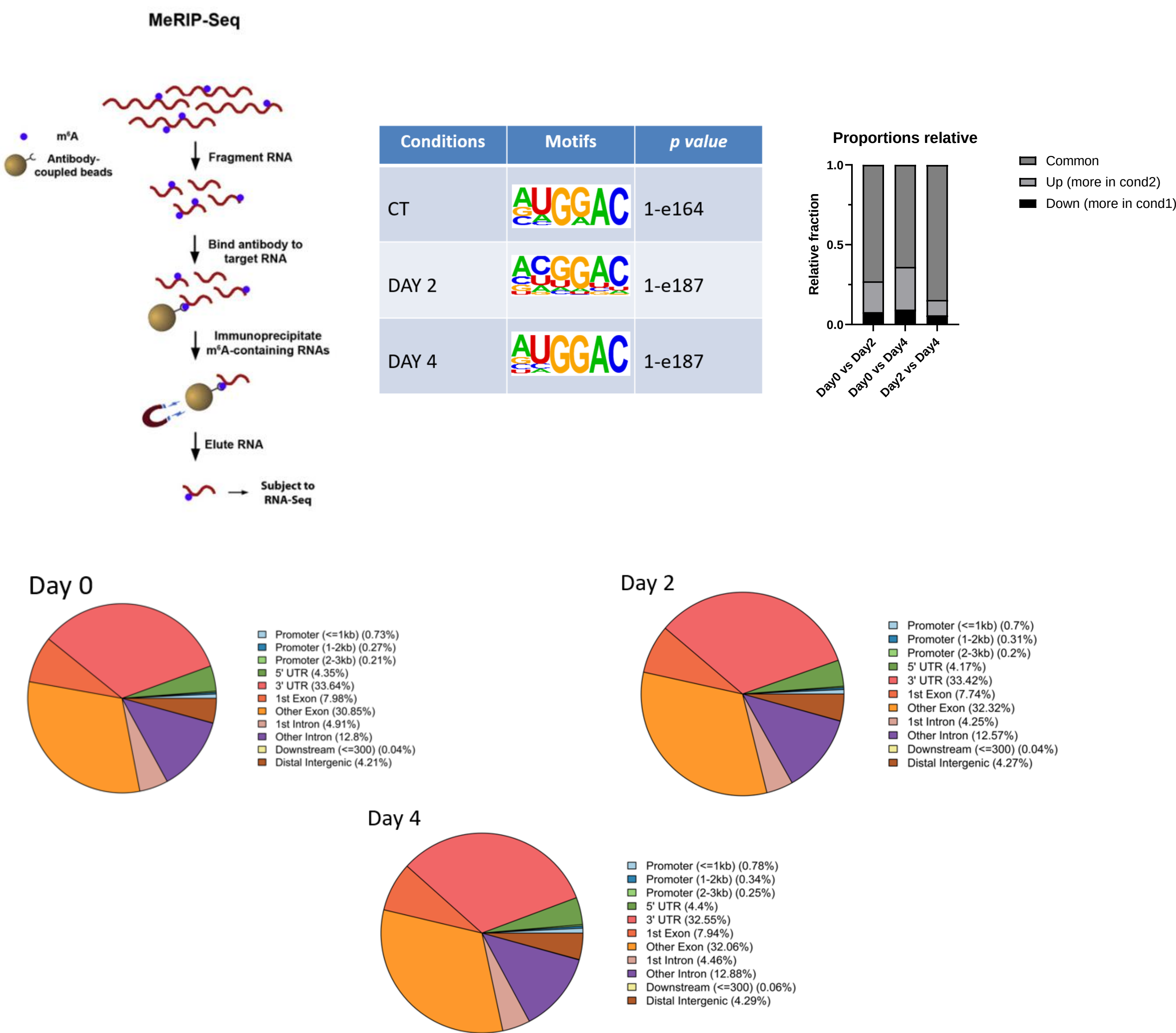


After the treatment of HUVECs cells with EndMT-promoting stimuli TGF-β2 and IL-1β, we verified the dedifferentiation of ECs by examining the progressive increase of the expression of mesenchymal genes (SM22 and SNAI1) and a progressive decrease of the expression of endothelial genes (CD31 and VECAD).

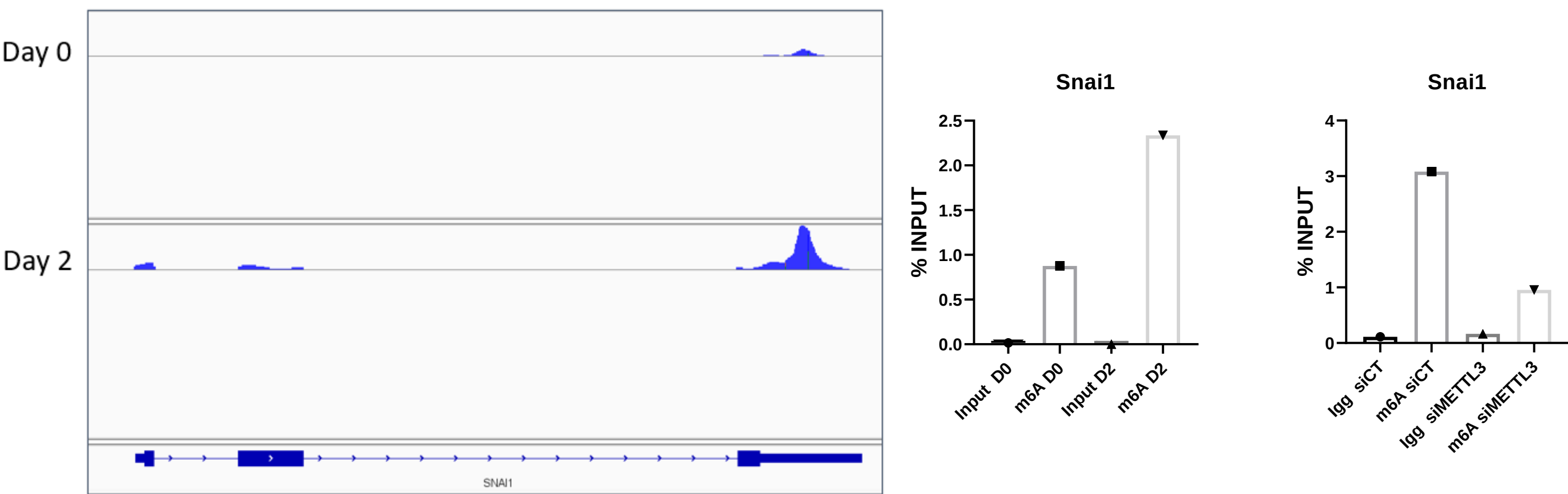


We established that the absence of METTL3 and METTL14 slow down the EndMT induced by IL-1β and TGF-β2, demonstrating the role of the m6A machinery in the promotion of the EndMT

2. Defining the EndMT-dependent m6A epitranscriptome

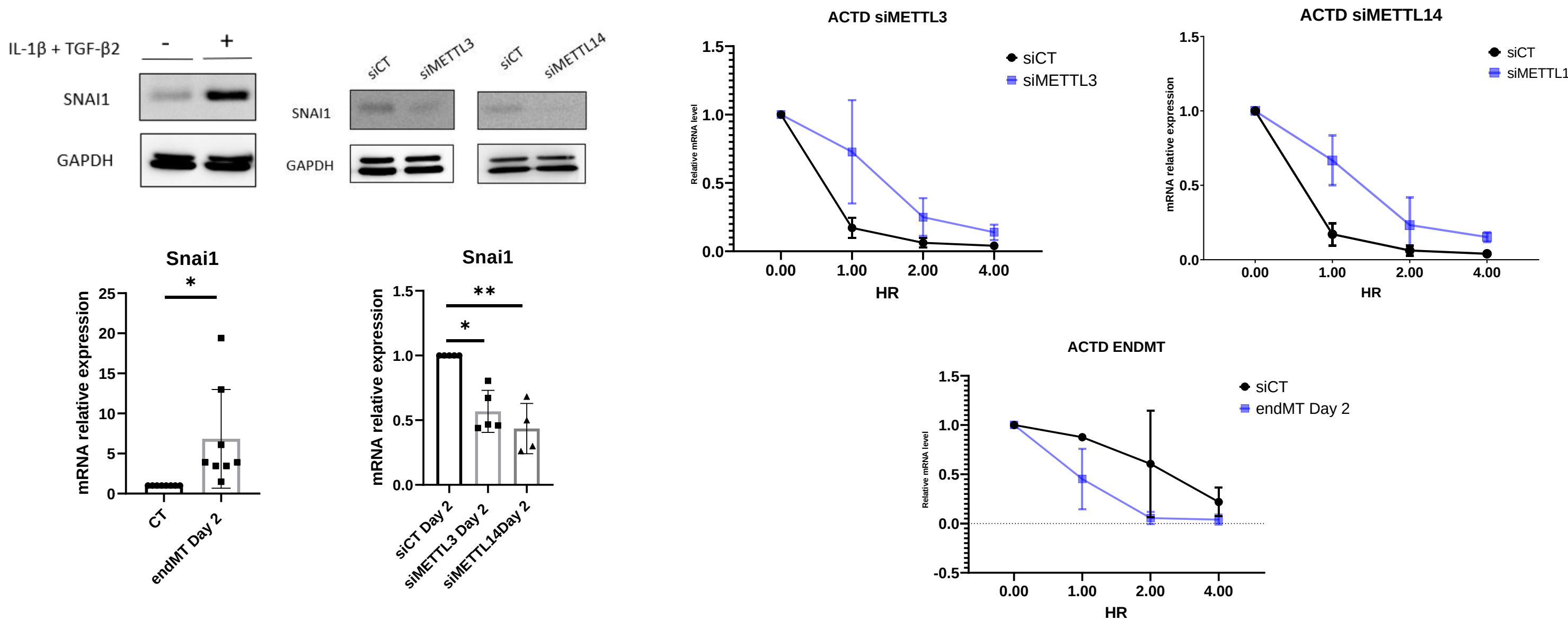


3. m6A deposition on the 3'UTR of SNAI1 changes during the EndMT



We focused on m6A deposition on the 3'UTR of SNAI1, a TF involved in the early steps of EndMT.

4. Differential methylation of SNAI1 affects expression and stability of the transcript



Conclusion

Our results provide a mechanism of regulation of cancer progression by modulation of EndMT through RNA m6A modification.

We demonstrated that differential methylation during EndMT affects expression and stability of the transcript of SNAI1