Role of Podocytes in Diabetic and Hypertensive Renal Diseases and Their Nanoscale Evaluation by Expansion Microscopy

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Diabetic Nephropathy (DN) is a leading cause of end-stage renal disease and affects 30% of diabetic patients. Thus, 70% of diabetic patients are protected from DN, indicating that, besides hyperglycemia, DN requires additional factors to develop. Despite major advances in our understanding of the disease, the molecular pathogenesis remains far from clear. A major barrier to further progress is the lack of a suitable diabetic animal model that mimics human DN. A hallmark of DN is glomerulosclerosis. Leakage of the glomerular filtration barrier (GFB) is one of the first clinical signs in DN and is associated with the effacement of podocyte foot processes (FP) and podocyte detachment. To diagnose these alterations required electron microscopy, since the fine structure of the GFB is in the nanoscale range. The currently first-line therapy is blocking Angiotensin II (Ang II) or its main receptor, the AT1R. Thus, the present study had two major aims. First, to develop suitable rat models allowing to assess the role of hypertension for the development of DN and to specify the importance of Ang II signaling in podocytes in this context. Second, to establish and to verify a method of Expansion Microscopy (ExM), which enables the nanoscale visualization and quantification of podocyte FP alterations using light microscopy. To this end, the transgenic rats TGRCyp1a1Ren2 developing hypertension after food supplementation with indol-3-carbinol, were crossed with the TGRNeph-hAT1R rats overexpressing the AT1R specifically in podocytes. In part of rats, STZ-diabetes and high blood pressure were induced alone (HBP) or in combination (D-HBP). The results of this thesis demonstrate that the synergistic action of diabetes and HBP is required to induce rapid renal damage in diabetic rats since neither HBP alone nor STZ-diabetes alone was able to induce a comparable deterioration in renal function and morphology. AT1R overexpression in podocytes strongly accelerates the disease progression, specifically in D-HBP conditions, probably by increasing their sensitivity to be detached in the defined stress conditions. Further, this thesis demonstrated that ExM is a useful tool to diagnose and quantify FPE in DN. The results highly correlate with data obtained in the same tissue samples by established procedures using super-resolution microscopy (SIM). Electron microscopy approved the findings. The podocyte FP widths strongly correlate with the severity of albuminuria and the damage index and with the drop in GFR. AT1R signaling in podocytes strongly accelerated FPE in DN probably by increasing their sensitivity to be detached in stress conditions. In summary, this work demonstrates that renal damage in diabetic rats requires the synergistic action of HBP with hyperglycemia and that AT1R signaling in podocytes strongly aggravates the disease progression. Moreover, ExM is a suitable method to quantify nanoscale alterations in the podocyte FP structure during different glomerular diseases.