‘Molecular and cellular mechanisms responsible for the initiation and progression of clear cell renal cell carcinoma '

Clear cell renal cell carcinoma (ccRCC) is the most common adult renal neoplasm and its incidence is still increasing. Approximately 30% of patients with ccRCC have metastatic disease at the time of diagnosis, whereas in another 30%, recurrence develops after complete resection of the primary tumor. Drug resistance occurs almost inevitably after a median of 6–15 months of treatment, leading to cancer progression and, eventually, death. Currently, the best predictors of patient outcome are models that combine clinical parameters, such as performance status, with pathological features such as tumor–node–metastasis (TNM) stage, tumor size, and Fuhrman grade. However, with increased knowledge of the biology of ccRCC development and progression, these models might not fully represent tumor biology and therefore fall short in adequately predicting outcome of the individual patient. Therefore, it is important to diagnose developing tumors at the earliest possible stage and indicate biomarkers characteristic for the initiation of the neoplastic process and related to tumor progression.

The main objective of the project is the comprehensive analysis of the molecular events activated by inflammation leading to neoplastic transformation and progression in normal epithelial renal cells and identification of novel biomarkers of ccRCC initiation, development and progression .

In our study, we want to combine existing knowledge about the role of inflammation with our preliminary results indicating a crucial role of a negative regulator of inflammatory response, Monocyte Chemotactic Protein-1 Induced Protein, in inhibiting the development and progression of ccRCC. We will examine how the inflammation caused by the lack of *Zc3h12a* gene, coding MCPIP1 protein, activates normal cells for a neoplastic change and induction of tumorigenesis in the kidney. In our study, we will use cell lines derived both from the primary and secondary tumor, primary normal cells as well as cells isolated from tissue-specific gene expression mouse mutants lacking *Zc3h12a* gene, and tissues from cancer patients. We will also use the unique mice model lacking *Zc3h12a* gene, coding for Mcpip1, in the renal epithelial cells tracked by enhanced Green Fluorescent to induce the neoplastic process *in vivo* and track their fate over time.

We believe that the proposed research line will significantly contribute to a further understanding of the molecular and cellular mechanisms that regulate the process of ccRCC development and will allow to better understand the role of inflammation and its regulatory protein, MCPIP1, in initiation process of neoplastic change and progression of tumorigenesis. The understanding of the mechanisms responsible for tumor initiation might help to develop new diagnostic methods and improve clinical benefits. The identification of the regulatory pathways of neoplastic transformation may be beneficial for a more precise prediction of clinical outcomes and may be used to identify subsets of patients that may be at risk of developing cancer