Research and preclinical development of innovative and predictive therapeutic strategies for the optimization of the treatment of brain tumors

Replication of glioblastoma (GBM) cells in the brain of patients is the main cause of their death. In order to understand the biophysical mechanisms underlying GBM replication, it is necessary to adopt and combine optical tweezer, atomic force microscopy, multi-channel fluorescence imaging for both calcium and chloride ions, live cell imaging, electrophysiology, immunohistochemistry and RNA-seq. Large and frequent calcium flare are observed which are loosely coupled to motility. Multichannel imaging with both calcium and chloride dyes showed that large spontaneous calcium flares are often coupled with chloride influxes, which were localized. In round cells undergoing mitosis, either no or small calcium flares are detected during the metaphase/anaphase transition, but large calcium flares were frequently seen during telophase and cytokinesis, when the volume of the dividing GBM increases. Patch clamp recordings show the existence of Cl^- currents which are regulated by the intracellular Ca2+ and the activation of inward and outward Cl- currents control both swelling shrinking of dividing GBM.

In the present PhD thesis we aim to find and optimize cocktails of FDA approved drugs able to block replication and infiltration of GBM and at the same time to let neurons and healthy glia unarmed. The choice of these drugs will be based on experiments already obtained or under way. We will use U87 GBM cell lines and also GBM from patients. We will also perform RNA-seq on GBM from patients in order to develop personalized cocktails, I.e. guided by the sequencing of specific GBM from the patient. The work will reinforce the patent “Composition for the use in the treatment of glioma and glioma-induced epilepsy Patent n. 1020212000022106, filed August 2021, from which we expect clinical applications.

Relevant References

1) L. Andolfi, et al. (2014). "Investigation of adhesion and mechanical properties of human glioma cells by single cell force spectroscopy and atomic force microscopy." PLoS One **9**(11): e112582.

2) Xiaoyun Li, et al. (2020). "Mechanisms of malignancy in glioblastoma cells are linked to mitochondrial Ca(2) (+) uniporter upregulation and higher intracellular Ca(2+) levels." J Cell Sci **133**(6).

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