Transcriptional activation induced in macrophages by Toll-like receptor (TLR) ligands: from expression profiling to a model of TLR signaling.

Abstract:
Toll-like receptors (TLR) sense microbial compounds and bridge innate and adaptive immunity by activation of antigen-presenting cells. TLR-induced signaling via intracellular adaptor molecules, including MyD88 and TRIF, drives transcriptional activation of genes including pro-inflammatory cytokines and cell activation markers. To globally assess the activation programs triggered by individual TLR in macrophages, we used microarray-based gene expression profiling of the murine macrophage cell line RAW264.7. Here we describe that the TLR4 ligand LPS more strongly modulates gene expression compared to ligands for TLR 2, 3, 7, and 9. Taking advantage of the known dependency of TLR on given adaptor molecules, we operationally define sets of MyD88 and TRIF "private" genes. We conclude with a TLR signaling model that incorporates both negative and synergistic interactions of MyD88- and TRIF-controlled signaling pathways as deduced from the microarray data presented.