Julia Latowska-Łysiak
Department of Molecular Neurooncology
IBCH PAN

Characterization of selected circular RNAs in glioblastoma multiforme - biogenesis of circular RNAs and their potential functions

Abstract

Glioblastoma multiforme (GBM) is the most aggressive and fatal type of brain tumor, which, despite the enormous development of medicine, remains a cancer with ineffective treatment methods. It is caused by multiple factors, such as the presence of the blood-brain barrier, vast molecular heterogeneity within the tumor, high aggressiveness, and rapid infiltration of healthy tissue, as well as the frequent development of cell resistance to chemotherapy and radiotherapy. These processes are closely related to the presence of glioma stem cells in the tumor, which are largely responsible for tumor progression, as well as the occurrence of a phenomenon called epithelial-mesenchymal transition, which causes the loss of cell adhesion and an increase in their migration potential. Therefore, it is essential to better understand the molecular basis responsible for the development of GBM, which may be crucial in the further search for therapeutic and diagnostic targets.

GBM is characterized by aberrant expression of multiple noncoding RNAs, including circular RNAs (circRNAs). Circular RNAs are a class of covalently closed, lacking 5'- and 3'-ends RNAs that are abundantly expressed in the brain and have recently been found to play a variety of roles in cancer development and progression. They can influence various cellular processes by interacting with other molecules - their interaction with microRNA has been widely described so far, but it is known that they can also affect RNA-binding proteins (RBPs), which are also modulators of circRNA biogenesis. The diagnostic value of circRNAs and circRNA/RBP complexes is still largely unknown. Therefore, this study focused on comparing the expression profile of circRNA and RBP based on RNA sequencing from patient tumors and healthy brain samples. This approach enabled to initially determine the relationship between these molecules and the potential impact of RBP on the level of

circRNA expression. The analysis also allowed for the selection of downregulated circRNA candidates.

The next part of the work was devoted to the study of selected circular RNAs - circATXN10 and circFAM188A, with a special interest in their potential role in processes related to the development of GBM. The series of functional assays and experiments utilizing the "loss-of-function" and "gain-of-function" approaches allowed to establish their relationship with their linear counterpart and interaction with other molecules such as proteins or microRNAs, as well as their potential impact on processes related to migration and invasion of GBM cells.

The last part of this dissertation focused on studying the impact of selected RBPs on downregulated circRNAs. This allowed to initially determine one of the presumable reasons for the disrupted expression profile of circATXN10 and circFAM188A in GBM cells.

The obtained results provide information on the expression profile of RBPs and circRNAs, which may lay the foundations for further and more comprehensive studies of selected molecules in the context of GBM progression. The performed analysis confirmed the vast heterogeneity of GBM tumors at the molecular level. Moreover, the participation of selected circRNAs in processes related to tumor development, as well as the impact of RBPs on the biogenesis of circular RNAs, was proven, which additionally demonstrated the need for further study of these molecules to better understand the molecular basis of GBM.