MELANOMA GROUP

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OVERVIEW

Melanomas are a prime example of how basic and translational research has been translated into improved prognosis for affected patients. Nevertheless, clinical responses are still incomplete. The long-term goals of our Group are to identify new progression biomarkers and therapeutic agents. Focusing on stress response programmes involving apoptosis, autophagy and endosome mobilisation, we have discovered lineage-specific oncogenes that define the melanoma 'fingerprint'. Transcriptomic and proteomic analyses of the melanoma secretome have enabled us to define how tumour cells remodel the (lymph)angiogenic vasculature and avoid immune recognition. Moreover, we have generated a unique set of animal models for non-invasive imaging of melanoma progression *in vivo*. These systems have led to the validation of nanoparticle-based treatments that are currently being tested in clinical trials. Our ultimate objective is to improve the management of patients with otherwise refractory metastatic melanomas.

"Combining a series of –omic studies with *in vivo* imaging in mouse models, we have identified a melanoma-associated signature of prometastatic genes that make this tumour uniquely aggressive."

RESEARCH HIGHLIGHTS

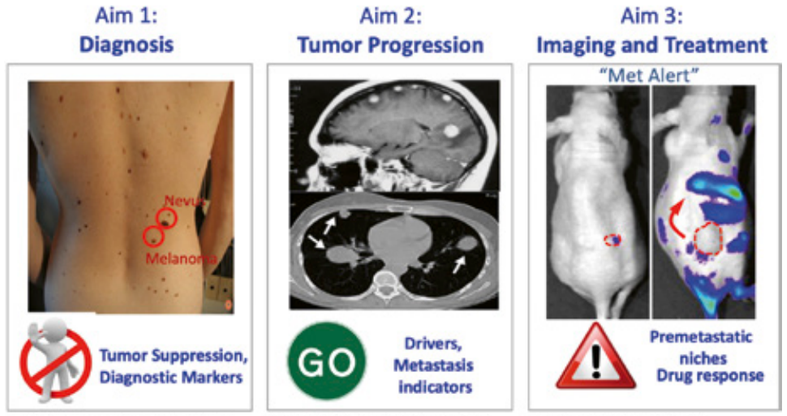

Figure 1 Main objectives of the CNIO Melanoma Group aimed to identify new progression biomarkers and validate more efficient anticancer agents. Indicated are main experimental systems and representative publications.

CNIO Melanoma Group: objectives and model systems

Melanomas are aggressive solid tumours and provide a prime example of how integrated basic and clinical research has significantly improved patient prognosis. Nevertheless, despite great successes achieved with targeted and immune-based therapies, sustained clinical responses are still limited. Moreover, the field lacks molecular markers of diagnosis, and the knowledge on how melanomas progress and metastasise is largely incomplete. In addition, one of the main hurdles to advance in this disease is the lack of animal models to monitor melanoma initiation and progression *in vivo*. To this end, our Group focuses on 3 main objectives (FIGURE 1):

- → **Aim 1.** Oncogenic pathways selectively deregulated in melanoma that may represent new diagnostic indicators.
- → **Aim 2.** Risk factors and prognostic markers.
- → **Aim 3.** Animal models that allow for non-invasive monitoring of pre-metastatic niches.

Lineage-specific oncogenic dependencies in melanoma

One of the long-term objectives of the Melanoma Group is to discover **new melanoma drivers**. We have previously identified a cluster of endolysosomal-associated genes that distinguish melanoma from over 35 additional malignancies (Alonso-Curbelo *et al.*, *Cancer Cell* 2014). Further analyses of lysosomal-dependent pathways also revealed unique features of autophagy genes (ATG5) in melanoma (García-Fernández *et al.*, *Autophagy* 2016). Other melanoma-enriched regulatory mechanisms were identified by focusing on RNA binding proteins (RBPs). We selected RBPs because they are largely unexplored in melanoma. Performing a series of genome wide studies, we found novel roles of the RBPs CPEB4 and CUGBP1 in the modulation of mRNA stability, with targets involving master specifiers of the melanocyte lineage (Perez-Guijarro *et al.*, *Nat Commun* 2016; Cifdaloz *et al.*, *Nat Commun* 2017).

Most recently, we identified additional RBPs in a screen for modulators of melanoma progression. Specifically, we discovered a selected set of RBPs as unexpected binding partners of p62/SQSTM1, a factor we had selected for analysis based on previous reports in the literature linking this protein to autophagy. However, proteomic, transcriptomic and interactomic analyses showed that p62 was largely dispensable for autolysosome maturation in melanoma cells, again differentiating this disease from other tumour types. Instead, we found that p62 acts via a subset of RBPs, exemplified by CUGBP1, as a global coordinator of mRNA half-life of a spectrum of pro-metastatic factors. These include FERMT2 and other transcripts with no previous links to melanoma (FIGURE 2). The relevance of these data is emphasised by follow-up analyses of patient prognosis revealing p62 and FERMT2 as adverse determinants of disease-free survival. These studies were recently published in *Cancer Cell* (*Cancer Cell*, 2019), and were spotlighted on the cover of the journal.

'MetAlert' mice for the visualisation of premetastatic niches in melanoma and as a platform for gene discovery and target validation

We have also made great progress in regards to one of the most pressing needs in the melanoma field, namely, the mechanisms that enable melanoma cells to disseminate already from lesions of barely 1 mm in depth. Last year, we reported a series of mouse models of melanoma that have the unique feature of revealing how these cells act 'a distance' from very early stages of tumour development, activating the lymphatic vasculature and preparing metastatic niches before their colonisation (Olmeda *et al.*, *Nature* 2017). These 'MetAlert' animals, together with histological validation in patient biopsies, revealed the growth factor MIDKINE as a new driver of lymphangiogenesis and melanoma metastasis. We have now exploited the MetAlert mice for pharmacological analyses of anticancer agents. These studies revealed the dsRNA-based mimic BO-112 as potent blockers of neolymphangiogenesis and melanoma metastasis (Olmeda *et al.* in preparation). BO-112, a derivative of the polyplex BO-110 generated at the CNIO, is now being tested in Phase I clinical trials. ■

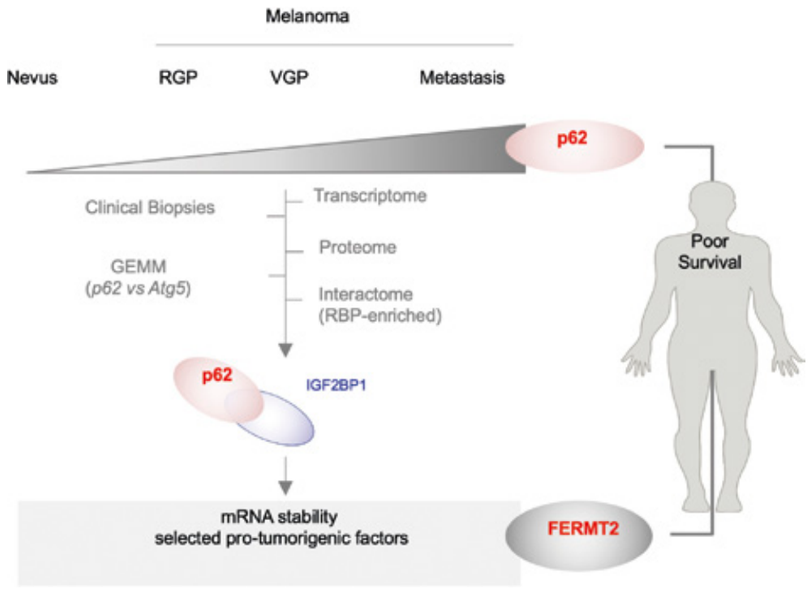

Figure 2 New functions for pro-metastatic drivers in melanoma. Schematic representation of a set of pro-tumourigenic factors with no previous links to melanoma identified by addressing the expression and functional requirement of p62/SQSTM1 in this disease. Different from roles of p62 in autophagy described in a broad spectrum of types, this protein was found in melanoma to bind a selected set of RNA binding proteins (RBPs), here exemplified by CUGBP1. -Omic studies in cell lines combined with histopathological studies in genetically modified mouse models (GEMM) and histopathological validation in clinical biopsies identified the scaffolding factor FERMT2 as a downstream target of the p62-CUGBP1 axis. Both, p62 and FERTM2 were found overexpressed in advanced melanomas, representing new indicators of poor prognosis.

PUBLICATIONS

- Karras P, Riveiro-Falkenbach E, Cañón E, Tejedo C, Calvo TG, Martínez-Herranz R, Alonso-Curbelo D, Cifdaloz M, Perez-Guijarro E, Gómez-López G, Ximenez-Embun P, Muñoz J, Megias D, Olmeda D, Moscat J, Ortiz-Romero PL, Rodríguez-Peralto JL, Soengas MS (2018). p62/SQSTM1 Fuels melanoma progression by opposing mRNA decay of a selective set of pro-metastatic factors. *Cancer Cell*. PMID: 30581152.
- Martinez-Useros J, Moreno I, Fernandez-Aceñero MJ, Rodriguez-Remirez M, Borrero-Palacios A, Cebrian A, Gomez Del Pulgar T, Del Puerto-Nevado L, Li W, Puime-Otin A, Perez N, Soengas MS, Garcia-Foncillas J. (2018). The potential predictive value of DEK expression for neoadjuvant chemoradiotherapy response in locally advanced rectal cancer. *BMC Cancer* 18, 144.
- Bagati A, Moparthy S, Fink EE, Bianchi-Smiraglia A, Yun DH, Kolesnikova M, Udartseva OO, Wolff DW, Roll MV, Lipchick BC, Han Z, Kozlova NI, Jowdy P, Berman AE, Box NF, Rodriguez C, Bshara W, Kandel ES, Soengas MS, Paragh G, Nikiforov MA (2018). KLF9-dependent ROS regulate melanoma progression in stage-specific manner. *Oncogene*. PMID: 30664687.
- García-Rodríguez S, Rosal-Vela A, Botta D, Cumba Garcia LM, Zumaquero E, Prados-Maniviesa V, Cerezo-Wallis D, Lo Buono N, Robles-Guirado JÁ, Guerrero S, González-Paredes E, Andrés-León E, Corbí Á, Mack M, Koch-Nolte F, Merino R, Zubiaur M, Lund FE, Sancho J (2018). CD38 promotes pristane-induced chronic inflammation and increases susceptibility to experimental lupus by an apoptosis-driven and TRPM2-dependent mechanism. *Sci Rep* 8, 3357.

PATENT

- Soengas González MS, Olmeda Casadome D, Cerezo Wallis D (2018). MDK inhibitors for overcoming cancer resistance to immunotherapy. *EP18382494.5.*

AWARDS AND RECOGNITION

- Coordinator, *ASEICA-Mujer* (Spanish Association for Research Against Cancer).
- Top100 "Mujeres Líderes de España", *Mujeres & Cía*.
- *Placa de Honor* 2018, *Asociación Española de Científicos*.
- Most influential female scientists and clinical doctors-2018, *Yo Donna/El Mundo*.
- Founding Member, "Influential Woman from Galicia", WomenTalent.