Glioblastoma and the gut–brain axis: exploring the role of peripheral serotonin and the enteric nervous system

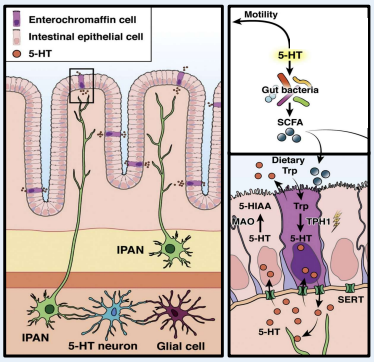
Maria M. HAYKAL[1], Cédric PAPE[1], Sarah LAVIELLE[1] , Océane MARTIN[1]

[1]University Bordeaux, CNRS, IBGC, UMR5095, 33000 Bordeaux, France

Glioblastoma is the most aggressive primary brain tumor in adults, with a poor prognosis despite the standard Stupp protocol. Increasing evidence highlights the gut–brain axis as a key modulator of brain diseases, with communication occurring through immune, metabolic, and **neural pathways**. Among these, the neural route via the **enteric nervous system** (ENS) and **peripheral serotonin** (5-HT) is of particular interest, as more than 90% of 5-HT is produced by intestinal enterochromaffin cells under ENS control.

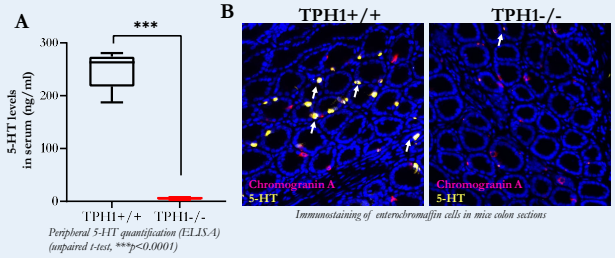
Aims & Objectives

We aim to determine whether and how the ENS influences glioblastoma progression and treatment response. To address this, we use *TPH1* knockout mice – lacking peripheral serotonin production – to dissect the contribution of ENS-dependent serotonin signaling to brain tumor dynamics.



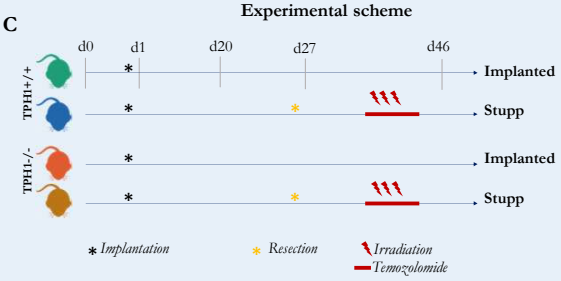
Adapted from Margolis *et al.*, Gastroenterology, 2021

TPH1-/- mice lack peripheral serotonin

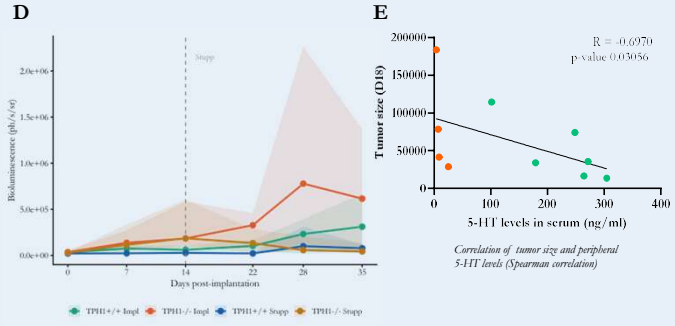


*Peripheral 5-HT quantification (ELISA) (unpaired t-test, ***p<0.0001)*

Immunostaining of enterochromaffin cells in mice colon sections

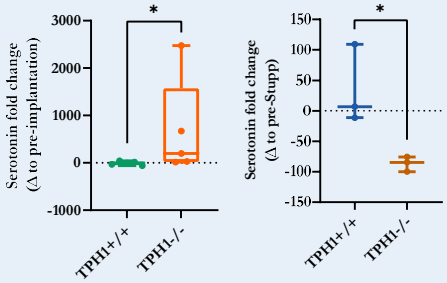


Accelerated tumor growth and impaired response to Stupp protocol in TPH1-/- mice

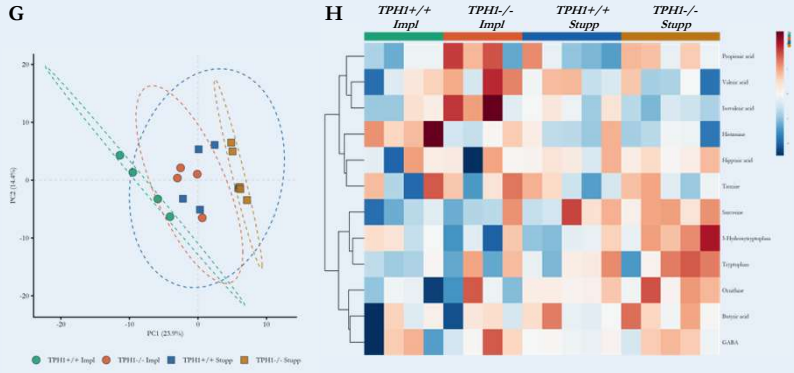


Correlation of tumor size and peripheral 5-HT levels (Spearman correlation)

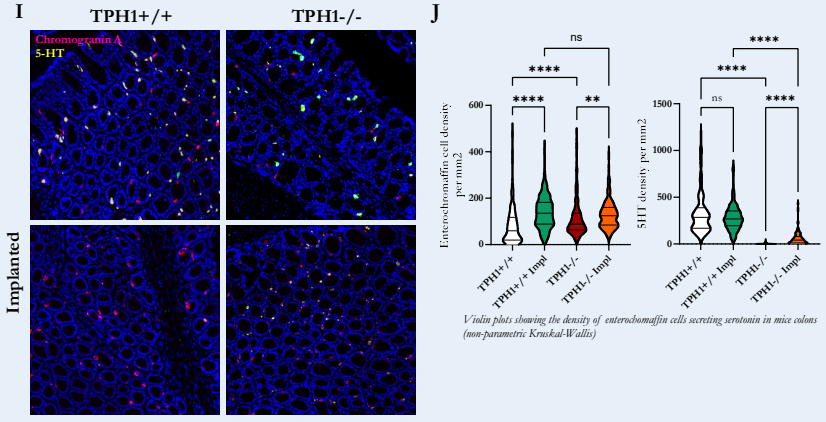
Peripheral serotonin is increased after tumor implantation and reduced by stupp protocol



TPH1 deficiency alters microbiota-associated plasma metabolites under Stupp protocol



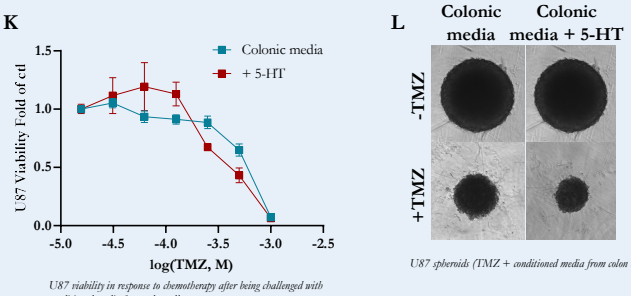
Colonic serotonin is restored in TPH1-/- tumor-bearing mice



Immunostaining of enterochromaffin cells in mice colon sections

Violin plots showing the density of enterochromaffin cells secreting serotonin in mice colons (non-parametric Kruskal-Wallis)

Serotonin sensitizes glioblastoma cancer cells to chemotherapy



U87 viability in response to chemotherapy after being challenged with conditioned media from colon cells

U87 spheroids (TMZ + conditioned media from colon cells)

Perspectives

- **Define the brain immune landscape** in *TPH1*+/+ vs *TPH1*-/- mice to (5-HT–dependent effects involve **immune modulation?)**
- **Characterize ENS involvement** in gut–brain communication during glioblastoma progression.
- **Develop a gut–brain-on-chip platform** to dissect the mechanistic pathways driving **GB growth and therapy response**

Take home message

Peripheral serotonin limits glioblastoma progression : TPH1-/- mice show **larger tumors, lower systemic 5-HT**, and an **inverse correlation** between tumor burden and circulating serotonin.