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ZBTB20 promotes TLR-triggered innate immune responses by repressing IkappaBalpha gene transcription

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Abstract

The ability of the innate immune system to recognize and eliminate invading microbial pathogens has been largely attributed to Toll-like receptors (TLRs) and TLR-triggered immune response. Although many factors mediate the transduction of TLR signals, the molecular mechanisms involved in the full activation of TLR-triggered innate immunity remain to be fully elucidated. ZBTB20, also named DPZF, HOF, and ZNF288, belongs to BTB/POZ (broad complex tramtrack bric-a-brac/poxvirus and zinc finger) zinc finger family. ZBTB20 was found to participate in neurogenesis and function as a key transcription repressor of alpha-fetoprotein gene in liver. However, the roles of ZBTB20 in immune system remain unknown. Here we generated myeloid cell-specific ZBTB20 knockout mice by the LysM-Cre/loxP approach and found these mice were resistant to endotoxin shock and Escherichia coli-caused sepsis. ZBTB20 deficiency attenuated the TLR-triggered production of proinflammatory cytokines and type I interferon in macrophages, which attributed to the higher abundance of IkappaBalpha and impaired activity of the transcription factor NF-kappaB. Futhermore, chromatin immunoprecipitation (ChIP)-sequence assay showed that ZBTB20 specifically bound to IkappaBalpha gene promoter. We found that ZBTB20 was a transcriptional repressor capable of specifically inhibiting IkappaBalpha promoter-driven transcriptional activity. Therefore, ZBTB20 functions a key regulator governing IkappaBalpha gene transcription, inhibits IkappaBalpha protein expression and enhances NF-kappaB activation, which leading to enhanced TLR-triggered innate inflammatory response. Our results demonstrate that transcriptional repressor ZBTB20 is needed to promote the full activation of TLR signaling and present a new model for the regulation of TLR-triggered innate immune responses.