lncRNA-based approach to counteract EMT

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In the recent years, we showed (i) that the EMT master gene Snail conveys Polycomb repressive complex 2 (PRC2) on specific epithelial gene chromatin sites (Snail-target epithelial gene promoters) through the enrolment of the lncRNA HOTAIR, thus promoting EMT features in solid tumor cells (Battistelli et al[1]); (ii) that a higher-order chromatin structure allowing the interaction between HOTAIR promoter and distal enhancer, promotes HOTAIR transcription and that the liver-specific transcription factor HNF4α modifies HOTAIR chromatin topology ((Battistelli et al[2]); (iii) the possibility to translate these findings into an RNA-based therapeutic perspective since we proved that the expression of the HOTAIR module containing the sole Snail-binding domain (HOTAIR-sbid) without the PRC2-interaction domain, acts as dominant negative against endogenous HOTAIR thus preventing EMT in HCC cells ((Battistelli et al[3]). In both murine and human tumor cells, HOTAIR-sbid impaired the ability of HOTAIR to bind Snail and, in turn, trigger H3K27me3/EZH2-mediated repression of Snail epithelial target genes. Notably, HOTAIR-sbid expression was proven to reduce cellular motility, invasiveness, anchorage-independent growth, and responsiveness to TGFβ-induced EMT.
These data provide evidence on a lncRNA-based strategy to effectively impair the function of a master EMT transcriptional factor.
This study defines an innovative RNA-based strategy to interfere with a pivotal function of the tumor related lncRNA HOTAIR, comprising a dominant negative mutant that was computationally designed and that impairs epithelial-to-mesenchymal transition.

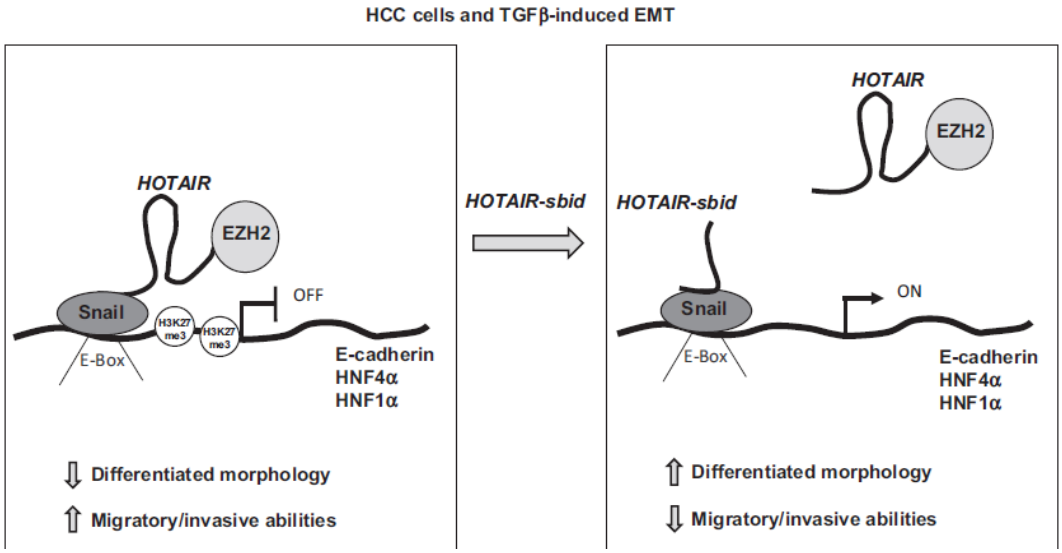

Figure 1: Schematic representation of HOTAIR-sbid activity in cancer cells and in TGFβ-induced EMT.

References

1. Battistelli et al., Oncogene 2017 doi: 10.1038/onc.2016.260

2. Battistelli et al., Cell Death and Diff 2019 doi: 10.1038/s41418-018-0170-z
3. Battistelli et al., Cancer Research 2021 doi: 10.1158/0008-5472.CAN-20-1764