

HEREDITARY ENDOCRINE CANCER GROUP

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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 *PARP1* expression and *PBRM1* mutations as predictive markers of progression free survival in patients with clear cell renal cell carcinoma. In thyroid cancer, telomere shortening leads to a reorganisation of the 5p subtelomeric region, facilitating the accumulation of alterations at the *TERT*-locus.”

RESEARCH HIGHLIGHTS

Massive sequencing technologies to advance pharmacogenomics knowledge

Next generation sequencing technologies have boosted the discovery and clinical implementation of novel markers of drug treatment response. We illustrate this with 2 contributions:

i) Generation of a comprehensive germline landscape of pharmacogenetic actionable variants contained in diagnostic exomes. In this study, we analysed data from 5001 individuals who underwent exome sequencing for genetic diagnosis to provide population frequencies of clinically relevant pharmacogenetic alleles and to estimate the contribution of novel loss-of-function variants.

ii) Identification of *PARP1* expression and *PBRM1* mutation as predictive biomarkers in patients with clear cell renal cell carcinoma. Through analysis of genomic, transcriptomic, and clinical data of the IMmotion151 trial in patients treated with atezolizumab plus bevacizumab or sunitinib, we found that tumour *PARP1* expression was a predictor of progression-free survival regardless of treatment arm, while *PBRM1* mutations exerted an interaction only with sunitinib treatment (FIGURE 1).

Comprehensive molecular analysis of immortalisation hallmarks in thyroid cancer reveals new prognostic markers

Around 1 in 2000 individuals in Spain develop thyroid cancer fatal disease. Comprehensive molecular studies on thyroid tumours are needed to identify prognostic molecular

biomarkers that will allow the early detection, and thus the personalised management and follow-up, of this rare but life-threatening cancer. We extensively characterised cancer immortalisation-related alterations in a series of 106 thyroid tumours enriched with clinically-aggressive carcinomas to define disease prognostic markers. Using a custom-designed RNA-seq panel, we identified 5 telomerase holoenzyme-complex genes over-expressed in clinically-aggressive tumours compared to tumours from long-term disease-free patients, with *TERT* and *TERC* denoted as independent prognostic markers by multivariate regression model analysis. Characterisation of alterations related to *TERT* re-expression revealed that promoter mutations, hypermethylation and/or copy gains exclusively co-occurred in clinically-aggressive tumours. Quantitative-FISH analysis of telomere lengths showed a significant shortening in these carcinomas, which matched with a high proliferative rate measured by Ki-67 immunohistochemistry. RNA-seq data analysis indicated that short-telomere tumours exhibit increased transcriptional activity in the 5 Mb-subtelomeric regions, site of several telomerase-complex genes. Gene upregulation enrichment was significant for specific chromosome-ends such as the 5p, where *TERT* is located. Co-FISH analysis of 5p-end and *TERT* loci showed a more relaxed chromatin configuration in short telomere-length tumours compared to normal telomere-length tumours. Overall, our findings support that telomere shortening leads to a reorganisation of the 5p subtelomeric region, facilitating the transcription and accumulation of alterations at the *TERT*-locus, and unveil a FISH-based assay as a potential cytogenetic tool to predict disease prognosis in thyroid cancer. ■

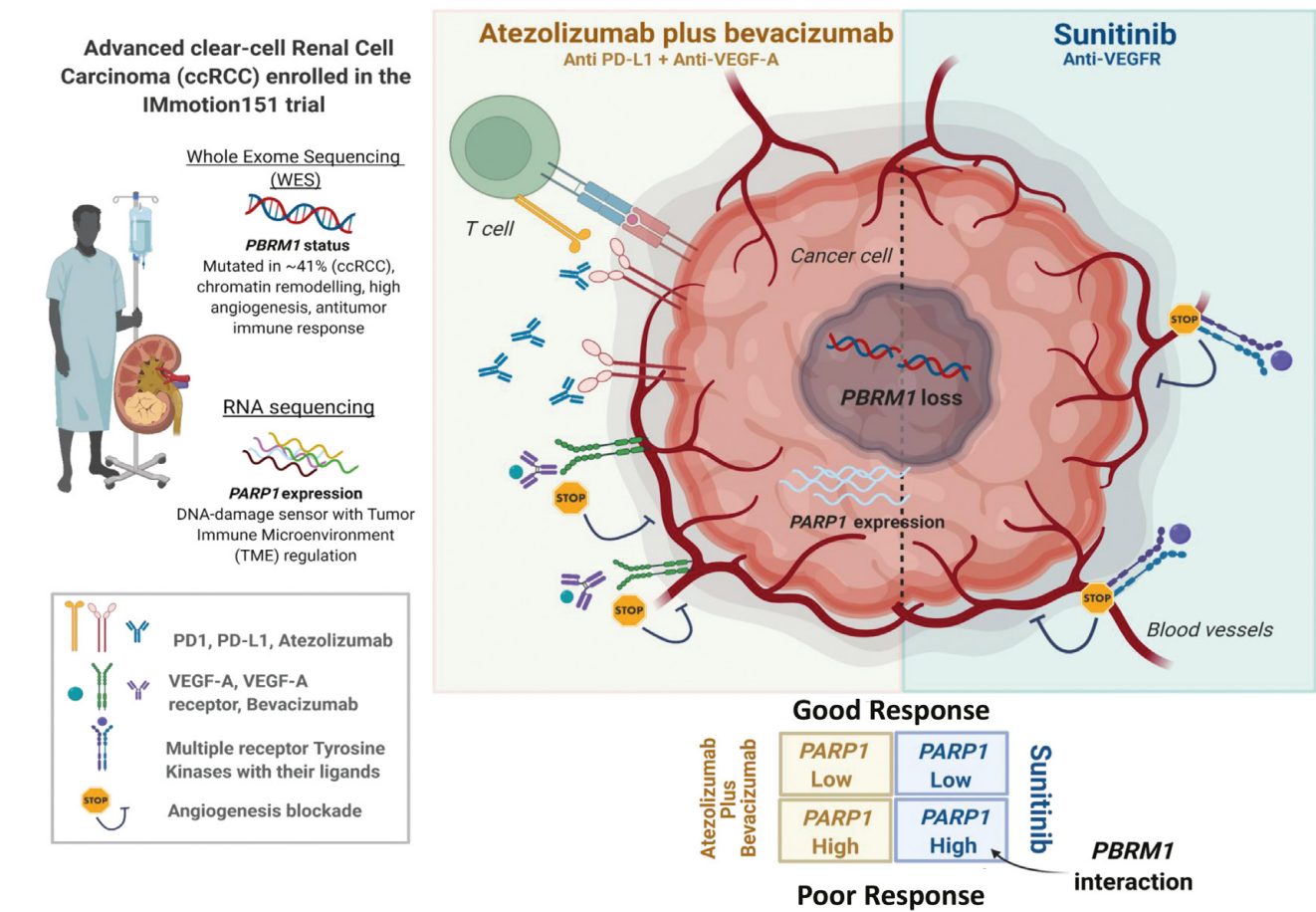


FIGURE 1 Low *PARP1* expression and *PBRM1* loss associate with improved Immunotherapy/antiangiogenic response in clear cell renal cancer patients.

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