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 that 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 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.

“Our ongoing projects are showing us that the untreatable nature of brain metastasis could be questioned by the identification of vulnerabilities that could be exploited therapeutically.”

RESEARCH HIGHLIGHTS

We reported the possibility to challenge brain metastasis by targeting altered molecular patterns present in pro-metastatic components of the microenvironment. During this year, we expanded our knowledge about the functional reprogramming affecting this metastasis-associated cell type (reactive astrocytes) as well as the benefits that it provides to cancer cells. This particular aspect has brought our attention to additional cell types in the microenvironment including microglia/macrophages and T cells that infiltrate the brain when affected by metastasis. The newly established networks among different components of the metastasis-associated microenvironment represent an active area of investigation in the laboratory since they are a novel source for therapeutic targets.

Given our unprecedented success obtained with a recent therapeutic strategy targeting the microenvironment both in experimental models and in patients with brain metastasis, we further explored the possibility of applying this rationale earlier in order to prevent brain metastasis instead of just treating it. We found a potential mechanism that could be inhibited right after metastatic cells crossed the blood-brain barrier and that has a major impact on experimental animals by preventing the formation of metastasis.

In addition, our newly developed drug-screen platform (METPlatform) has enabled us to identify new compounds with anti-metastatic activity that have been validated in vivo in experimental models and in patient-derived organotypic cultures.

Not only are we interested in developing new treatments, but we also try to understand why classic treatments, such as radiotherapy, do not provide greater benefits to patients. In this sense, we have identified a mechanism that could explain the low responses to this therapy in vivo and an inhibitor that could target it, thus increasing the anti-tumor effects with reduced radiation doses.

Figure (a) Targeting altered components of the microenvironment (astrocytes) and their related networks with other cellular components such as microglia/ macrophages or T cells. (b) METPlatform uses organotypic cultures to identify new potential anti-metastatic drugs. (c) Resistance to radiation could be reversed by a blood-brain barrier permeable compound.

• PUBLICATIONS
  - Wingrove E, Liu ZZ, Patel KD, Amed-Eisa T, Melnick A, Politi K, Monteiro C, Zhu L, Valiente M, Chiang VL, Nagano DK (2019). Transiently hyperplastic brain metastasis is partially due to the increasing number of systemic therapies that work extra-cranially but that are unable to provide the same therapeutic benefit in the brain.

• AWARDS AND RECOGNITION
  - EMBO Young Investigator Award.
  - Ana de Pablos Aragonese was recipient of a “la Caixa” MBIF VISIT Postdoctoral Fellowship.
  - Neliia Prigo received an AECC Probiotical Fellowship and a Spanish Society for Biochemistry and Molecular Biology (SEBBM) Award for the best publication of the year (2nd position).