Proposition de Stage de M2/Thèse – 2027

Effects of the Alzheimer amyloid beta peptide on glioblastoma cell mechanics and invasive properties

Summary

Cells can sense and respond to external forces and **mechanotransduction** events appear to be critical for most cellular functions, including cell migration and invasion. This M2 internship project will study mechanotransduction in the context of **glioblastoma (GBM)**, the most aggressive brain tumour, and **Alzheimer's disease**. The project will focus on the role of the Alzheimer amyloid beta (Aβ) peptide in GBM cell mechanics, migration and invasive properties.

Context and objectives

The relationship between **Alzheimer disease** and **brain tumours** is an emerging field with conflicting results so far. In particular, for GBM, some studies show an inverse correlation between Alzheimer disease and GBM [1,2].

We will study the influence of the Alzheimer amyloid beta (Aβ) peptide on glioblastoma (GBM) cell mechanics and metabolic activity. Our hypothesis is that the Aβ peptide modifies **GBM cell mechanics to perturb their invasive properties**. This project will be performed in collaboration with Galya Staneva (Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria). We will use patient-derived GBM cells that we have previously characterized both mechanically at the intracellular level. Our preliminary results show that the Aβ peptide **localizes in close proximity to mitochondria and the nucleus** (Fig. 1A) suggesting a potential effect on mitochondria mechanics and metabolic activity. We have also shown that the Aβ peptide reduces **GBM cell proliferation and migration** while it increases **cytoplasmic rigidity** (Fig. 1B).

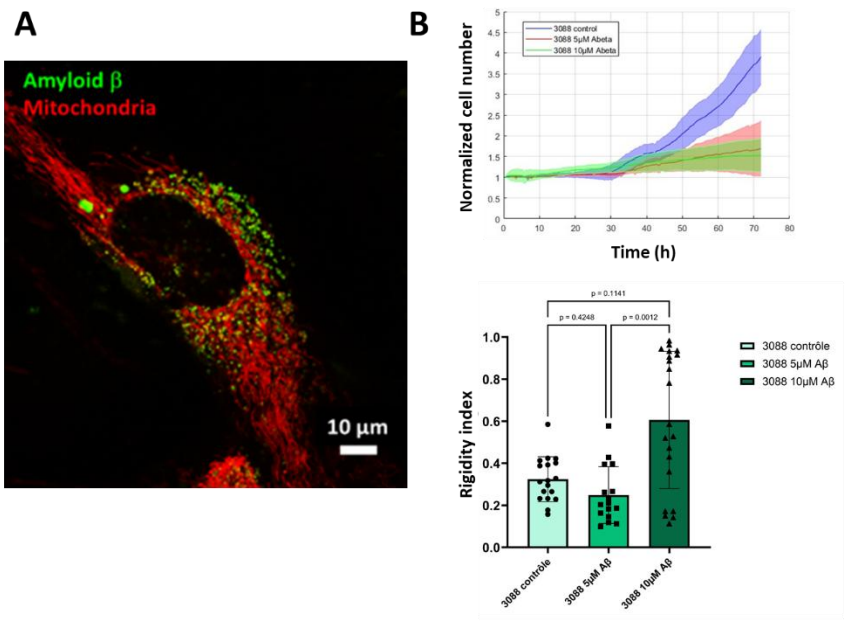


Figure 1: *(A) Localization of fluorescent amyloid beta (Aβ) peptide (green) in glioblastoma (GBM) patient-derived U3088 cells, after 48h of incubation with 5 µM Aβ. Mitochondria were labelled using PKMito-Red (red). (B) Top. Quantification of U3088 cell proliferation in control situation (blue curve) and when treated with 5 µM (red curve) or 10 µM (green curve) Aβ peptide. The Iprasense CytoNote lens-free microscopy holographic device was used to track the cells for 72 hours. Bottom. Quantification of the rigisity of the cytoplasm using optical tweezers-based viscoelastic relaxation experiments. Results (A, B) were obtained after incubation in culture conditions (37°C, 5% CO_2).*

The intern will: 1) confirm and extend our previous results on **cell proliferation and 2D migration** in other GBM cell lines and in control non tumoural RG cells; 2) measure the **mechanics of the nucleus**

and mitochondria of GBM cells in the presence of the Aβ peptide; 3) measure the **membrane lipid order** and **membrane tension** in the presence of the Aβ peptide using Di-4-ANEPPDHQ and Flipper-TR fluorescence imaging respectively; and 4) perform control experiments with an **inactive ('reverse') Aβ peptide**. We hope to demonstrate a **direct role of the Aβ peptide** in GBM cell mechanics, proliferation and migration. Longer term experiments will be based on 3D models of GBM invasion to further test the mechanical links between Alzheimer disease and GBM.

References

1. Xia, S., Chen, H. & Tang, T. Risk of Death from Alzheimer's Disease Associated with Brain Tumor, Glioma, and Glioblastoma. *J Alzheimers Dis* **96**, 623–631 (2023).
2. Brehler, M. *et al.* Quantitative analysis of Alzheimer's disease pathology in glioblastoma patients. 8 (2021) doi:10.1117/12.2580725.

Key words: mechanotransduction; glioblastoma; Alzheimer's disease; amyloid beta; optical tweezers; microfluidics; FRET; FLIM; mitochondria; nucleus; membranes; tension

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