The nuclear hypoxia-regulated NLUCAT1 long non-coding RNA variant is endowed of protumoral activity in lung adenocarcinoma

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Lung cancer is the leading cause of cancer death worldwide, with poor prognosis and a high rate of recurrence despite early surgical removal. It is therefore essential to identify new prognostic markers and new therapeutic targets. We are interested in gene regulation related to hypoxia, a factor associated with relapse of lung adenocarcinomas (LUAD). While long non-coding RNAs (lncRNA) are increasingly recognized as major gene expression regulators through various molecular mechanisms, their roles in cancer development and hypoxic response are still largely unexplored. Combining profiling studies on early stages LUAD biopsies and on A549 LUAD cell line cultured in normoxic or hypoxic conditions, we identified a subset of 8 lncRNAs that are both correlated to the hypoxic status of tumors and regulated by hypoxia in vitro. We focused on a new nuclear transcript, named NLUCAT1 that is strongly up-regulated by hypoxia in vitro and correlated to hypoxic markers and bad prognosis in LUAD samples. Full molecular characterization of NLUCAT1 including RNAscope® RNA FISH showed that it is a large 9807 nt nuclear transcript variant of LUCAT1 composed of 6 exons and mainly regulated by NFκB and NRF2 (NFE2L2) transcription factors. Targeted deletion of NLUCAT1 using a CRISPR/CAS9 strategy in the A549 LUAD cell line, revealed a decrease in proliferative and invasive properties, an increase in oxidative stress and a higher sensitivity to cisplatin-induced apoptosis. Interestingly, the analysis of NLUCAT1-deficient cells transcriptome revealed repressed gene networks controled by NRF2, HIF and NFκB transcription factors, suggesting that this transcript could exert a positive feedback on these pathways. We identified 4 genes of the NRF2-regulated gene network that were downregulated in NLUCAT1 knockout cells and we demonstrated that their concomitant RNA interference significantly increased the ROS-dependent caspase activation of LUAD cells, thus partially mimicking the consequences of NLUCAT1 inactivation. Overall, our data demonstrate that NLUCAT1 is a regulatory nuclear lncRNA which exerts pro-tumoral activity and may represent a new potential therapeutic target in LUAD.