ABSTRACT:

Cancer, despite significant advances in diagnosis and treatment, is the second most common cause of death in economically advanced countries. The main reason for the failure of anticancer therapy is the development of chemoresistance, which can be either internal or acquired, and is primarily mediated by the activation of various key regulators (eg MDR, PI3K/Akt, etc.). Genetic and epigenetic mechanisms are involved in activating these pathways. Significant epigenetic mechanisms that can participate in chemoresistance include regulation of gene expression by microRNA (miRNA) and long noncoding RNA (lncRNA). Deregulated expression of these non-coding RNAs has been observed in many diseases and their involvement in the initiation and progression of malignant tumors has been demonstrated.

In this study, we investigated the expression of long non-coding RNA MIAT in hypoxia (1% O_2) in chemosensitive and chemoresistant neuroblastoma cell lines (NBL), as hypoxia is a significant negative prognostic factor of many tumors and is involved in chemoresistance. Relative expression of MIAT was influenced by the number of cultured cells, where expression was increased by culturing more cells. MIAT expression was also significantly increased after 6 hours of NBL culture UKF-NB-4 in hypoxic conditions, and maximum reached 48 h followed by a slight decrease. To elucidate the context of MIAT and chemoresistance, we determined its expression in the NBL cell line panel of chemosensitive cells and cells chemoresistant to cisplatin and some other cytostatics. The chemoresistance of the used lines was verified by IC_{50} determination. We have demonstrated a significant increase in MIAT expression in the cisplatin-resistant NBL line UKF-NB-4^{CDDP} and SK-N-AS^{CDDP}. In the lines resistant to ellipticin, doxorubicin and vincristine, we have shown a significant decrease in MIAT expression. We verified the effect of hypoxia in the context of chemoresistance to cisplatin on induction of MIAT expression, these contexts have not been described so far. In order to confirm the importance of MIAT lncRNA in adapting to the hypoxic conditions of NBL and its impact in cisplatin resistance, further experiments, especially MIAT knock-down studies, are required.

Keywords: chemoresistance, lncRNA, hypoxia, neuroblastoma