Diabetic Nephropathy

Background:
Diabetic kidney disease one of the most frequent microvascular long-term complications in diabetic patients and is a major cause for the need of dialysis. Glomerular damage seems to play a key role in the development of diabetic nephropathy. Thickening of the glomerular basement membrane, glomerular cell hypertrophy and podocyte loss are among the main pathological changes occurring during diabetic nephropathy and can lead to proteinuria.
Endothelial dysfunction has been suggested to play an important role in the pathogenesis of glomerular damage during diabetic kidney disease. Indeed, alteration of the glomerular endothelial cell function and integrity is a leading cause of microalbuminuria observed in early diabetic kidney disease. Injury to glomerular endothelial cells may lead to podocyte damage, while podocyte loss further exacerbates glomerular endothelial cell injury, forming a vicious cycle.
Currently therapies in diabetic nephropathy are focusing on strictly glycemia control and adequate arterial pressure levels. However, a few of them are targeting the endothelial damage or podocyte-endothelial crosstalk which plays a critical role in DN progression.

It has been suggested that antiangiogenic treatments for diabetic kidney disease could provide therapeutic benefits. Indeed, antiangiogenic factors such as VEGF inhibitors have been demonstrated to suppress renal damage and glomerular alterations in a diabetic mouse model. However, some other data have showed that Anti-VEGF injections could be detrimental for the endothelial cells. Furthermore, the new formed blood vessels remain immature to be well functional. Thus, new molecules targeting the vascular endothelium could possibly improve renal prognosis in patients with early stages of diabetic nephropathy.
We have previously shown that Alk1/BMP9 signaling plays an important function to maintain vascular integrity in diabetic animals. Loss of Alk1 signaling in diabetic animals led to dissociation of vascular junctions and increased vascular leakage. Given its role in the maintenance of endothelial quiescence and integrity, we evaluated the effects of Alk1 suppression on kidney integrity and renal function in diabetic mice.

Methods:
We used mice with conditional deletion of Alk1 in the endothelium (Alk1ΔEC) to evaluate the role of Alk1 in glomerular filtration in STZ-induced diabetic mice. These mice were euthanized two months after the onset of diabetes and urine and serological analyzes were performed, along with immunohistochemical studies.

Results: We demonstrated that Alk1 haploinsufficiency worsens microalbuminuria and induce podocyte loss. Furthermore, a significant increase in glomerular apoptosis was observed in Alk1ΔEC mice. Together, these data suggest that Alk1/Bmp9 signaling plays a critical role in the maintenance of glomerular endothelial cells and has important functions to maintain glomerular integrity and could be a new target of therapy in diabetic nephropathy