IDENTIFICATION OF NEW THERAPEUTIC TARGETS AND BIOMARKERS OF PROGRESSION OF KIDNEY CANCER THROUGH ORGANOID MODELS AND XENOGRAFTS GENETICALLY DESIGNED BY CRISPR

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1. Abstract

Based on our own experience and state-of-the-art studies, we postulated that CRISPR/Cas9-edited human pluripotent stem cell (hPSC)-derived kidney organoids would provide an ideal system for modeling clear cell renal cell carcinoma progression and its formation of metastases. Leveraging our multidisciplinary approach with basic and clinical teams, we used CRISPR-engineered kidney organoids for the identification of novel targets and biomarkers of clear cell renal cancer progression in isogenic organoids and their derived xenograft models.

Additionally, the project has demonstrated the utility of renal organoid models of clear cell renal cancer to recapitulate the early steps of this deadly disease due to VHL disruption as defects in the generation of endothelial and in metabolic reprogramming. On the other hand, with xenograft models (PDX) we have been able to determine certain signaling pathways as possible therapeutic targets and/or prognostic biomarkers, for subsequent clinical validation with a series of patients with clear cell renal carcinoma.

2. Results

1. We found that hPSC-derived kidney organoids genetically modified by CRISPR/Cas9 provide an ideal system for modeling the progression of clear cell renal tumors.

2. The use of genetically modified renal organoid models to recapitulate the early steps of renal tumors due to VHL gene disruption as defects in endothelium generation and metabolic reprogramming.

3. Genetically modified kidney organoids (VHL ko) do not form frank tumors in in vivo models of intrarenal injection (orthotopic). For this reason, other genetic modifications will be necessary to generate complete cell transformation and malignant tumor growth.

4. Using PDX we have been able to determine certain signaling pathways as possible therapeutic targets and/or prognostic biomarkers, although this part of the study is not yet completely finished.

3. Relevance with possible future implications

The generation of renal organoid models of clear cell tumors will have a direct impact on drug screening applications. In addition, within the project we have also generated primary organoids from patients that can be of great interest when detecting possible drugs in patients who do not respond. These models as well as the primary cells will be registered in the Biobank of the Hospital Clínic to make them available to the entire scientific community through their incorporation into the portfolio of services of the Biomodels and Biobanks Platform of the Carlos III Health Institute.

On the other hand, the signaling pathways we have discovered in the PDX studies may pave the way in the future as possible therapeutic targets and/or prognostic biomarkers for patients with clear cell renal tumors.

4. Scientific bibliography generated

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