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Rediscovering potential molecular targets for glioma therapy through the analysis of the cell of origin, microenvironment, and metabolism

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Abstract

Gliomas are the most common type of malignant brain tumors. Despite significant medical advances, gliomas remain incurable and are associated with high mortality. Although numerous biomarkers of diagnostic value have been identified and significant progress in the prognosis of the outcome has been made, the treatment has not been parallelly improved during the last three decades. This review summarizes and discusses three aspects of recent discoveries related to glioma, with the objective to highlight the advantages of glioma-specific drugs targeting the cell of origin, microenvironment, and metabolism. Given the heterogeneous nature of gliomas, various cell populations have been implicated as likely sources of the tumor. Depending on the mutation(s) acquired by the cells, it is believed that neuronal stem/progenitor cells, oligodendrocyte progenitor cells, mature neurons, and glial cells can initiate cell transformation into a malignant phenotype. The level of tumorigenicity appears to be inversely correlated with the maturation of a given cell population. The microenvironment of gliomas includes non-cancer cells such as immune cells, fibroblasts, and cells of blood vessels, as well as secreted molecules and the extracellular matrix, and all these components play a vital role during tumor initiation and progression. We will discuss in detail how the tumor microenvironment can stimulate and drive the transformation of non-tumor cell populations into tumor-supporting cells or glioma cells. Metabolic reprogramming is a key feature of gliomas and is thought to reflect the adaptation to the increased nutritional requirements of tumor cell proliferation, growth, and survival. Mutations in the IDH gene can shape metabolic reprogramming and may generate some vulnerabilities in glioma cells, such as abnormal lipid metabolism and sensitivity to endoplasmic reticulum stress (ERS). We will analyze the prominent metabolic features of malignant gliomas and the key pathways regulating glioma metabolism. This review is intended to provide a conceptual background for the development of glioma therapies based on the properties of tumor cell populations, microenvironment, and metabolism.

Keywords: Drug target; ER stress; Glioma; Lipid droplets; Microenvironment; metabolism.