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TRPC5-mediated podocyte calcium toxicity drives progressive glomerular disease

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Chronic kidney disease is a major cause of mortality and morbidity worldwide. Damage to the filter barrier formed by the podocytes in the kidney is a critical step of kidney disease. Podocytes are terminally differentiated cells, which cannot be replaced in adults. If enough podocytes are lost the kidney function breaks down. The complex cytoskeletal arrangement necessary to create the filter structure is regulated by calcium currents through transient receptor potential channels. One of earliest clearly visible sign of podocyte damage is the cytoskeletal rearrangement known as foot process effacement. Transient receptor potential channel 5 (TRPC5) has recently been show to play an essential role in the initiation of this process. However, the role of TRPC5 in disease progression remains unknown. We hypothesized that the continuous calcium influx caused by sustained TRPC5 activation, as in a chronic disease setting, could lead to calcium toxicity and podocyte death.

To test this hypothesis, we activated TRPC5 pharmacologically in conditionally immortalized mouse podocytes. We used cell viability assays, confocal microscopy, and flow cytometry to examine the relationship between TRCPC5 activation and cell death and mitochondrial damage typical for calcium toxicity.

Our results showed that sustained TRPC5 activation can lead to irreversible podocyte injury and death in a dose and time dependent manner. Exploring the underlying mechanisms we observed signs of mitochondrial damage, as a result of sustained TRPC5 activation. These included mitochondrial swelling, fragmentation, increased production of reactive oxygen species and mitochondrial permeability transition leading to irreversible damage to the podocytes.

This study revealed that sustained TRPC5 activation leads to podocyte death by Calcium toxicity initiating mitochondrial damage and mitochondrial permeability transition. Further we show that it is possible to protect podocytes from the detrimental effects of chronic TRPC5 activation with a novel TRPC5 blocker ML204. Podocyte loss is the critical step in the development of irreversible glomerulosclerosis causing chronic kidney disease. We suspect that continuous TRPC5 activation in a chronic disease scenario leads to podocyte loss up to a point of no return with irreversible glomerulosclerosis. Therefore blocking TRPC5 might prove to be a valuable therapeutic strategy. One of the major advantages of TRPC5 as therapeutic target is the fact that it is only expressed in the kidney and in the nervous system. The TRPC5 knockout mouse therefore has no major health impairment. A TRPC5 blocking drug, which could stop the progression of chronic kidney disease, thus seems a promising possibility.