Induction of iNOS by Chlamydia pneumoniae requires MyD88-dependent activation of JNK.

Abstract:
Innate immune cells produce NO via inducible NO synthase (iNOS) in response to certain infections or upon stimulation with cytokines such as IFN-gamma and TNF. NO plays an important role in host defense against intracellular bacteria including Chlamydia pneumoniae as a result of its microbicidal activity. In MyD88-deficient mice, which succumb to C. pneumoniae infection, iNOS induction is impaired 6 days postinfection, although pulmonary levels of IFN-gamma and TNF are elevated as in wild-type mice at this time-point. Here, we demonstrate that induction of iNOS in macrophages upon C. pneumoniae infection is controlled by MyD88 via two pathways: NF-kappaB activation and phosphorylation of the MAPK JNK, which leads to the nuclear translocation of c-Jun, one of the two components of the AP-1 complex. In addition, phosphorylation of STAT1 and expression of IFN regulatory factor 1 (IRF-1) were delayed in the absence of MyD88 after C. pneumoniae infection but not after IFN-gamma stimulation. Taken together, our data show that for optimal induction of iNOS during C. pneumoniae infection, the concerted action of the MyD88-dependent transcription factors NF-kappaB and AP-1 and of the MyD88-independent transcription factors phosphorylated STAT1 and IRF-1 is required.