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Intratumor heterogeneity, microenvironment, and mechanisms of drug resistance in glioma recurrence and evolution

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Abstract

Glioma is the most common lethal tumor of the human brain. The median survival of patients with primary World Health Organization grade IV glioma is only 14.6 months. The World Health Organization classification of tumors of the central nervous system categorized gliomas into lower-grade gliomas and glioblastomas. Unlike primary glioblastoma that usually develop de novo in the elderly, secondary glioblastoma enriched with an isocitrate dehydrogenase mutant typically progresses from lower-grade glioma within 5-10 years from the time of diagnosis. Based on various evolutional trajectories brought on by clonal and subclonal alterations, the evolution patterns of glioma vary according to different theories. Some important features distinguish the normal brain from other tissues, e.g., the composition of the microenvironment around the tumor cells, the presence of the blood-brain barrier, and others. The underlying mechanism of glioma recurrence and evolution patterns of glioma are different from those of other types of cancer. Several studies correlated tumor recurrence with tumor heterogeneity and the immune microenvironment. However, the detailed reasons for the progression and recurrence of glioma remain controversial. In this review, we introduce the different mechanisms involved in glioma progression, including tumor heterogeneity, the tumor microenvironment and drug resistance, and their pre-clinical implements in clinical trials. This review aimed to provide new insights into further clinical strategies for the treatment of patients with recurrent and secondary glioma.

Keywords: evolution mechanism; glioma; secondary glioma; strategies; tumor heterogeneity.