THE PATHOGENIC ROLES OF TOLL-LIKE RECEPTOR 4 SIGNALING IN DIABETIC TUBULOPATHY

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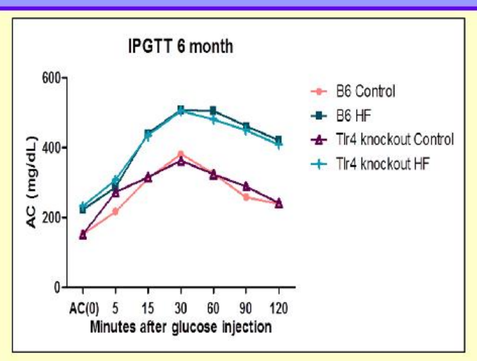
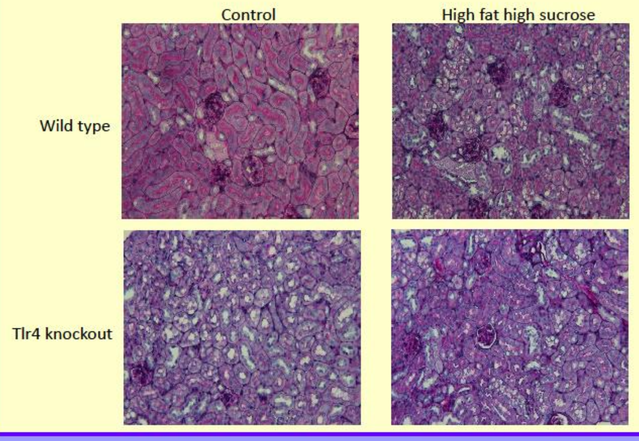
Objectives:

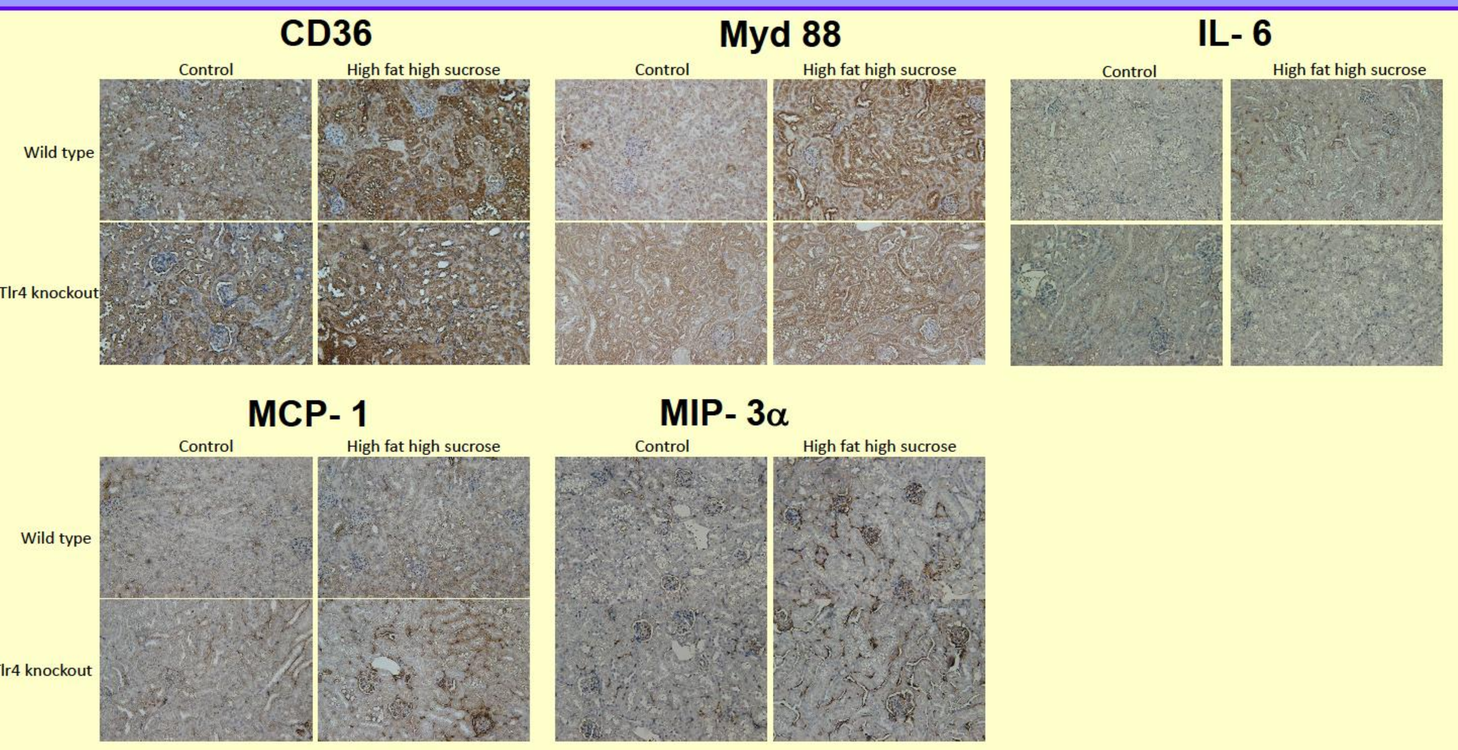
Diabetic tubulopathy emerges as a new angle to investigate the pathogenesis of diabetic nephropathy. Evidence has shown that high glucose induces proinflammatory and profibrotic features in proximal tubular cells. This in turn triggers the tubulointerstitial pathology in diabetic nephropathy. Toll-like receptor 4 (TLR4) signaling has recently been reported to promote tubular inflammation in type 1 diabetes mice model, but its molecular mechanisms are yet to be examined. This study aims to dissect the molecular mechanisms of TLR4 signaling-mediated diabetic tubulopathy.

Methods:

Wild type (WT) C57BL/6 and TLR4 knockout (KO) mice were induced into diabetes by high fat high sucrose (HFHS) diet. Intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin tolerance test (IPITT) were used to demonstrates the glucose metabolism in study groups. Mice were grouped into WT with control diet, WT with HFHS diet, TLR4KO with control diet and TLR4KO with HFHS diet. PAS stain was employed to delineate the pathology in diabetic mice kidneys. Immunohistochemistry was used to illustrate the altered expressions of TLR4 signaling molecules in the four study groups.







Results:

HFHS diet resulted in insulin resistance in WT and TLR4KO mice. IPGTT and IPITT data indicated that TLR4KO mice fed with HFHS diet were able to maintain better glucose homeostasis than WT mice. HFHS diet induced more vacuolization and thyroidization of tubules in WT than in TLR4KO mice. HFHS diet activated CD36, Myd88, and IL6 expression in renal tubules. The HFHS diet-mediated activation of CD36 was more prominent in WT than in TLR4KO mice. The upregulation of Myd88 and IL6 was not that strong in TLR4KO as in WT mice. Monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein-3α (MIP-3α) were mainly expressed in the glomeruli and interstitium, but not tubules. HFHS diet led to enhanced MCP-1 and MIP-3α expression. The enhanced expression of these two pro-inflammatory cytokines was attenuated in TLR4KO mice.

Conclusions:

Our results suggested that compared to WT mice, TLR4KO mice were able to maintain better glucose homeostasis when fed with HFHS diet and suffered less extensive tubulopathy. Diabetic tubulopathy not only signal through tubular TLR4 and CD36 but also through pro-inflmmatory cytokines in a paracrine manner.

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