The influence of angiopoietin-like protein 3 on macrophages polarization and its effect on the podocyte EMT in diabetic nephropathy

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Background: Podocyte injury, which involves the podocyte epithelial-mesenchymal transition (EMT) process, is a crucial factor contributing to the progression of diabetic nephropathy (DN) and proteinuria. Our study aimed to examine the protective properties of Angiopoietin-like protein 3 (Angptl3) knockout on podocyte damage and macrophage polarization in DN mice and podocytes treated with HG. Furthermore, we also sought to investigate the underlying molecular mechanism responsible for these effects.
Methods: DN was induced in B6;129S5 mice through intraperitoneal injection of 40 mg/kg of streptozotocin (STZ). Subsequently, the changes in renal function, podocyte apoptosis, inflammatory factors (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], and interleukin-1β [IL-1β]), IL-10, TGF-β1, IL-1Ra, IL-10Ra, and nephrin were evaluated. Moreover, we investigated the mechanism underlying the role of Angptl3 in macrophages polarization, podocyte injury, podocyte EMT.
Results: Our findings revealed that Angptl3 knockout significantly attenuated STZ or HG-induced renal dysfunction and podocyte EMT. In both in vivo and in vitro studies, Angptl3 knockout led to (1) promote the transformation of M1 type macrophages into M2 type macrophages; (2) amelioration of the reduced expression of nephrin, synaptopodin, and podocin; (3) inhibition of NLRP3 inflammasome activation and release of IL-1β; and (4) regulation of α-SMA expression via the macrophage polarization. (5) After HG treatment, there was an increase in pro-inflammatory factors and foot cell damage. These changes were reversed upon Angptle knockdown.
Conclusion: Our study suggests that the knockout of Angptl3 alleviates podocyte EMT and podocyte injury by regulating macrophage polarization.