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."

RESEARCH HIGHLIGHTS

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 (RAB7) and RNA binding proteins (CEFL1, CUGBP1 and IGF2BP1) with lineage-specific protumorigenic functions that are not shared by over 25 cancer types (Alonso-Curbelo *et al.*, *Cancer Cell* 2014; García-Fernández *et al.*, *Autophagy* 2016; Perez-Guijarro *et al.*, *Nat Commun* 2016; Cifdaloz *et al.*, *Nat Commun* 2017; Karras *et al.*, *Cancer Cell*, 2019). In addition, we have pursued melanoma-secreted factors that exert long-range activities, particularly in the generation of premetastatic niches. A prime interest of our Group has been modulators of neolymphangiogenesis, as this is an early stage in melanoma dissemination. Exploiting "lymphoreporter" models generated by Sagrario Ortega's Group at CNIO, we developed the first *"Melanoma-MetAlert"* mice. These animals have the unique feature of allowing for spatio-temporal analyses of tumour-activated lymphangiogenesis *in vivo* as a way to define premetastatic niches (Olmeda *et al.*, *Nature* 2017). *'MetAlert'* animals, in combination with human tissue specimens, revealed the growth factor MIDKINE (MDK) as a new melanoma driver with a potent ability to act in a systemic manner to promote neolymphangiogenesis and melanoma metastasis (Olmeda *et al.*, *Nature* 2017). Our expertise in lymphangiogenesis also contributed to collaborative studies to define an unexpected crosstalk of lymphatic genes with lipid metabolism and autophagy (Mece *et al.*, *Nat Commun* 2022). In the course of these studies, we generated computational tools and experimental models that have served to characterise novel dsRNA binding proteins and various immune modulators. In particular, our ability to mine large tumour datasets has helped us to describe immune suppressive roles of IL22 favouring lung metastasis (Briukhovetska *et al.*, *Immunity* 2023).

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 of MDK, 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 (cDC1). 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. ■

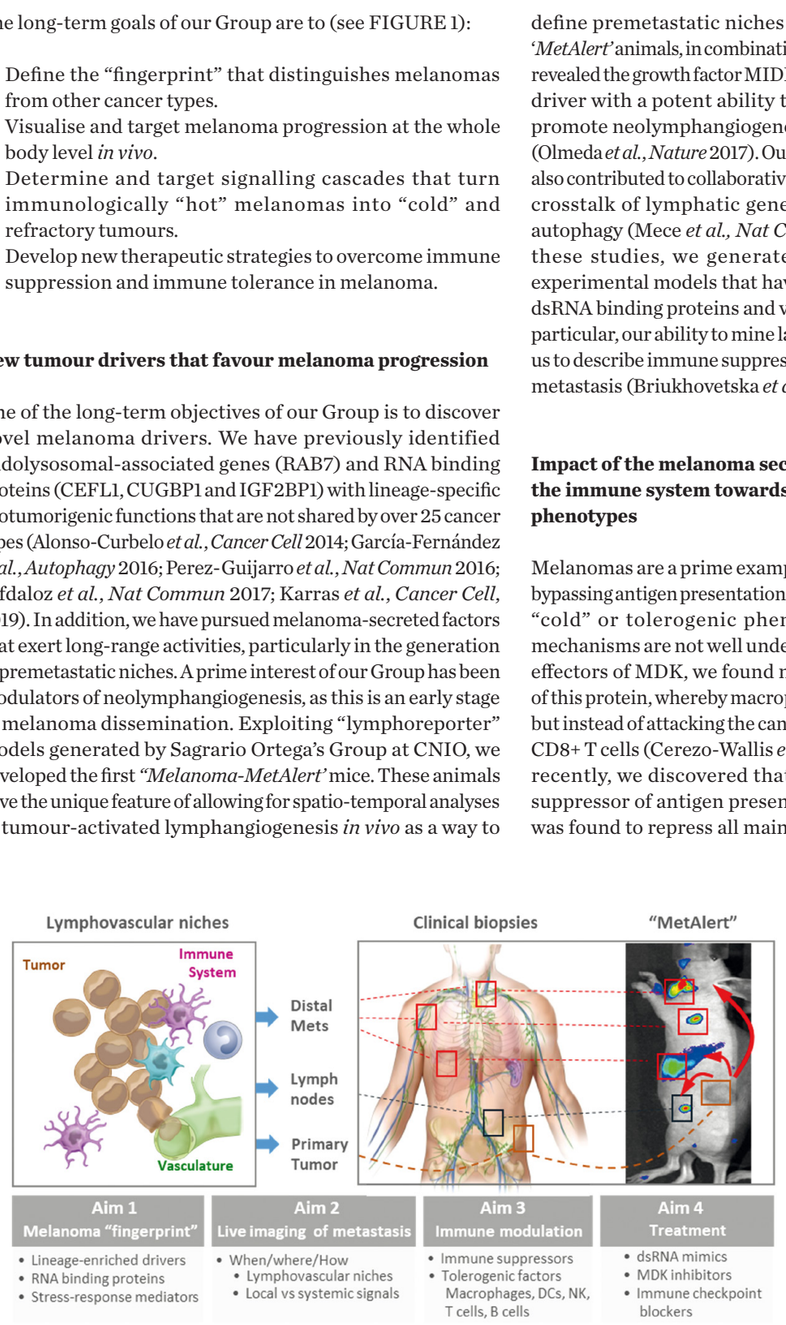

FIGURE 1 Melanoma Group at glance: main aims and experimental models to identify new tumour drivers and therapeutic targets, with a particular emphasis on the crosstalk between lymphatic vasculature and the immune system.

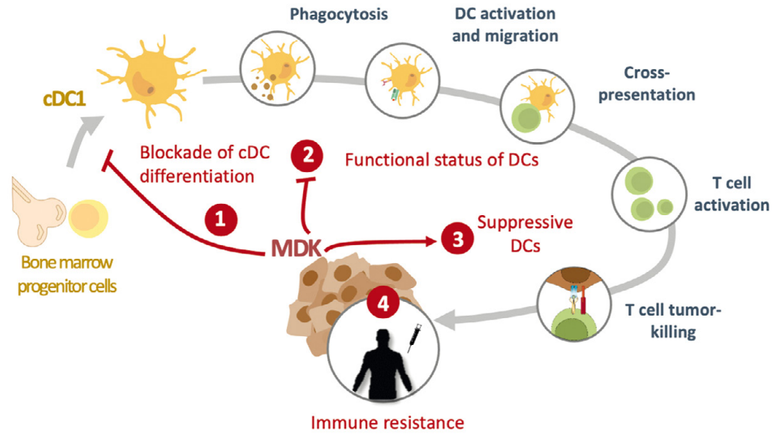

FIGURE 2 Multi-stage rewiring of dendritic cell (DC) differentiation and function by tumour-secreted Midkine (MDK). MDK was found to block DC differentiation and impair all main DC associated functions (phagocytosis, activation, cross-presentation, and T cell activation), shifting DCs into suppressive features. Ultimately, these DC-driven effects reduce the efficacy of immune-based therapies.

PUBLICATIONS

- Marine JC, Soengas MS (2022). Cell position matters in tumour development. *Nature* 604, 248-250.
- Briukhovetska D, Suarez-Gosalvez J, Voigt C, Markota A, Giannou AD, Schübel M, Jobst J, Zhang T, Dörr J, Märkl F, Majed L, Müller PJ, May P, Gottschlich A, Tokarew N, Lücke J, Oner A, Schwerdtfeger M, Andreu-Sanz D, Grünmeier R, Seifert M, Michaelides S, Hristov M, König LM, Cadilha BL, Mikhaylov O, Anders HJ, Rothenfusser S, Flavell RA, Cerezo-Wallis D, Tejedo C, Soengas MS, Bald T, Huber S, Endres S, Kobold S (2022). T cell-derived interleukin-22 drives the expression of CD155 by cancer cells to suppress NK cell function and promote metastasis. *Immunity*. PMID: 36630913.
- Meçe O, Houbaert D, Sassano ML, Durré T, Maes H, Schaaf M, More S, Ganne M, García-Caballero M, Borri M, Verhoeven J, Agrawal M, Jacobs K, Bergers G, Blacher S, Ghesquière B, Dewerchin M, Swinnen JV, Vinckier S, Soengas MS, Carmeliet P, Noël A, Agostinis P (2022). Lipid droplet degradation by autophagy connects mitochondria metabolism to Prox1-driven expression of lymphatic genes and lymphangiogenesis. *Nat Commun* 13, 2760.
- Catena X, Contreras-Alcalde M, Cerezo-Wallis D, Juan-Larrea D, Olmeda D, Calvo TG, Mucientes C, Oterino S and Soengas MS (2022). Systemic effects of melanoma-secreted MIDKINE in the inhibition of dendritic cell differentiation and function. *BioRXiv*. doi: https://doi.org/10.1101/2022.12.28.521901.

AWARDS AND RECOGNITION

- Excellence in Science Award by the *Colegio de Biólogos y Biólogas de Galicia*, Spain.
- International Award in Oncology, *Ramiro Carregal* 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 Contra el Cáncer, ASEICA*).
- Elected EMBO Member.
- Top 100 Women Leaders in Spain, *Mujeres & Cia*.