Role of the immune system and the metabolic exchanges related to the microbiota-gut-brain axis, in the context of glioblastoma

Cédric Pape[1], Camille Amelot[1], Sébastian Lillo[2], Maria Haykal[1], Océane Martin[1]

[1]symbioMIND team, Institut de Biochimie et Génétique Cellulaires, Bordeaux, France
[2]GBmetabo team, Institut de Biochimie et Génétique Cellulaires, Bordeaux, France

Introduction

Context and aims

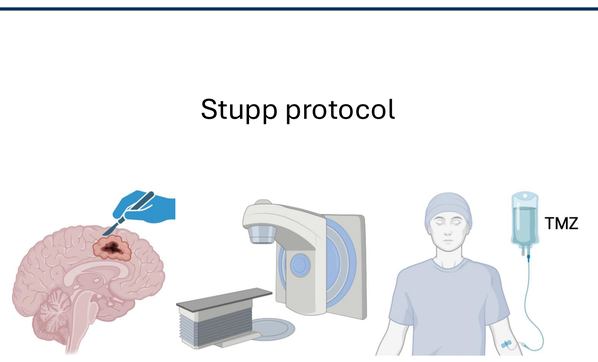
Glioblastoma (GB) is the most common primary malignant tumor of the adult brain[1]. The standard care consists of a resection of the tumor, followed by radiotherapy and chemotherapy (temozolomide, TMZ)[2]. Despite that, the prognosis of the GB remains poor, with a median survival rate of 15 months after diagnosis[1].

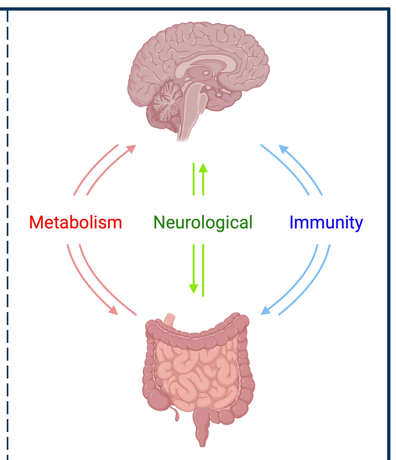
Recent studies have already highligthed a relationship between gut-microbiota dysbiosis and brain conditions, such as Alzheimer's and Parkinson's diseases[3] ; but very few is known about the link between the gut microbiota and the GB.

This project aims to understand the dialogue established between the gut-microbiota and the tumor, through two axis: the immune system and the metabolic exchanges, notably with the SCFAs, produced by the gut-microbiota.

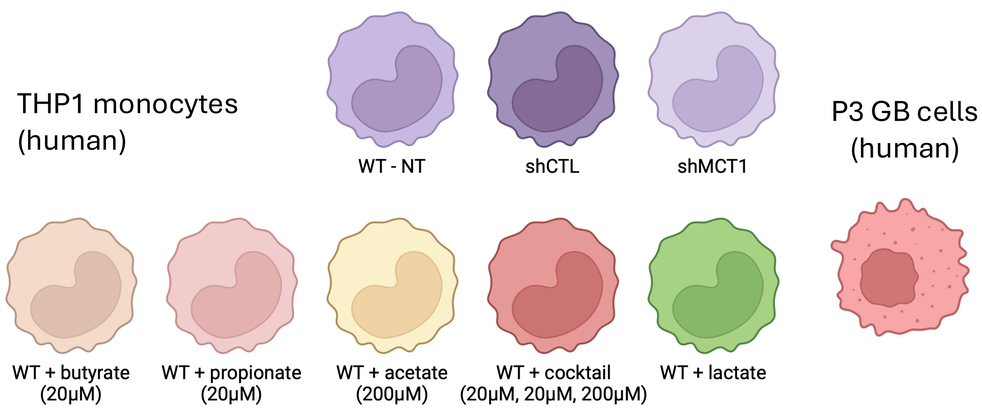
It will be done by:

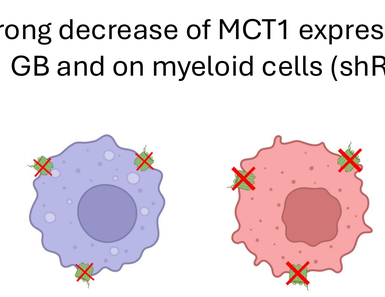
→ A characterization of the immune populations and the metabolites implicated in the context of GB
→ A modulation of these immune populations and metabolic exchanges
→ The study of treatment's impacts on the immune system and the metabolic exchanges

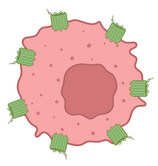


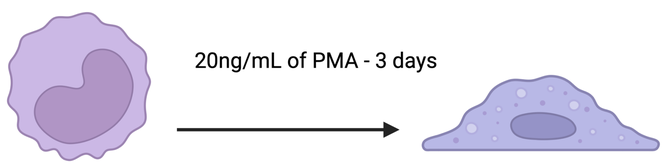


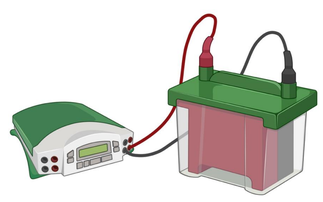
Materials and methods

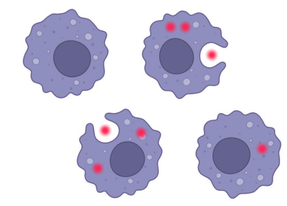


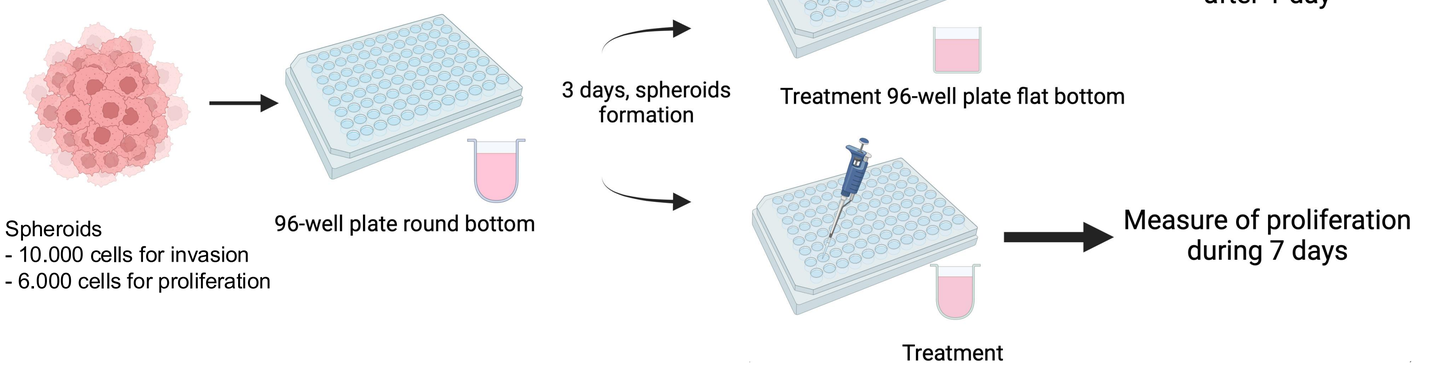






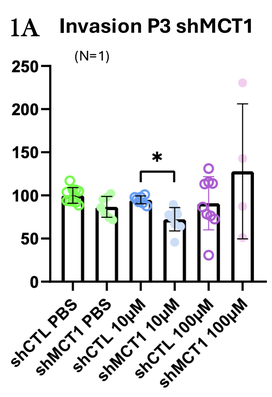


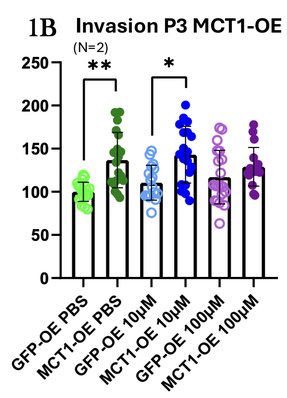


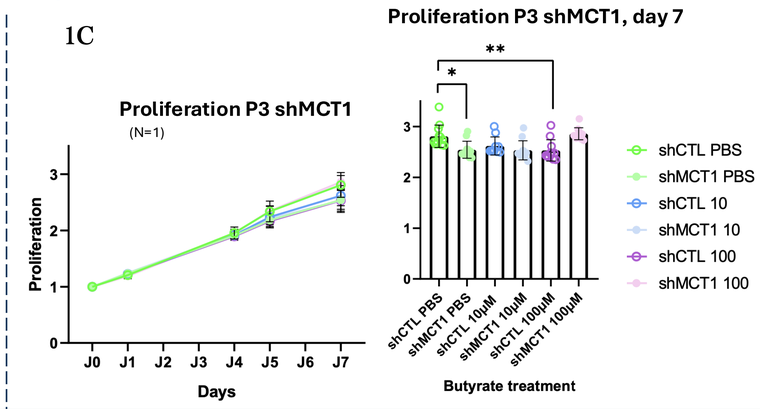


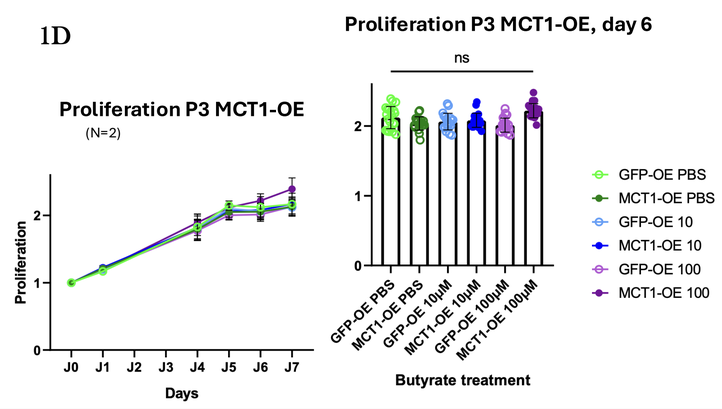
Results

MCT1 over-expression but not depletion increases invasion of GB cells (P3), and does not have an important effect on proliferation; regardless of butyrate treatment





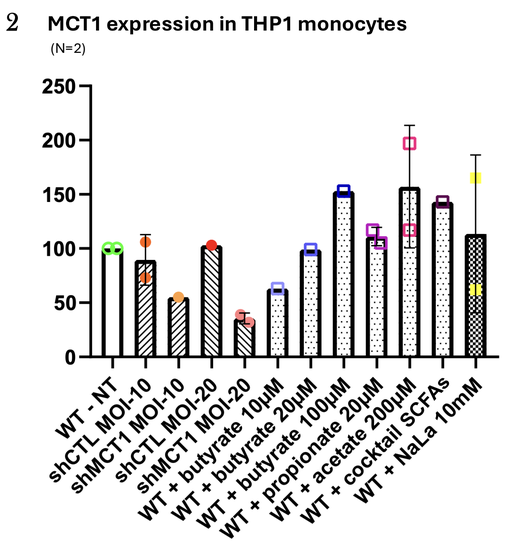


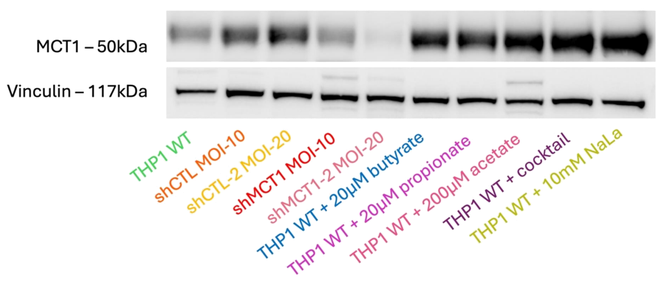


Invasive index of P3 cells depleted for MCT1 (**1A**) or over-expressing MCT1 (**1B**). Proliferative index of P3 cells depleted for MCT1 (**1C**) or over-expressing MCT1 (**1D**). Barplots are representing the last day of proliferation. Mean +/- SD is represented.

→ **MCT1 over-expression increases GB cells invasion**
→ **Butyrate doesn't seem to have an impact on the invasion**
→ **Neither MCT1 levels nor butyrate seem to have an impact on GB cells proliferation**

MCT1 is decreased in shMCT1 cells; SCFAs seem to increase MCT1 expression, while the effect of lactate is variable

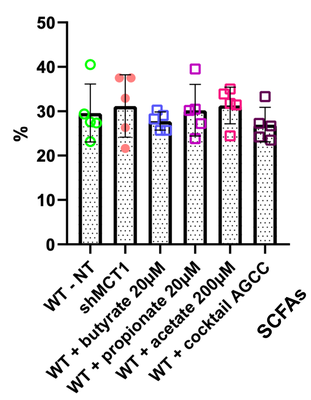


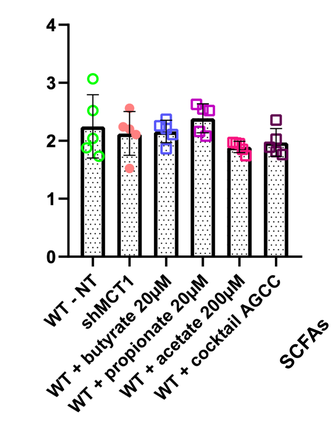


Western Blot analysis on THP1 cells (**2**).

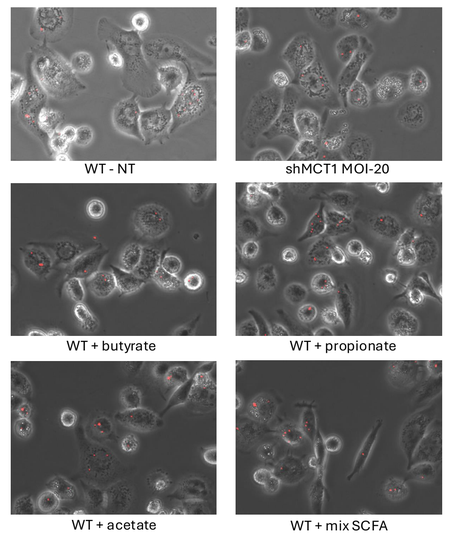
→ **MCT1 is knocked-down at 65% in shMCT1 MOI-20 condition (45% only in shMCT1 MOI-10 condition)**
→ **Butyrate treatment increases MCT1 expression**
→ **SCFAs alone or combined, at physiological concentrations, increase MCT1 expression**
→ **Lactate shows different effects on MCT1 expression**

Neither MCT1 depletion nor SCFAs treatments seem to have an effect on THP1 phagocytosis capacity





Percentage of macrophages phagocyting (**3A**), and number of beads per phagocytic macrophage (**3B**); in different conditions, with MCT1 knock-down and under SCFAs treatments (**3C**).

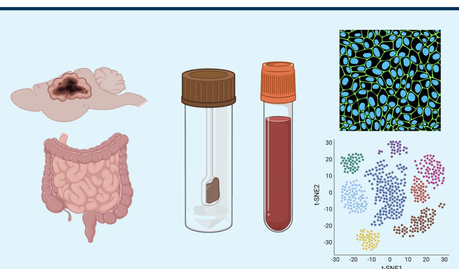


→ **Neither MCT1 depletion nor SCFAs treatments impact THP1 macrophages phagocytic capacities**

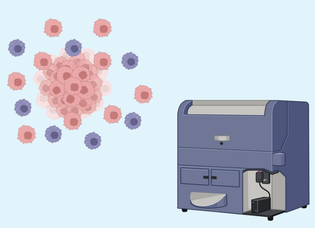
Conclusion

Perspectives

→ ***In vivo*** **experiment to characterize the immune landscapes in both the brain and the gut, and the metabolite exchanges (in the feces, the blood, the organs)**



→ ***In vitro*** **co-cultures between GB cells and myeloid cells, with or without treatments**
→ **Phagocytosis assays between macrophages and GB cells**
→ **Flow cytometry experiments to determine the impact of SCFAs and other metabolites on macrophages polarisation**



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