Innate immune responses to Gram-negative bacteria depend on the recognition of lipopolysaccharide (LPS) by a receptor complex that includes CD14 and TLR4. In dendritic cells (DCs), CD14 enhances the activation not only of TLR4 but also that of the NFAT family of transcription factors, which suppresses cell survival and promotes the production of inflammatory mediators. NFAT activation requires Ca2+ mobilization. In DCs, Ca2+ mobilization in response to LPS depends on phospholipase C γ2 (PLCγ2), which produces inositol 1,4,5-trisphosphate (IP3). Here, we showed that the IP3 receptor 3 (IP3R3) and ITPKB, a kinase that converts IP3 to inositol 1,3,4,5-tetrakisphosphate (IP4), were both necessary for Ca2+ mobilization and NFAT activation in mouse and human DCs. A pool of IP3R3 was located on the plasma membrane of DCs, where it colocalized with CD14 and ITPKB. Upon LPS binding to CD14, ITPKB was required for Ca2+ mobilization through plasma membrane-localized IP3R3 and for NFAT nuclear translocation. Pharmacological inhibition of ITPKB in mice reduced both LPS-induced tissue swelling and the severity of inflammatory arthritis to a similar extent as that induced by the inhibition of NFAT using nanoparticles that delivered an NFAT-inhibiting peptide specifically to phagocytic cells. Our results suggest that ITPKB may represent a promising target for anti-inflammatory therapies that aim to inhibit specific DC functions.