Abstract

The expression, responsiveness and regulation of mouse Toll-like receptors (TLRs) in bone marrow-derived macrophages (BMDM) were investigated prior to and following the development of diabetes. Expression of TLR3 and TLR5 was significantly higher in newly diabetic non-obese diabetic (NOD) mice when compared with pre-diabetic and control strains of mice. The TLR3 ligand poly(I)poly(C) triggered up-regulation of its own receptor in NOR and pre-diabetic NOD, but TLR3 was already highly expressed in diabetic NOD mice. Expression levels of TLR3 correlated with poly(I)poly(C)-triggered IFN activity. LPS triggered down-regulation of TLR4 in pre-diabetic NOD, NOR and BALB/c, while levels of TLR4 remained consistently elevated in type 1 diabetic NOD and type 1 diabetic NZL mice. Dysregulation of TLR expression in the diabetic state correlated with increased nuclear factor kappa B (NF-kB) activation in response to the TLR4 ligand LPS and higher expression of IL-12p40, tumor necrosis factor α (TNFα), IL-6 and inducible nitric oxide synthase but lowered expression of IL-10. Exposure of bone marrow precursor cells from NOD mice to a hyperglycemic environment during differentiation into macrophages resulted in elevated levels of TLR2 and TLR4 and the cytokine TNFα. The results indicate that macrophage precursors are influenced by systemic changes in diabetes favoring altered TLR expression and sensitivity that may influence susceptibility to macrophage-mediated diabetes complications and explain inappropriate responses to infection in diabetes.