MICROENVIRONMENT & METASTASIS JUNIOR GROUP

Héctor Peinado
Junior Group Leader

Staff Scientist
Susana García

Post-Doctoral Fellows
Marta Hergueta, Laura Nogués

Graduate Students
Elena Castellano, Teresa González, Alberto Hernández, Lucía Robado

Technicians
Sara Sánchez-Redondo, Vanesa Santos

Students in Practice
Eduardo Garvín (July-September)

OVERVIEW

Our Group aims to understand the crosstalk between tumour cells and their microenvironment during metastatic progression. Microenvironmental cues are important at all steps of the metastatic process, for which the recruitment of a variety of stromal cells is crucial. Secreted factors play an essential role in this mechanism including soluble factors and extracellular vesicles. These mechanisms of cell-cell communication have become as a *novel language* of cancer that we aim to decode. We are interested in: 1) understanding how tumour cells crosstalk with stromal cells involved in lymph node and distal metastasis in melanoma, lymphoma, prostate cancer and malignant peripheral nerve sheath tumours; 2) the influence of obesity in melanoma and breast cancer metastasis; and 3) the use of secreted extracellular vesicles (EVs) as surrogate markers of tumour progression. Our studies are focused on deciphering novel biomarkers of metastatic progression and the molecular mechanisms involved, with the aim to define novel therapeutic targets to block metastatic spread.

"We are interested in understanding how tumour cells corrupt the tumour microenvironment along metastatic progression and the main mechanisms involved, with the aim to develop novel anti-metastatic therapies."

(*Universidad Francisco de Vitoria*, Madrid, Spain), Ane Rubio (since September) (*Universidad Complutense de Madrid*, Madrid, Spain)

Visiting Scientists
Alberto Carretero (*Hospital Universitario 12 de Octubre*, Madrid, Spain), María Isabel Gónzalez (until March) (*Hospital Gregorio Marañón*, Madrid, Spain)

RESEARCH HIGHLIGHTS

Novel approaches in liquid biopsies

We are developing state-of the art technologies to implement EV-based liquid biopsies in the diagnosis and prognosis of patients with melanoma. We have found that the detection of BRAFV600E mutation in circulating EVs from the lymphatic exudate obtained post-lymphadenectomy can be used to identify melanoma patients at risk of relapse (FIGURE).

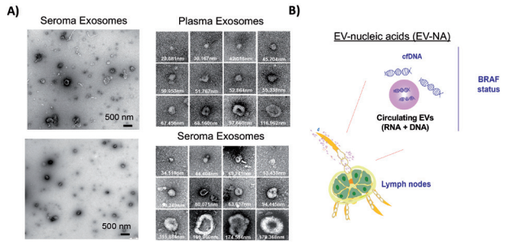

FIGURE Use of EVs in liquid biopsies. (**A**) Electron microscopy images of exosomes derived from plasma and exudative seroma from melanoma subjects. (**B**) Scheme of the analysis performed for the detection of BRAF mutations in EV nucleic acids (EV-NA) in EVs.

Novel mechanisms driving in local and distal metastasis

We are investigating the mechanisms involved in melanoma and prostate cancer metastasis. We found that nerve growth factor receptor (NGFR) is overexpressed in metastatic melanoma cells, secreted in EVs, and that it is shuttled to lymphatic endothelial cells inducing lymphangiogenesis and metastasis. We are also studying the use of NGFR inhibitors as a new strategy to block melanoma metastasis. Finally, we are defining the role of secreted EVs in prostate cancer lymph node metastasis.

Impact of high fat diet in metastasis

We are currently analysing how obesity influences metastasis through systemic and local changes in melanoma and breast cancer. We are interested in defining how obesity impacts breast cancer lung metastasis by reinforcing pro-coagulant activities. We are testing novel approaches to reduce tumour-platelet interactions and develop anti-metastatic therapies.

We are also analysing how adipose tissue reinforces melanoma metastasis by promoting tumour cell homing and metastatic behaviour.

Tumour-stroma interactions in metastasis

We are studying how alterations in the lymph node microenvironment influence lymphoma progression. We are analysing the role of NGFR in lymph node stromal cells and its influence in follicular lymphoma. We are also exploring novel therapeutic strategies against malignant peripheral nerve sheath tumours (MPNSTs). We are currently testing a combination therapy with MEK inhibitors and anti-angiogenic antibodies as a novel treatment for MPNSTs. ■

PUBLICATIONS

- Hoshino A *et al.* (incl. Peinado H) (2020). Extracellular vesicle and particle biomarkers define multiple human cancers. *Cell* 182, 1044-1061.
- Fuentes P, Sesé M, Guijarro PJ, Emperador M, Sánchez-Redondo S, Peinado H, Hümmer S, Ramón Y Cajal S (2020). ITGB3-mediated uptake of small extracellular vesicles facilitates intercellular communication in breast cancer cells. *Nat Commun* 11, 4261.
- Martinez-Lage M, Torres-Ruiz R, Puig-Serra P, Moreno-Gaona P, Martin MC, Moya FJ, Quintana-Bustamante O, Garcia-Silva S, Carcaboso AM, Petazzi P, Bueno C, Mora J, Peinado H, Segovia JC, Menendez P, Rodriguez-Perales S (2020). In vivo CRISPR/Cas9 targeting of fusion oncogenes for selective elimination of cancer cells. *Nat Commun* 11, 5060.
- Toda H *et al.* (incl. Peinado H) (2020). Plasma-derived extracellular vesicles from Plasmodium vivax patients signal spleen fibroblasts via NF-kB facilitating parasite cytoadherence. *Nat Commun* 11, 2761.
- Colletti M *et al.* (incl. Peinado H) (2020). Neuroblastoma-secreted exosomes carrying miR-375 promote osteogenic differentiation of bone-marrow mesenchymal stromal cells. *J Extracell Vesicles* 9, 1774144.
- Hergueta-Redondo M, Peinado H (2020). The influence of secreted factors and extracellular vesicles in ovarian cancer metástasis. *EJC (Supplements)* 15, 38-48.
- Palacios-Ferrer JL *et al.* (incl. Peinado H) (2020). Metabolomic profile of cancer stem cell-derived exosomes from patients with malignant melanoma. *Mol Oncol*. PMID: 33052601.
- Galardi A *et al.* (incl. Peinado H) (2020). Proteomic profiling of retinoblastoma-derived exosomes reveals potential biomarkers of vitreous seeding. *Cancers (Basel)* 12, 1555.
- Ma W, Gil HJ, Escobedo N, Benito-Martín A, Ximénez-Embún P, Muñoz J, Peinado H, Rockson SG, Oliver G (2020). Platelet factor 4 is a biomarker for lymphatic-promoted disorders. *JCI Insight* 5, e135109.