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Nogo positively regulates TLR signal pathway and inflammatory gene expression in macrophages

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ABSTRACT

Our research goal is the development of novel strategies to augment inhibitory function of various immune inhibitory receptors such as a unique inhibitory Fc receptor, FcγRIIB, and Paired immunoglobulin-like receptor (Pir) B. To this end, we have been searching novel physiological ligands for these inhibitory receptors.

Nogo was identified as an inhibitor protein of axonal outgrowth in the central nervous system. Although Nogo, particularly the isoform B, is expressed ubiquitously in various tissues and cells such as T and B cells and macrophages, its function in immune cells, if any, has not been studied. Interestingly, Nogo was recently found to bind PirB. Since PirB is known to be inhibitory to Toll-like receptor (TLR) 9 signaling pathway in B cells, we are interested in analyzing whether Nogo can also modulate TLR signaling. In this study, we show Nogo-A/B deficient macrophages exhibit marked defects in induction of inflammatory cytokines both in the mRNA and protein levels following the activation of various TLRs. Particularly after TLR9 stimulation, deficiency in Nogo resulted in a delay of degradation of IκB-α and of phosphorylation of p38 MAP kinase, although the uptake of TLR9 ligand was found to be normal. Our results suggest that Nogo plays a role in TLR-mediated signal transduction and inflammatory gene expression in macrophages. Analysis of a possible signaling crosstalk between those of Nogo and PirB is underway..