Dissecting the pro-tumoural role of the essential amino-acid transporter complex CD98/LAT1

Cormerais Y 1, Giuliano S 1, LeFloh R 1, Front B 1, Durivault J 1, Tambuté E 1, Massard PA 1, de la Ballina LR 3, Endou H 4, Wempe MF 5, Manuel Palacin 1, Parks SK 1 and Pouyssegur J 1,2

1. Centre Scientifique de Marató, MC
2. Institute for Research on Cancer and Aging (IRCAN), University of Nice, Centre A, Lascassagne, Nice, FR
3. Institute for Research in Biomedicine, University of Barcelona and CIBERER, SP
4. Research & Development, Fuji Biosys Co. Ltd.
5. School of Pharmacy, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045, USA

Introduction
The CD98/LAT1 heterodimer is a multifunctional transmembrane complex that is overexpressed in many cancers and is a bad prognostic marker.

The CD98 glycoprotein interacts with integrins to regulate migration, proliferation and adhesion-induced intracellular signaling.

In this study, we assessed the pro-tumoural role of each component of the CD98/LAT1 complex using genetic knock outs of the colorectal adenocarcinoma cell line LS174T.

Results
FIG.1: CD98 and LAT1 expression, localization and activity are interdependent

FIG.2: LAT1 knockout strongly decreases mTORC1 activity and cancer cell proliferation while CD98 invalidation has no effect

FIG.3: Genetic disruption or pharmacological inhibition of LAT1 abolishes mTORC1 and growth of CD98 KO cells

FIG.4: Rescued CD98 expression in LAT1 KO cells does not restore proliferation

FIG.5: Pharmacological inhibition of LAT1 suppresses mTORC1 activity and proliferation in multiple cancer cell lines

FIG.6: LAT1 is essential for mTORC1 activity and tumour growth in vivo while CD98 is dispensable

Conclusion
- LAT1 is essential for mTORC1 activity and tumour growth
- These roles of LAT1 are independent of the CD98 / integrin axis
- Targeting LAT1 activity is a promising therapeutic strategy in multiple cancer types
- Tumour cells tested appear to lack a redundant mechanism for essential amino acids uptake strengthening the idea of developing the LAT1 inhibitor JPH203 as an anticancer strategy in the clinic