

Zebrafish Model Yields Novel Insights into Brain Tumor-Microglia Interactions

Mihir Gupta*

Department of Neurosurgery, University of California San Diego, La Jolla, CA. United States of America

***Corresponding Author:** Mihir Gupta, Department of Neurosurgery, University of California San Diego, La Jolla, CA. United States of America

Received: August 27, 2019; **Published:** October 01, 2019

DOI: 10.31080/ASNE.2019.02.0114

In the July 2019 issue of eLife, Chia and colleagues harness a powerful zebrafish brain tumor model to address fundamental questions regarding the immune microenvironment supporting early brain tumorigenesis [1]. The zebrafish has emerged as an intriguing, and perhaps unexpected, model system to study a number of developmental, behavioral, toxicologic and even oncologic processes relevant to human disease [2]. The small size and optical transparency at the larval stage, combined with the growing armamentarium of genetic editing tools, make the zebrafish a powerful system for studying the normal and diseased brain [3].

Prior studies of brain tumors in humans and mice have illuminated the complex microenvironment present in advanced, macroscopically apparent disease. These studies have elucidated the critical roles of macrophages and microglia in promoting tumor growth through a variety of mechanisms such as extracellular matrix modification, angiogenesis induction, and cross-talk with other immune cells to create an immunosuppressive environment [4]. However, the mechanisms governing the earliest interactions between immune and tumor cells have long been unclear. Furthermore, unraveling the unique roles of different immune components and cell type-specific pathways has proven difficult. Since zebrafish larvae survive with only the innate immune system for the first 4-6 weeks post-fertilization [5], the organism represents a unique opportunity to study innate immune responses in the absence of an adaptive immune system.

Chia and colleagues draw upon their prior experience establishing the zebrafish brain tumor model, which in a previous publication elucidated key insights into the interactions between pre-neoplastic cells and macrophages/microglia [6]. Briefly, cells

overexpressing a dominant active form of the human AKT1 gene in the larval brain released Sdf1b (Cxcl12b), which recruited macrophages and microglia to developing tumors in a Cxcr4-dependent manner; the activated immune cells directly interacted with the tumor cells and promoted proliferation [6].

In the present study, the authors interrogate the mechanisms underlying the interactions between microglia and brain tumor cells. They find that intracellular calcium levels are significantly higher and cyclically oscillate in pre-neoplastic cells. Calcium promotes the release of ATP, which in turn activates the P2y12 receptor on microglia, stimulating contact with pre-neoplastic cells and driving their proliferation in an NMDA receptor-dependent manner [1].

Intriguingly, this mechanism had previously been discovered in the context of microglial attraction towards neurons with high calcium levels due to injury or activity [7], and has now been shown for the first time to underlie early microglia-brain tumor cell interactions. The authors identify the critical next question in this line of study is to identify how exactly microglia promote proliferation of early pre-neoplastic cells. The possibilities include ligand-receptor interactions; modulation of tumor cell calcium levels; and/or direct transfer of cytoplasmic contents, as has been observed between macrophages and melanoma cells in mouse models [8].

This work represents an important addition to the growing understanding of the immune microenvironment of intrinsic brain tumors. Although seemingly distinct from the complex milieu at play in the human brain, the zebrafish brain tumor model may have implications for targeted inhibition of glioma cell infiltration and metastasis to distant parts of the brain — phenomena that are

responsible for treatment failure but remain poorly understood. It is also exciting to consider whether the cyclical oscillations of calcium in the pre-neoplastic cells in this model may indicate regulation by circadian machinery, as has been observed in leukemia stem cells [9]. Ultimately, this study is a crucial reminder that even in the era of burgeoning high-throughput techniques, it is imperative to harness creative, multidisciplinary approaches to answer fundamental mechanistic questions in brain tumor pathobiology.

Bibliography

1. Chia K., *et al.* "Brain tumours repurpose endogenous neuron to microglia signalling mechanisms to promote their own proliferation". *Elife* 8 (2019).
2. Singleman C and Holtzman NG. "Growth and maturation in the zebrafish, *Danio rerio*: a staging tool for teaching and research". *Zebrafish* 11 (2014): 396-406.
3. Basnet RM., *et al.* "Zebrafish Larvae as a Behavioral Model in Neuropharmacology". *Biomedicines* 7 (2019).
4. Hambardzumyan D., *et al.* "The role of microglia and macrophages in glioma maintenance and progression". *Nature Neuroscience* 19.1 (2016): 20-27.
5. Novoa B and Figueras A. "Zebrafish: model for the study of inflammation and the innate immune response to infectious diseases". *Advances in Experimental Medicine and Biology* 946 (2012): 253-275.
6. Chia K., *et al.* "Tumor initiating cells induce Cxcr4-mediated infiltration of pro-tumoral macrophages into the brain". *Elife* 7 (2018).
7. Eyo UB., *et al.* "Modulation of microglial process convergence toward neuronal dendrites by extracellular calcium". *Journal of Neuroscience* 35 (2015): 2417-2422.
8. Roh-Johnson M., *et al.* "Macrophage-Dependent Cytoplasmic Transfer during Melanoma Invasion In Vivo". *Cell* 43.5 (2017): 549-62e6.
9. Puram RV., *et al.* "Core Circadian Clock Genes Regulate Leukemia Stem Cells in AML". *Cell* 165.2 (2016): 303-316.

Volume 2 Issue 11 November 2019

© All rights are reserved by Mihir Gupta.