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Recipient Toll-like receptors contribute to chronic graft dysfunction by both MyD88 and TRIF dependent signaling

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Toll-like receptors (TLRs) recognize specific molecular patterns derived from microbial components (exogenous ligands) or stressed cells (endogenous ligands). Stimulation of these receptors leads to a pronounced inflammatory response in a variety of acute animal models.
Chronic allograft dysfunction (CAD) was regarded as a candidate disease to test whether TLRs influence chronic fibrosing inflammation. Potential endogenous renal TLR ligands have now been detected by a significant upregulation of biglycan (BGN), glucose regulated protein 94 (GRP-94), heat shock protein 60 (HSP-60), heat shock protein 70 (HSP-70) and high mobility group box chromosomal protein 1 (HMGB1) in the acute and chronic transplant setting. In a genetic approach to define the contribution of TLR2, TLR4 and their adaptor proteins MyD88 and TRIF to CAD, kidney transplantation of TLR-wild type grafts to recipients deficient in TLR2, TLR4, TLR2/4, MyD88 and TRIF was performed. TLR- and adaptor-protein-deficiency significantly improved excretory function of chronic kidney grafts by 55% to 75%. Histopathologic signs of chronic allograft damage were significantly ameliorated. In grafts T-cells, DCs, and foremost macrophages, were reduced, by up to 4,5 fold. The intragraft concentrations of IL-6, IL-10, MCP-1 and IL-12p70 were significantly lower. TLR-, MyD88- and TRIF-deficient recipients showed a significant reduction in fibrosis. α-smooth muscle actin (α-SMA) positive cells were decreased by up to 9 fold and collagen I and III by up to 2 fold. These findings highlight the functional relevance of TLRs and their two major signaling pathways in graft infiltrating mononuclear cells in the pathophysiology of CAD. TLR signaling blockade may be a therapeutic option for the prevention of CAD.