MELANOMA GROUP

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OVERVIEW

Melanomas are prime examples of aggressive diseases where basic and translational research have significantly improved patient prognosis. Nevertheless, clinical responses are still incomplete. The long-term goals of our Group are to identify new progression biomarkers and therapeutic agents. We are particularly interested in mechanisms of cellular stress that, being selectively deregulated in melanoma, define lineage-specific vulnerabilities (publications in Nature, Cancer Cell, Nature Cell Biology, Nature Communications, among others).

Our laboratory has also reported first-in-class lymphoreporter (MetAlert) mice for non-invasive imaging of pre-metastatic niches in melanoma (Nature). These systems have led to the identification of new mechanisms of immune resistance (Nature Medicine) and the generation of nanoparticle-based treatments (Cancer Cell, EMBO Mol Med), with derivatives now being tested in clinical trials. Our ultimate objective is to improve the management of patients with otherwise refractory metastatic melanomas.

“We have visualised and targeted (pre)metastatic niches in melanoma and defined mechanisms of immune suppression with clinical implications for cancer patients.”
The long-term goals of our Group are to (see FIGURE 1): 1. Define the “fingerprint” that distinguishes melanomas from other cancer types. 2. Visualise and target melanoma progression at the whole body level in vivo. 3. Determine and target signalling cascades that turn immunologically “hot” melanomas into “cold” and refractory tumours. 4. Develop new therapeutic strategies to overcome immune suppression and immune tolerance in melanoma.

New tumour drivers that favour melanoma progression

One of the long-term objectives of our Group is to discover novel melanoma drivers. We have previously identified endolysosomal-associated genes (BART7 and RNA binding proteins (CEFL1, CUGBP1 and IGF2BP1) with lineage-specific endolysosomal genes (RAB7) and RNA binding proteins and various immune modulators. In particular, our ability to mine large tumour datasets has helped us to describe immune suppressive roles of EL22 favouring lung metastasis (Brukhovetskia et al., Immunity 2022).

Impact of the melanoma secretome in the rewiring of the immune system towards tumour-promoting phenotypes

Melanomas are a prime example of tumours quite efficient at bypassing antigen presentation and promoting immunologically “cold” or tolerogenic phenotypes, but the underlying mechanisms are not well understood. Analysing downstream effectors, we found new immune suppressive roles of this protein, whereby macrophages are recruited to tumours, but instead of attacking the cancer cells, promote dysfunctional CD8+ T cells (Cerezo-Wallis et al., Nat Medicine 2020). More recently, we discovered that MDK acts as a multifaceted suppressor of antigen presentation. Mechanistically, MDK was found to repress all main aspects of the differentiation, activation, and function of dendritic cells (DCs), particularly of conventional type 1 (cDCs). Moreover, we uncovered an MDK-associated signature in DCs that defines bad prognosis and resistance to immune checkpoint blockers actively used in human patients (FIGURE 2). MDK-associated downregulation of cDC1-dependent immune scores were also identified in a variety of other tumour types, further emphasising the translational relevance of MDK as a target to boost antigen presentation in otherwise immune refractory cancers (Catena et al., BioRxiv 2022; Catena et al., submitted).

In light of the tumour-promoting and immune-suppressive roles of MDK, we are actively pursuing this protein as a therapeutic target. We have previously reported dsRNA mimetics that repress MDK mRNA expression (Olmeda et al., EMBO Mol Med 2021) and are now developing small molecule inhibitors and blocking antibodies.

• PUBLICATIONS


• AWARDS AND RECOGNITION

  • Excellence in Science Award by the Colegio de Biólogos y Biólogas de Galicia, Spain.

  • International Award in Oncology, Ramón Carague Foundation, Spain. Leadership in Science Award (“Premio Liderando en Ciencia”), Comunidad Autónoma de Madrid, Spain.

  • President, Spanish Association for Cancer Research (Asociación Española de Investigación de Cáncer, AEICCA).

  • Elected EMBO Member.

  • Top 100 Women Leaders in Spain, Mapfre & Cía.