Focal segmental glomerulosclerosis (FSGS) is a complex and diverse subset of renal glomerular disorder. Despite its rarity, its prevalence is increasing. FSGS is subdivided into either primary or secondary. Primary FSGS is believed to be immunological, involving a still unidentified circulating factor harmful to podocytes. Secondary forms encompass FSGS triggered by viruses, toxic or cytokine-induced podocyte damage, genetic diseases, and maladaptive forms due to increased mechanical stress. Podocytes, crucial for maintaining the glomerular filtration barrier architecture, and therefore to maintain renal function, are the primary sites of the injury in FSGS. Depending on the FSGS type, various stresses lead to podocyte death or detachment from the glomerular basement membrane, initiating a signaling cascade resulting in characteristic segmental scarring. The lack of therapeutic progress in FSGS stems from the difficulty in categorizing patients based on uniform pathophysiological groups related to podocyte injuries. Identifying specific biomarkers for these stresses could facilitate targeted treatment.

At the subcellular level, it is obvious that as highly dynamic organelles mitochondria could play a central role in FSGS. Therefore, utilizing mitochondria as cellular stress indicators will provide valuable insights into FSGS triggers. Thus, here, our goal is to identify metabolic signatures and biomarkers of different FSGS-inducing stresses. For this aim, podocytes will be exposed to various FSGS-mimicking stresses, such as aldosterone, palmitate (PA), oxidized LDL, or angiotensin 2. Untargeted metabonomics using nuclear magnetic resonance spectroscopy will be combined to, respirometry experiments, and to deep mitochondrial phenotyping to better decipher disturbed metabolic pathways.

Exposition to aldosterone for 24 hours lead to an 16,58% and 17,32% increase of metabolic activity compared to the vehicle condition for the concentrations of 500 and 750 nM, respectively, as demonstrated through MTT assays. Similarly, 48-hour exposure to aldosterone shows a significant increase in metabolic activity of 11.32% at concentrations as low as 100nM and up to 1000nM compared to the vehicle condition. In contrast, exposure to palmitate at concentrations of 150 and 300 µM for 24 hours results in a decrease of 22,2% and 45%, respectively, in metabolic activity. This decrease was also seen following a 48-hour exposure.

Initial metabonomics results from the extracellular media, following exposure to 500 nM aldosterone, indicate no increases of lactate rate after 24 hours but a slight increase of 11,95% in it compared to control condition. Glucose rate also showed an increase of 5% following 24 hours but no changes after 48-hour aldosterone exposure. Concurrently, ongoing analysis of intracellular media from aldosterone-treated podocytes aims to enhance our understanding of results obtained from extracellular media. To complete these results, palmitate analyses are planned.

This study indicates that two different stresses, recognized as contributors to podocyte dysfunction in FSGS, yield distinct signals, making them promising sources of biomarkers.

Following these comprehensive analyses will contribute to a more thorough comprehension of podocyte responses and metabolic alterations in the context of FSGS-inducing stresses.