OVERVIEW

Brain metastasis is the most common neurological complication of cancer and, in spite of the progress made with local (i.e., surgery and radiation) and systemic (i.e., targeted therapy, immunotherapy) therapies, prognosis remains poor. Indeed, the increased incidence of brain metastases is partially due to systemic therapies that work extra-cranially but do not provide the same therapeutic benefit in the brain. 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 and patient-derived material to challenge this unmet clinical need. Our research has identified novel brain metastasis mediators, characterised the metastasis-associated microenvironment, designed better experimental models, and explored novel methods to target brain metastasis as well as to prevent or revert the frequent impact of metastasis on brain function.

“We challenged mass effect as the only source of neurocognitive impairment in brain metastases and instead suggest that a molecular programme present in cancer cells could underlie such a process.”
RESEARCH HIGHLIGHTS

How brain metastases impair neural communication

We published a manuscript that suggests an alternative way to look at the impact brain metastasis can cause on brain function. Rather than the compression and destruction of neurons in the peritumoral area derived from the mass effect as the tumour grows, we showed that the molecular profile of cancer cells might generate aberrant ways in which they influence surrounding intact neural circuits. By exploiting different brain metastasis models, we showed that they recapitulate the heterogeneous interaction observed in patients with respect to the negative influence on neuronal communication. As such, we detected differences in the peritumoral electrophysiology from different models that correlated with the decrease in both inhibitory synapses as well as calcium activity. Furthermore, simply analysing brain activity associated with the presence of different brain metastasis models depicted a novel biomarker. In brief, computational analysis of brain activity using artificial intelligence demonstrates the possibility to predict the presence and the subtype of metastasis in the brain. Both aspects (the use of a novel biomarker as well as the molecular mediators of the impact on brain activity) are currently being followed-up to be exploited clinically through the National Network of Brain Metastasis, RENACER.

Development of preventive strategies against brain metastasis

Our systematic dissection of metastasis colonisation of the brain has made it possible to define different steps. By focusing on the early moments after extravasation, we are studying the process by which virtually all potentially metastasis-initiating cells rely on pre-existing vessels to survive, using the process termed vascular co-option. Deconstructing the crosstalk between co-opting metastatic cells and co-opted endothelial cells is giving us new molecular insights to develop preventive strategies to stop the development of micrometastases.

Consolidating RENACER as a pioneering strategy for a more efficient translation

The National Network of Brain Metastasis (RENACER) initiated in 2021 has expanded to 18 hospitals throughout the country, attracted competitive grants, and initiated clinical studies and trials (NCT0653754, NCT0688919) based on the use of Patient-Derived Organotypic Cultures (PDOC). Furthermore, the unique resource of patient-derived material generated over these years is allowing us to initiate research projects starting from findings in human data.

Progress on the co-evolution of the metastasis-associated microenvironment

Our programme exploring the evolution of the microenvironment into a pro-tumoral niche to be exploited for novel therapies against brain metastases has been significantly expanded. We have deepened our knowledge on metastasis-associated astrocyte heterogeneity as well as on the process by which they are reprogrammed to acquire new roles as a local immunomodulatory cell type. Indeed, we have interrogated strategies to manipulate CD8+ T cells and evaluate by which they are reprogrammed to acquire new roles as a focused networks. The National Network of Brain Metastasis (RENACER) led by Manuel Valiente has made it possible to define different steps. By focusing on the early moments after extravasation, we are studying the process by which virtually all potentially metastasis-initiating cells rely on pre-existing vessels to survive, using the process termed vascular co-option. Deconstructing the crosstalk between co-opting metastatic cells and co-opted endothelial cells is giving us new molecular insights to develop preventive strategies to stop the development of micrometastases.

• PUBLICATIONS

• Journal cover
  See also: Cancer Cell DOI: https://doi.org/10.1016/j.ccell.2023.07.020 (30 August 2023).

• Valiente M*, Sepúlveda JM, Pérez A (2023). Emerging targets for cancer treatment: SD1554/RAIM. EMBO Open, 10, 07351. (*) Corresponding author.

• Zhu L, Markou, Barra F, Pena-García M, Valiente M (2023). Protocol to generate mouse organotypic brain cultures for drug screening and evaluation of anti-metastatic efficacy. STAR Protoc. 4, 102194. (*) Corresponding author.
