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Identification and characterization of regulatory RNAs (sdRNA and snoRNA) in glioblastoma multiforme - their involvement in cancer development and progression

Abstract

Glioblastoma (GBM) is the most malignant brain tumor in adults. Due to the high resistance of this cancer to treatment, the median survival of patients remains low, and its recurrence is almost certain. Therefore, it is crucial to understand the pathophysiological mechanisms underlying this cancer. One of the main reasons for the aggressive nature of GBM is its high heterogeneity, caused by the presence of diverse tumor cell populations, including GBM stem cells (GSCs). GSCs play a key role in tumor development, differentiation,
and mechanisms responsible for invasion. As GBM progresses, it becomes resistant to treatment, which is closely related to the tumor microenvironment. The tumor microenvironment has immunosuppressive properties, helping cancer cells evade the immune system's response.

In order to search for new diagnostic and therapeutic strategies for GBM, more research is focused on understanding the role of non-coding RNAs in the development and progression of this cancer. Reports on small nucleolar RNAs (snoRNAs) and sno-derivedRNAs (sdRNAs) in GBM are scarce. Therefore, this dissertation covers research focusing on identifying and characterizing these molecules in GBM. The analysis of the sequencing results and the performed validation allowed for the selection of sdRNA candidates potentially involved in the development of this cancer. Further assessment of the level of selected candidates in hypoxic conditions and the GSC fraction suggests a different involvement of both snoRNAs and sdRNAs in the carcinogenesis process. The obtained results also confirmed the presence of this molecules in extracellular vesicles (EVs), which may indicate their potential role in intercellular communication. In turn, immunoprecipitation

of proteins binding selected sdRNAs and snoRNAs allowed for a preliminary assessment of their mechanism of action.

Given the unknown biogenesis of sdRNA molecules, the analysis of the secondary structures of selected snoRNAs was conducted, to assess the location of the sdRNA sequences present in them. However, more in-depth analyses, including those based on changes in FUS protein levels, as well as immunoprecipitation of proteins involved in the processing of precursor snoRNAs, were also performed. These analyses provided valuable insights into the potential involvement of these molecules in the formation of sdRNAs, further strengthening the scientific basis of this research.

The search for biomarkers, especially those present in patients' plasma, is also becoming an indispensable element of cancer research. This study confirmed the presence of the tested molecules in the plasma of patients diagnosed with GBM, suggesting their involvement in cancer recurrence.

The presented results not only confirmed the increased levels of the vast majority of identified sdRNA molecules, as well as their precursor snoRNAs, in GBM, suggesting their involvement in the carcinogenesis process, but also provided a preliminary analysis of the potential biogenesis of selected sdRNAs, as well as their potential role in this cancer. These findings significantly contribute to the understanding of the molecular mechanisms responsible for the development and progression of GBM, particularly based on new classes of regulatory RNAs - snoRNAs and sdRNAs derived from them. This understanding could potentially pave the way for the development of more effective treatment methods and improved diagnostics for patients in the future.