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CD14 can do it alone

Activation of dendritic cells (DCs) through Toll-like receptors (TLRs) results in the activation of various signalling pathways and transcription factors, leading to the transcription of many cytokines. One such cytokine is interleukin-2 (IL-2), but the signalling pathways and transcription factors involved in its production by DCs have not been described. Now, Granucci and colleagues show that lipopolysaccharide (LPS)-induced IL-2 production by DCs depends on NFAT (nuclear factor of activated T cells) activation by CD14, but surprisingly is independent of TLR4.

IL-2 production by T cells is known to depend on the NFAT pathway, so the authors sought to determine whether a similar pathway is engaged in DCs. Stimulation of DCs with a subtype of LPS that requires the CD14 co-receptor as well as TLR4 and MD2 (also known as LY96) for signalling resulted in an influx of extracellular Ca^{2+} and NFAT nuclear translocation, and these were required for IL-2 production. Other components of the NFAT pathway, such as lipid rafts, SRC kinases and phospholipase Cγ2, were also necessary for LPS-induced Ca^{2+} mobilization by DCs.

Surprisingly, activation of the NFAT pathway by LPS was intact in DCs that were deficient for TLR4 or any of its signalling adaptor molecules. By contrast, the NFAT pathway was not activated in LPS-stimulated CD14-deficient DCs, and these cells did not produce IL-2; however, tumour necrosis factor (TNF) and IL-6 production remained intact at high doses of LPS. Co-culture of CD14-deficient DCs with soluble CD14 and LPS did not restore IL-2 production. So, signalling through membrane-localized CD14 is necessary and sufficient for the induction of the NFAT pathway in DCs.

The authors next determined whether activation of NFAT through CD14 had any other physiological functions in DCs. They showed that LPS-induced activation of NFAT was required for the induction of pro-apoptotic genes, such as *Nur77*, and for apoptotic cell death of terminally differentiated DCs — an event that is necessary to maintain self tolerance and prevent autoimmunity. Blocking this pathway resulted in an accumulation of DCs *in vivo* and an increase in T cell priming.

Unlike DCs, macrophages (which also express CD14) do not die after LPS-induced activation, and this study shows that Ca^{2+} mobilization, NFAT and *Nur77* are not induced in bone marrow-derived macrophages following LPS stimulation. However, the enforced induction of Ca^{2+} mobilization with thapsigargin along with LPS stimulation resulted in NFATc2-dependent macrophage cell death, indicating that the Ca^{2+}–NFAT pathway does not have a role downstream of LPS signalling in macrophages.

This study shows that the NFAT pathway is activated in DCs by LPS downstream of CD14 and has an important role in regulating the DC life cycle; it therefore identifies CD14 as a potential therapeutic target for diseases such as sepsis. In addition, this study highlights important differences in the response of macrophages and DCs to LPS.

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ORIGINAL RESEARCH PAPER Zanoni, I. *et al.* CD14 regulates the dendritic cell life cycle after LPS exposure through NFAT activation. *Nature* 14 June 2009 (doi:10.1038/nature08118)