Toll-like receptors (TLRs) exist on both myeloid and intrinsic renal cells contributing to the initiation of innate immunity during renal infection with uropathogenic Escherichia coli. Toll-interleukin 1 receptor (IL-1R) (TIR)8/SIGIRR is an orphan receptor of the TLR/IL-1R family, which suppresses TLR signaling of immune cells and is highly expressed in the kidney. Lack of TIR8/SIGIRR is associated with enhanced renal chemokine signaling upon exposure to lipopolysaccharide (LPS). This was because of TIR8/SIGIRR expression on resident intrarenal myeloid cells rather than tubular epithelial cells which express it on basolateral and luminal membranes. The lack of TIR8/SIGIRR does not enhance TLR/IL-1R signaling in tubular epithelial cells as was observed in monocytes. TIR8/SIGIRR is induced in monocytes treated with LPS or tumor necrosis factor and interferon-gamma in a dose-dependent manner but was downregulated in treated tubule epithelial cells. This cell type-specific regulation and function did not relate to mRNA splice variants but was associated with N- and O-glycosylation of the receptor in renal cells of myeloid and nonmyeloid origin. Our studies show that resident myeloid cells contribute to TLR-mediated antimicrobial immunity in the kidney and that this function is controlled by TIR8/sigirr. TIR8/SIGIRR does not suppress TLR signaling in
tubular epithelial cells, which supports their role as sensors of microbial infection in the kidney.