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Meeting abstract

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TLR2 and TLR4 signaling in macrophages is negatively regulated by a Lyn-PI3K module and promoted by SHIP1

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We demonstrate here that the Src family kinase Lyn negatively regulates Toll-like receptor (TLR) signaling in bone marrow-derived macrophages (BMMΦs) and *in vivo*. Lyn-/- BMMΦs produced and secreted significantly more IL-6, TNF-α, and IFN-α/β compared to WT BMMΦs, indicating that Lyn is able to control both MyD88- and TRIF-dependent signaling pathways downstream of TLR4. CD14 was not involved in this type of regulation. Moreover, Lyn attenuated proinflammatory cytokine production in BMMΦs in response to the TLR2 ligand, FSL-1. In agreement with these in vitro experiments, Lyn-deficient mice produced higher amounts of proinflammatory cytokines than WT mice after i. v. injection of LPS or lipopeptide. Though Lyn clearly acted as a negative regulator downstream of TLR4, it did not, different to what was proposed previously, alter the process of LPS tolerance. Stimulation with a low dose of LPS resulted in reduced production of proinflammatory cytokines after a subsequent stimulation with a high dose of LPS in both WT and Lyn-/- BMMΦs as well as *in viv*o. Mechanistically, Lyn interacted with PI3K and in correlation, PI3K inhibition resulted in increased LPS-triggered cytokine production. In this line, SHIP1-deficient BMMΦs, exerting enhanced PI3K-pathway activation, produced less cytokines compared to WT BMMΦs. In conclusion, Lyn is a negative regulator of TLR-induced cytokine production in vitro and in vivo and acts, at least in part, via PI3K.