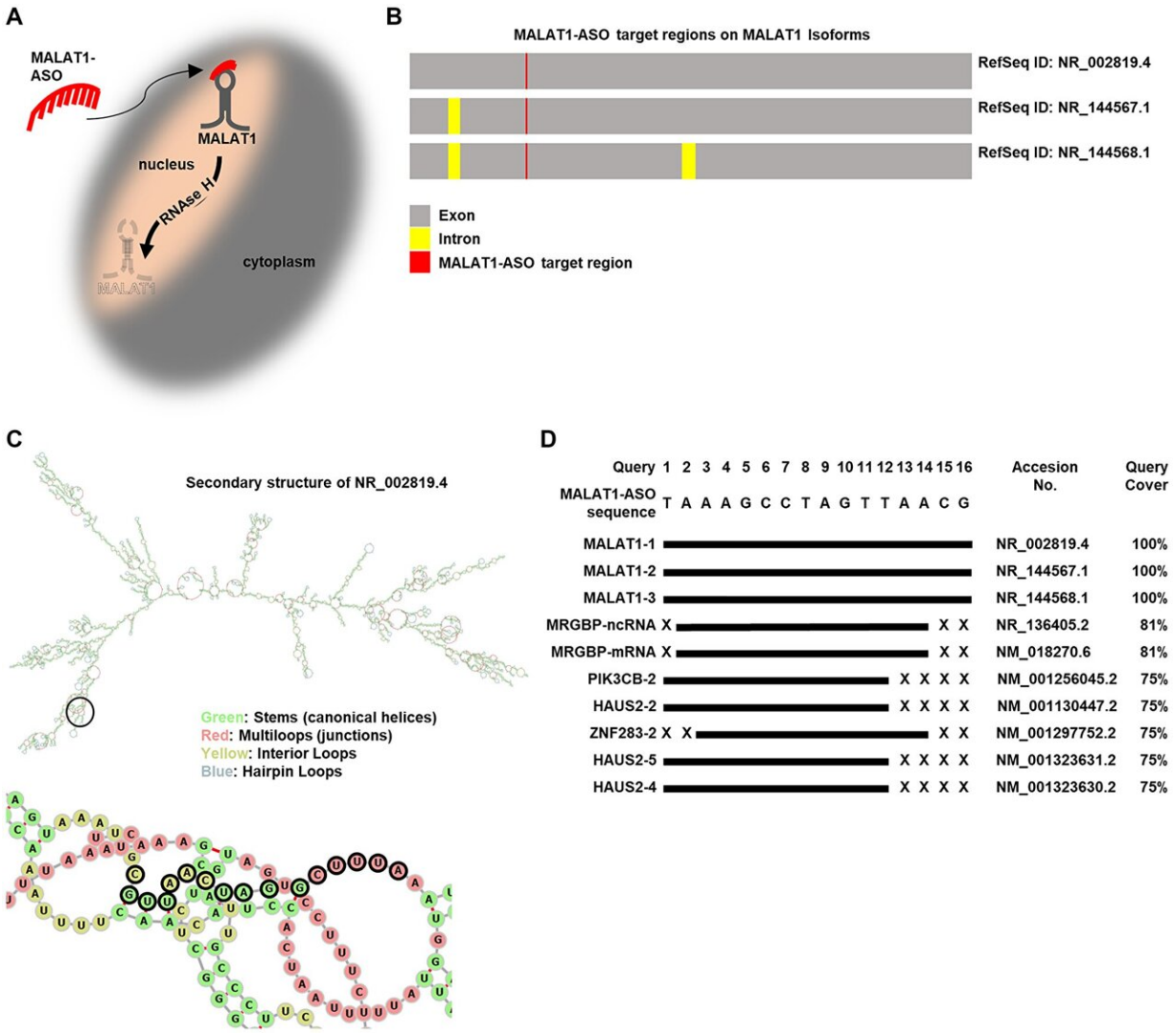
Deconstructing the role of MALAT1 in MAPK-signaling in melanoma

May 30 2023



MALAT1-ASO specifically targets MALAT1-lncRNAs. (**A**) Schematic illustration of the MALAT1-ASO bypassing the cell-membrane and entering the nucleus of melanoma cells to inhibit MALAT1 through target-binding and

RNAse H mediated degradation. (**B**) Schematic illustration of the three MALAT1 isoforms that are targeted by MALAT1-ASO, highlighting intron, exon and MALAT1-ASO target-binding regions. (**C**) Top: Secondary RNA-structure (MFE) of NR_002819.4 and the target binding region of the MALAT1-ASO (black circle). Below: Selected cutout and zoom of the secondary structure of the target region, showing that the MALAT1-ASO target site is an accessible structure for RNA-ASO binding. The nucleotides that are targeted by the MALAT1-ASO sequence are highlighted with black outline. Contrary to the complete structure (top), the selected cutout (bottom) does not include hairpin loops. (**D**) The top10 hits of matching targets to the MALAT1-ASO sequence in the human transcriptome show high specificity of MALAT1-ASO to MALAT1 isoforms. Other targets have at least three mismatches, indicating a low “off-target” binding probability of the MALAT1-ASO. Targets are ranked by the expect value (E-value). The graphical illustration of the target sequences corresponds to their mRNA sequences.
Credit: *Oncotarget* (2023). DOI: 10.18632/oncotarget.28447

A new research paper was published in *Oncotarget*, titled "Deconstructing the role of MALAT1 in MAPK-signaling in melanoma: insights from antisense oligonucleotide treatment."

The long non-coding RNA (lncRNA) MALAT1 is a regulator of oncogenesis and cancer progression. MAPK-pathway upregulation is the main event in the development and progression of human cancer, including melanoma and recent studies have shown that MALAT1 has a significant impact on the regulation of gene and protein expression in the MAPK pathway. However, the role of MALAT1 in regulation of gene and protein expression of the MAPK-pathway kinases RAS, RAF, MEK, and ERK in melanoma is largely unknown.

In this study, researchers Valentin Feichtenschlager, Yixuan James Zheng, Wilson Ho, Linan Chen, Ciara Callanan, Christopher Chen,

Albert Lee, Jose Ortiz, Klemens Rappersberger, and Susana Ortiz-Urda from the University of California San Francisco and Medical University Vienna demonstrated the impacts of antisense oligonucleotide (ASO)-based MALAT1-inhibition on MAPK-pathway gene regulation in melanoma.

"Our results showed that MALAT1-ASO treatment decreased BRAF RNA expression and protein levels, and MALAT1 had increased correlation with MAPK-pathway associated genes in melanoma patient samples compared to healthy skin," write the researchers.

Additionally, drug-induced MAPK inhibition upregulated MALAT1-expression, a finding that resonates with a paradigm of MALAT1-expression presented in this work: MALAT1 is downregulated in melanoma and other cancer types in which MALAT1 seems to be associated with MAPK-signaling, while MALAT1-ASO treatment strongly reduced the growth of melanoma cell lines, even in cases of resistance to MEK inhibition. MALAT1-ASO treatment significantly inhibited colony formation in vitro and reduced tumor growth in an NRAS-mutant melanoma xenograft mouse model in vivo, while showing no aberrant toxic side effects.

"Our findings demonstrate new insights into MALAT1-mediated MAPK-pathway gene regulation and a paradigm of MALAT1 expression in MAPK-signaling-dependent cancer types. MALAT1 maintains essential oncogenic functions, despite being downregulated," conclude the authors.

More information: Valentin Feichtenschlager et al, Deconstructing the role of MALAT1 in MAPK-signaling in melanoma: insights from antisense oligonucleotide treatment, *Oncotarget* (2023). DOI: 10.18632/oncotarget.28447