THE ROLE OF HYPOXIA IN A CELLULAR MODEL OF GLIOBLASTOMA

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Background and aim: Glioblastoma multiforme (GBM) is the most frequent and malignant type of brain cancer with a poor prognosis and survival rate of approximately 18months. GBM is characterized by a high cellular heterogeneity and its aggressiveness is linked above all to the particular infiltrating capacity and to the fine regulated involvement of the angiogenesis process. To date, the therapeutic strategies are limited and not conclusive. They include surgery, radiotherapy, chemotherapy and even using a combination of different modalities, it is still a lethal disease. In GBM there are necrotic areas in the core of the tumor surrounded by evidence of hypoxic response and neovascularization. It is known that hypoxia contributes to an aggressive phenotype in tumors, including features of resistance to apoptosis, drug resistance and increased invasiveness. The present study aimed to investigate the interaction between hypoxia and GBM, which may help to understand the mechanism underlying the regulation of differentiation of GBM cells.

Methods: This study was designed to explore the role of severe hypoxia, mimicking tumor microenvironment in GBM. Different tumoral cell lines were cultured and divided in two groups, hypoxic and normoxic, and analyzed at different time points. For the hypoxic treatment, cells were incubated in a hypoxic chamber with a 95:5mixture of N_2/CO_2. After the hypoxic treatment, we analyzed cellular count and viability, oxidative balance, the mitochondrial activity, and finally we investigated different cell survival pathways.

Results: We analyzed cell proliferation and overall metabolic activity of GBM cultures and we observed the capacity of these cells to grow both in hypoxic and in normoxic conditions. In this view, we investigated also caspases activation, the cell cycle and the production of ROS that increased in hypoxic condition. In addition, we studied different cell survival pathways involved in hypoxia, which expressions show how hypoxia can regulate GBM development.

Discussion: The GBM tumor microenvironment is heterogeneous and is characterized by hypoxic regions whose presence plays a significant role in GBM invasion, therapeutic resistance, and overall poor prognosis. The results showed that hypoxia represents a decisively feature of the tumor microenvironment, which is to reprogram GBM cell metabolism and driving tumor malignancy.

Conclusion: This preliminary study lays the basis for further investigations aimed at improving the understanding of the cellular mechanisms involved in the progression and proliferation of GBM, which could represent potential targets for innovative therapeutic strategies.