Titre du projet de thèse/Title of the PhD project :

Microtubule acetylation in glioblastoma resistance to radiotherapy

Disciplines : Cell Biology, Oncology

Résumé du projet de thèse *(1 page maximum, en anglais)*

Gliomas are malignant brain tumours that originate from glial cells, glial precursors or neural stem cells. Glioblastoma multiforme (GB) is the most common type of glioma with a very poor prognosis for patients. This type of cancer is rare, but devastating as there is no curative treatment available. The invasive character of GB is one of the main contributors to the poor prognosis as cells migrate away from the tumour core, evade therapy and initiate recurrence and ultimately cause the death of the patient (Drumm et al., 2019). While radiotherapy remains the most effective component of multimodal therapy for GB patients, it can promote migration of the cancer cells before their death (Merrick et al., 2021). The concept that radiation therapy may induce a more aggressive infiltrative phenotype in GB cells is consistent with the fact that increasing radiation doses does not improve outcome for GB patients. **This effect of radiation on GB invasion underscores the importance of developing anti-invasive therapies that complement and enhance conventional therapeutic approaches.**

Although frequently overlooked, MTs also play a key role in mesenchymal migration, which frequently characterizes GB cell migration, [1]. MT organization, dynamics and functions are regulated by protein interactions and by post-translational modifications of tubulins, among which the most common are acetylation and detyrosination [2]. Acetylation of K40 of α-tubulin has received particular attention because α-tubulin acetylation is altered in tumour cells [3]. However, whether and how it participates in cancer progression and in particular in cancer cell invasion are still unknown. Tubulin acetylation is controlled by ATAT1, the major tubulin acetyltransferase in mammals, and by deacetylases, HDAC6 and SIRT2. We have shown that microtubule acetylation, ATAT1 and HDAC6, but not microtubule detyrosination, are essential for mechanotransduction and mechanosensitive migration in normal glial cells [4]. However, the role of this post-translational modification in GB cell mechanics and invasion and irradiation-induced responses remains to be explored.

Based on our preliminary results showing that irradiation increases both migration speed and MT acetylation in GB cells, we hypothesize that radiation-induced MT acetylation promotes GB cell invasion. Hence, in this PhD project, we aim to assess MT acetylation in tumor samples and to determine the role of MT acetylation in GB cell responses to irradiation.

The student will **use**

(i) immunohistochemistry and spatial transcriptomics to analyze MTs acetylation in human tumor samples and correlate it with tumor cell properties under the supervision of Franck Bielle,

(ii) (glioblastoma cell lines and patient-derived glioblastoma cells to assess the impact of irradiation and microtubule acetylation in the invasive properties of GB cells under the supervision of Sandrine Etienne-Manneville. Cell invasion will be assessed under controlled *in vitro* conditions as well as *in vivo* invasion assays in zebrafish to determine if MT acetylation may serve as a target to improve therapeutic strategies.

This project should lead to (i) significant advances in our understanding of the invasive behavior and radioresistance of GBs, (ii) the identification of molecular and biophysical markers of invasive and radioresistant cells, and (iii) the identification of MT acetylation as a potential therapeutic target in the treatment of GBs.

1 Etienne-Manneville, S. Microtubules in cell migration. *Annu Rev Cell Dev Biol* **29**, 471-499, doi:10.1146/annurev-cellbio-101011-155711 (2013).

2 Janke, C. The tubulin code: Molecular components, readout mechanisms, and functions. *J Cell Biol* **206**, 461-472, doi:10.1083/jcb.201406055 (2014).