BRAIN METASTASIS JUNIOR GROUP

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OVERVIEW

Brain metastasis is the most common neurological complication of cancer. When metastatic cells reach the brain, prognosis is poor given that local therapies (i.e. surgery and radiation) have limited benefits for patients and the disease inevitably progresses. The rise in the number of patients with brain metastasis is partially due to the increasing number of systemic therapies that work extra-cranially but are unable to provide the same therapeutic benefit in the brain. Consequently, cancer cells present at this secondary site have additional time to evolve and to grow into clinically detectable lesions. In the laboratory, we study why and how cells from different cancer types (breast cancer, lung cancer and melanoma) are able to access the brain, survive and colonise this vital organ. We dissect the biology of these processes *in vivo* using experimental models in order to challenge the current status of this unmet clinical need.

"We have treated brain metastasis by targeting the microenvironment. We have used a novel therapy both in mice and in patients that reduces established metastasis in the brain and increases survival."

Graduate Students
Laura A. Álvaro (since July), Wendy E. Bindeman (until May), Catia P. Domingues, Pedro García, Lucía Zhu

Technicians
Lourdes Osuna, Natalia Yebra

Student in Practice
Ana de Pablos Aragoneses (FUAM Fellow, since September) (*Universidad Autónoma de Madrid*)

RESEARCH HIGHLIGHTS

We pioneered the first report proving the importance of glial heterogeneity associated with metastatic brain tumours. As previously shown in other diseases affecting the brain, understanding the contribution of specific glial subpopulations could provide novel therapeutic targets.

The use of genetic and pharmacological approaches has enabled us to discover the critical role of this disease-specific subpopulation of reactive astrocytes in brain metastasis, which is characterised by activation of the STAT3 pathway. Its presence, induced by metastatic cells, involves the establishment of an immunosuppressive local environment that favours tumour growth.

In collaboration with four different national and international clinical institutions we have proved the importance of this finding in patients with brain metastasis. Treatment of stage IV lung adenocarcinoma patients with the STAT3 inhibitor silibinin reduced brain metastasis in 75% of them, which led to an increased survival. This finding involves a proof-of-concept regarding the possibility of developing effective therapies against metastasis by targeting the microenvironment. ■

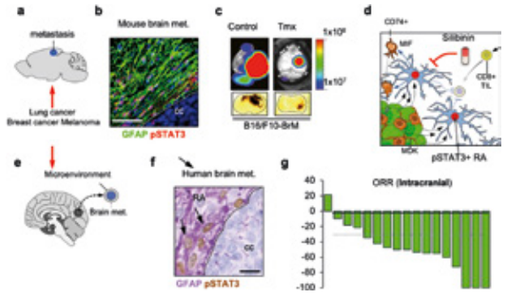

Figure A subpopulation of reactive astrocytes (GFAP), characterised by activated STAT3 (pSTAT3), is present in experimental brain metastasis models (**a**,**b**) and human samples (**e**,**f**). Targeting this glial subpopulation in mice (**c**) and humans (**g**) impaired the viability of intracranial metastasis. pSTAT3 reactive astrocytes are required to maintain a pro-metastatic niche (**d**).

PUBLICATIONS

- Priego N, Zhu L, Monteiro C, Mulders M, Wasilewski D, Bindeman W, Doglio L, Martínez L, Martínez-Saez E, Ramón y Cajal S, Megías D, Hernández-Encinas E, Blanco-Aparicio C, Martínez L, Zarzuela E, Muñoz J, Fustero-Torre C, Piñeiro-Yáñez E, Hernández-Laín A, Bertero L, Poli V, Sánchez-Martínez M, Menendez JA, Soffietti R, Bosch-Barrera J, Valiente M* (2018). STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. *Nat Med* 24, 1024-1035. (*) Corresponding author.
  See also:
  - *Trends Mol Med.* DOI: 10.1016/j.molmed.2018.07.002.
  - *Nat Rev Cancer.* DOI: 10.1038/s41568-018-0042-3.
  - *Nat Rev Neurol.* DOI: 10.1038/s41582-018-0037-4.
  - *Nat Medicine.* https://www.nature.com/collections/hdacbgbada.
- Er EE, Valiente M*, Ganesh K*, Zou Y, Agrawal S, Hu J, Griscom B, Rosenblum M, Boire A, Brogi E, Giancotti FG, Schachner M, Malladi S, Massagué J (2018). Pericyte-like spreading by disseminated cancer cells activates YAP and MRTF for metastatic colonization. *Nat Cell Biol* 20, 966-978. (*) Shared authorship.
  See also:
  - *Nat Cell Biol.* DOI: 10.1038/s41556-018-0162-8.
- Mustafa DAM, Pedrosa RMSM, Smid M, van der Weiden M, de Weerd V, Nigg AL, Berrevoets C, Zeneyedpour L, Priego N, Valiente M, Luider TM, Debets R, Martens JWM, Foekens JA, Sieuwerts AM, Kros JM (2018). T lymphocytes facilitate brain metastasis of breast cancer by inducing Guanylate-Binding Protein 1 expression. *Acta Neuropathol* 135, 581-599.
- Verdura S *et al.* (incl. Valiente M) (2018). Silibinin is a direct inhibitor of STAT3. *Food Chem Toxicol* 116 (Pt B), 161-172.
- Valiente M* *et al.* (2018). The evolving landscape of brain metastasis. *Trends Cancer* 4, 176-196. (*) Co-corresponding author.
  See also:
  - *Review of the year by Trends in Cancer*: http://crosstalk.cell.com/blog/best-reviews-we-published-in-2018-part-1.
- Preusser M *et al.* (incl. Valiente M) (2018). Recent advances in the biology and treatment of brain metastases of non-small cell lung cancer: summary of a multidisciplinary roundtable discussion. *ESMO Open* 3, e000262.

AWARDS AND RECOGNITION

- Research Award, Royal Academy of Science, University of Zaragoza. Spain.
- Clinic and Laboratory Integration Program (CLIP) Award, Cancer Research Institute, USA.
- Elected Member of the Scientific Committee of the European Association of Neuro Oncology.
- Keynote speaker at the Annual Congress of the European Society of Veterinary Oncology.
- Laura-Álvaro Espinosa was recipient of a *MINECO-Severo Ochoa* PhD Fellowship.
- Neibla Priego received the CNIO Award for Excellence in Research by Postdoctoral/Staff Investigators, CNIO Lab Day.
- Lucía Zhu received the 'Best Poster' Award at the CNIO Lab Day.
- *STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis,* by Priego *et al.*, was selected as paper of the month by the Spanish Society for Biochemistry and Molecular Biology.