Melanomas are inherently aggressive cancers for which 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. 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.

“We have identified oncogenic cascades that are uniquely deregulated in melanoma and as such, may represent novel targets for therapeutic intervention.”
CENIO Melanoma Group: objectives and model systems

Melanomas are aggressive solid tumours and provide a prime example of how integrated basic and clinical research have significantly improved patient prognosis. Yet, despite great success with targeted and immune-based therapies, sustained clinical responses are still limited. Moreover, the field lacks molecular markers of diagnosis, and the knowledge of how melanomas progress and metastasise is still largely incomplete. Therefore, these questions represent key unmet needs, as emphasised by a committee of experts in which M. Soengas participates (Merlino et al., Pigment Cell Melanoma Res 2016). In addition, one of the main hurdles slowing progress 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 areas of research (FIGURE 1):

→ Aim 1. Oncogenic pathways, which are selectively deregulated in melanoma and may represent new diagnostic indicators.

→ Aim 2. Risk factors and prognostic markers that underlie the unique ability of melanoma to metastasise from seemingly thin lesions.

→ Aim 3. Animal models that allow for non-invasive monitoring of premalignant niches, and as such, may serve as a platform for cost-effective genetic and pharmacological screens.

Lineage-specific oncoprogenic dependencies in melanoma

One of the long-term objectives of the Melanoma Group is the discovery of new melanoma drivers. We previously identified a cluster of endosomal-associated genes that distinguish melanoma from over 35 additional malignancies (Akonso-Curboelo et al., Cancer Cell 2014 and Oncotarget 2015). In collaboration with the group of P. Agostinis (University of Leuven, Belgium), we further explored therapeutically-relevant regulatory mechanisms and functions of the endosomal machinery in different cell types (Masi et al., FERS 2016). More recently, we also discovered unique features of autophagy (another key lysosomal-associated process) in melanoma. Employing human melanoma biopsies, combined with newly-generated mouse models, we identified selective heterozygous losses of ATG5 as a new risk factor for melanoma progression and as a main mediator of the resistance to targeted therapy (García-Fernández et al., Autophagy 2016).

RNA binding proteins and RNA-based anticancer agents in the control of melanoma cell proliferation and metastasis

Melanomas are long known for being associated with a plethora of changes in mRNA gene expression profiles. Still, the specific contribution of RNA binding proteins (RBPs), particularly, splicing modulators, remains virtually unexplored in this disease. We have identified tumour-selective roles of RBPs in melanoma defined by selective allelic loss of ATG5. Autophagy 12, 178-179. Pérez-Guzmán, E., Karnes, P., Hernández-Barriga, C., et al., (2016). The state of melanoma: challenges and opportunities. Pigment Cell Melanoma Res. 29, 404-411.

We have also made great progress regarding one of the most pressing needs in the field of melanoma, namely, the mechanisms underlying immune suppression (reviewed in Carera-Walls and Soengas, Curr Pharm Design 2016). This was achieved by combining the analysis of human melanoma biopsies with a new class of ‘Lymphoreporter’ mouse models that we generated in collaboration with Sagrario Ortega’s Transgenic Mouse Unit at the CNIO. Moreover, we have expanded the use of dsRNA nanoparticles as immunomodulatory agents. This information will be used to support clinical trials that are currently being performed by Biosense Therapeutics, a biotechnology company co-founded by M. Soengas.

CPEB4 and CUGBP1 in the regulation of mRNA stability, with unexpected targets involving master specifiers of the melanocyte lineage (FIGURE 2). We have also assisted F. Gebauer’s laboratory (the Centre for Genomic Regulation, Barcelona) with the identification of pro-metastatic roles of the translation regulator UNR in melanoma (Wurth et al., Cancer Cell 2016). Similarly, histopathological studies with our long-term collaborators, P. Ortiz-Romero and J.L. Rodríguez-Peralto (Hospital 12 de Octubre, Madrid), have validated the chromatin remodeler and RNA binding factor DEK as a risk factor for melanoma metastasis (Rivero-Falkenbalk, Pigment Cell Melanoma Res 2016).

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