HEREDITARY ENDOCRINE CANCER GROUP

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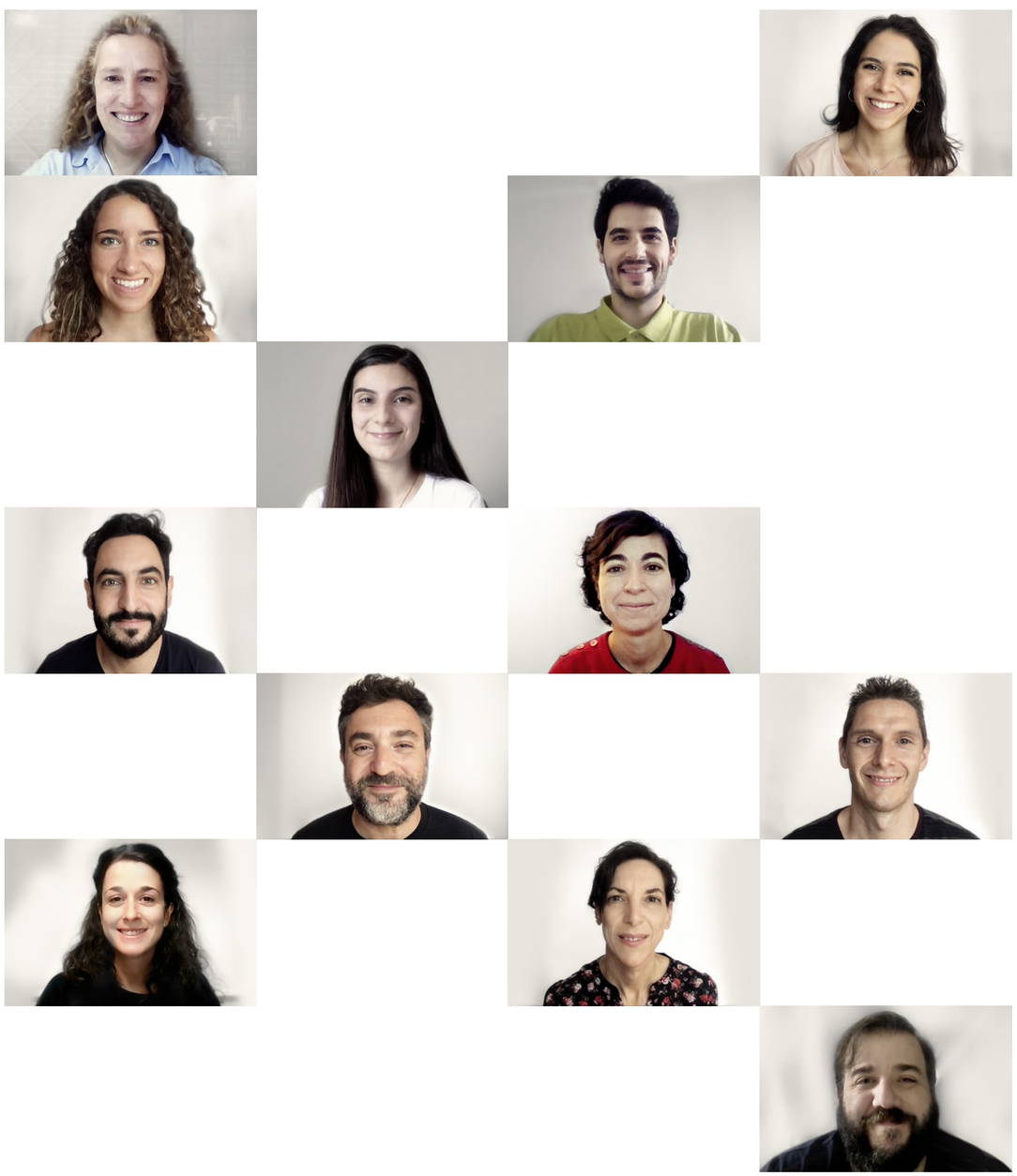
**Plan de Empleo Joven de la Comunidad de Madrid* (Youth Employment Plan, Community of Madrid)

***Titulado Superior* (Advanced Degree)



OVERVIEW

Our Group is mainly interested in identifying genetic risk factors involved in endocrine tumour susceptibility. Through a comprehensive analysis of tumour genomic features, we have been able to propose diagnostic and prognostic markers, to identify altered pathways that could be therapeutically targeted, and to identify new major susceptibility genes.

We are also interested in defining markers associated with differences in anticancer drug response and toxicity. We are applying targeted and whole-exome next-generation sequencing to a large series of clinically well-characterised patients. The aim is to identify new therapeutic approaches to personalise cancer treatment. These efforts will collectively improve the diagnosis, prognosis, and treatment of patients.

"We identified a miR-483-5p/ALCAM axis as a new player in pheochromocytoma at the metastatic niche and showed that mTOR pathway mutations correlate with poor prognosis in chromophobe renal cell carcinoma."

RESEARCH HIGHLIGHTS

mTOR pathway alterations in chromophobe renal cell carcinoma associated with poor outcome

Chromophobe renal cell carcinoma (chRCC) is a histologically and molecularly distinct class of rare renal tumour. Knowledge on drug targets is limited and treatments do not follow a molecular rationale. In the largest series of chRCC (n=92) so far, we performed an in-depth characterisation of the mTOR pathway through targeted NGS and immunohistochemistry (Roldán-Romero *et al.*, 2020). Furthermore, we investigated mutations in the electron transport chain Complex I genes by developing a bioinformatics approach able to identify mitochondrial variants using NGS off-target data (Lanillos *et al.*, 2020). Mutations in key components of the mTOR pathway (MTOR, TSC1, TSC2) occurred in 17% of primary tumours and were associated with the immunohistochemistry staining of phospho-S6 and PTEN, and with chRCC eosinophilic variant, supporting their biological relevance. Patients with mTOR pathway mutations had worse outcomes (overall survival: HR=5.5 and P=0.027; confirmed in TCGA with HR=10.3, P=0.006), and mutations in TP53 and telomere maintenance genes were enriched in metastatic cases. Overall, we showed that mTOR pathway mutations correlate with poor prognosis in chRCC, suggesting that mTOR inhibitors might be a good therapeutic option for patients with these alterations.

Overexpression of miR-483-5p is confined to metastases and linked to high circulating levels in pheochromocytoma/paraganglioma patients

Pheochromocytoma/paraganglioma (PPGLs) are rare neuroendocrine tumours. Approximately 15% of PPGL patients present with metastasis at diagnosis or over a long period after resection of the primary tumour, and there is a lack of prognostic molecular tumour markers that may improve the risk stratification. A comprehensive characterisation of miRNA profiles in primary tumours, metastases and liquid biopsies of PPGL patients, allowed us to identify high expression levels of miR-483-5p in metastatic tissues versus matched primary tumours (P=6.5 x 10-4), and in the serum of metastatic patients compared to non-metastatic cases (P=2.0 x 10-3). Moreover, circulating miR-483-5p discriminated metastatic patients with high accuracy (AUC=0.81, 95%CI=0.651-0.972, P=4.0 x 10-3). Integrative analyses of transcriptome data suggest that miR-483-5p plays a role in angiogenesis, wound healing and extracellular matrix organisation, while it regulates ALCAM expression in metastatic PPGL (FIGURE). ALCAM/CD166 is member of a subfamily of immunoglobulin receptors that promotes T-cell activation and proliferation via its interaction with CD6 and is involved also in the processes of cell adhesion and migration. It has been reported that ALCAM expression decreases with the progression of numerous tumours, which entails a poor prognosis. In fact, ALCAM-ALCAM interaction is dynamically regulated to turn tumour cells from a benign to a malignant phenotype by disrupting cell-cell adhesion and enabling tumour cell invasion and metastasis. In this regard, we observed a lower expression of ALCAM in metastases than in primary tumours (as opposed to miR-483-5p) in the published PPGL series, as well as in the whole TCGA PANCAN cohort extracted from the UCSC Xena browser (n=396 metastatic tissues and n=9712 primary tumours; P=5.8 x 10^{-102}). Importantly, previous reports demonstrated that miR-483-5p directly binds ALCAM and regulates its expression in lung and in liver cancer. Hence, the functional interaction miR-483-5p/ALCAM may shed light on the understanding of PPGL metastatic niche and warrants further investigation. The main conclusion of the study is that overexpression of miR-483-5p is linked to metastatic colonisation, and pinpoints circulating levels as a promising biomarker of metastatic PPGL. ■

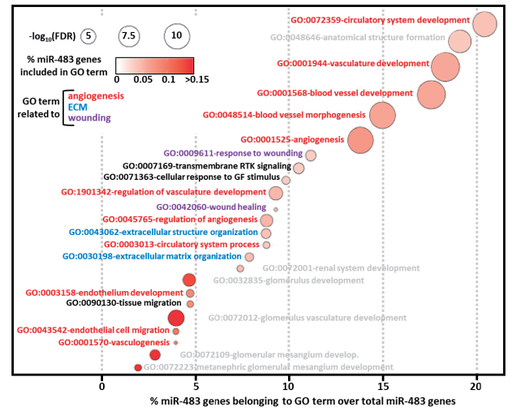


FIGURE Functional enrichment and integrative analysis reveal a link between miR-483-5p and angiogenesis, wounding and extracellular matrix differential traits, and uncovers miR-483-5p/*ALCAM* as new player in PPGL metastatic niche. Diameter of bubbles indicates the % of genes correlated with miR-483-5p levels (miR-483 genes) included in each specific GO term. Diameter is proportional to the -$\log_{10}$(FDR); X axis shows the % miR-483 genes present in each GO term over the total of miR-483 genes. GO terms: in red, genes related to angiogenesis; in blue, extracellular matrix (ECM); and in purple, wounding.

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AWARDS AND RECOGNITION

Cristina Rodríguez-Antona:

- Vice President of the Spanish Society of Pharmacogenetics and Pharmacogenomics, Spain.
- Vice-Chair of the Expert Panel of CYP3A4 and CYP3A5, the international Pharmacogene Variation Consortium (PharVar).
- Member of the Working Group in Precision Medicine, the *Asociación de Medicina de la Industria Farmacéutica en España*, Spain.