IkappaBbeta is an essential co-activator for LPS-induced IL-1beta transcription in vivo.

Inhibitor of ?B (I?B?) ? (I?B?) represents one of the major primary regulators of NF-?B in mammals. In contrast to the defined regulatory interplay between NF-?B and I?B?, much less is known about the biological function of I?B?. To elucidate the physiological role of I?B? in NF-?B signaling in vivo, we generated I?B?-deficient mice. These animals proved to be highly refractory to LPS-induced lethality, accompanied by a strong reduction in sepsis-associated cytokine production. In response to LPS, I?B? is recruited to the IL-1? promoter forming a complex with the NF-?B subunits RelA/c-Rel required for IL-1? transcription. Further transcriptome analysis of LPS-stimulated wild-type and I?B?-deficient BM-derived macrophages revealed several other genes with known regulatory functions in innate immunity arguing that a subset of NF-?B target genes is under control of I?B?. Collectively, these findings provide an essential proinflammatory role for I?B? in vivo, and establish a critical function for I?B? as a transcriptional coactivator under inflammatory conditions.