**GAP43-dependent mitochondria transfer from astrocytes enhances glioblastoma tumorigenicity**

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**Presenter:** Chi-Lin Ho **Date/Time:** 2024/03/21, 16:10-17:00

**Commentator:** Dr. Shih-Chieh Lin **Location:** Room 601

**Background:** Glioblastoma (GBM), a type of glioma, is the most common and aggressive form of brain cancer. Glioma exhibits a distinct cellular structure called tumor microtubes (MTs). Its major structural protein is called growth-associated protein 43 (GAP43), which plays an important role in intercellular communication, invasion, and therapy resistance. Aerobic glycolysis has been assumed to be the main energy pathway for cancer cells. However, recent reports suggest that mitochondrial respiration is an alternative energy source. This metabolic heterogeneity may arise via interaction with the tumor microenvironment (TME), which can transfer metabolic signals, including mitochondria, to tumor cells. Transfer of mitochondria has been demonstrated between different cell types and via other routes, such as exchange in vitro among GBM cells via MTs. In many studies, dynamic TME interactions are major drivers of tumor growth and therapeutic resistance in GBM.

**Objective:** To check whether GBM can acquire functional mitochondria from non-malignant cells in the TME and further investigate its impact on GBM.

**Results:** To find out whether host cells could transfer mitochondria to GBM, authors orthotopically implanted mouse GFP+GBM (SB28 and GL261) into mito::mKate2 mice and confirmed the existence of host mitochondria within GBM via confocal microscopy and Imaris. To further investigate the identity of the predominant mitochondria donor cell, the authors first ruled out tumor-infiltrating immune cells by bone marrow reconstitution mouse (to restrict mito::mKate2 expression only in bone marrow-derived immune cells). They observed astrocytes displayed higher mitochondria transfer rates to GBM than other brain-resident glial cells. During this process, authors also discovered that such mitochondrial transfer occurs via MTs, and the formation of MTs requires the expression of GAP43. The authors then investigated the impact of mitochondrial transfer on GBM. The augmented mitochondrial respiration and ATP production in recipient GBM had been observed, along with metabolic reprogramming. They changed cell cycle regulation, facilitating GBM’s proliferative and self-renewal capacity. Finally, the authors confirmed that after gaining mitochondria from astrocytes, GBM displayed higher tumorigenicity, which resulted in GBM leading to symptomatic or lethal disease much faster.

**Conclusion:** GBM can acquire mitochondria from brain glial cells, more specifically, from astrocytes via GAP43+ MTs. After gaining functional mitochondria, GBM was observed in the alternation of metabolic profiles, increased mitochondrial respiration, and changes in intracellular signaling. These alternations increased the tumorigenicity of GBM in animal models.

**Reference:**

Hoang-Minh, L. B. et al. Infiltrative and drug-resistant slow-cycling cells support metabolic heterogeneity in glioblastoma. EMBO J. 37, e98772 (2018).