Dendritic cell activation by Toll-like receptors (TLR) is crucial for the generation of protective immune responses. In addition to the common myeloid differentiation factor 88 (MyD88)-dependent signaling pathway, TLR4 engages the adaptor protein Toll/IL-1 receptor (TIR)-domain-containing adaptor inducing IFN-beta (TRIF), leading to interferon regulatory factor 3 (IRF-3) activation and type I interferon production. Using microarray expression profiling we now identify TRIF as a major regulator of the TLR4-triggered activation program of dendritic cells. We show that the expression of 47% of the genes that are responsive to TLR4 stimulation in wild-type dendritic cells is significantly altered in cells carrying a loss-of-function mutation of TRIF. Specifically, expression of IL-12, IL-18, and IL-23 was impaired in the absence of functional TRIF, suggesting that TLR4-promoted Th1 responses are TRIF-dependent. Furthermore, we provide evidence that TRIF regulates TLR4-mediated gene expression both by type I IFN-dependent and -independent mechanisms. Whereas dendritic cell production of CXCL10 and CCL12 was dependent on both TRIF and the type I interferon receptor, expression of IL-6 required TRIF but not type I interferon activity. Functional TRIF was also required for the normal induction of numerous genes considered important for host defense.
against diverse pathogens. Together, these data therefore identify TRIF as a crucial regulator of TLR4-dependent dendritic cell responses.