Abstract:

TNF is a major mediator of inflammation, immunity, and apoptosis. Pre-exposure to TNF reduces sensitivity to restimulation, a phenomenon known as tolerance, considered as protective in sepsis, but also as a paradigm for immunoparalysis. Earlier experiments in TNF-tolerant cells display inhibition of NF-kappaB-dependent IL-8 gene expression at the transcriptional level with potential involvement of C/EBPbeta. In this study, we have shown that a kappaB motive was sufficient to mediate transcriptional inhibition under TNF tolerance conditions in monocytic cells. Furthermore, in tolerant cells, TNF-induced NF-kappaB p65 phosphorylation was markedly decreased, which was accompanied by the formation of C/EBPbeta-p65 complexes. Remarkably, in C/EBPbeta(-/-) cells incubated under the conditions of TNF tolerance, neither impairment of transcription nor inhibition of p65 phosphorylation was observed. Finally, we showed that C/EBPbeta overexpression reduced p65-mediated transactivation and that association of C/EBPbeta/p65 specifically prevented p65 phosphorylation. Our data demonstrate that C/EBPbeta is an essential signaling component for inhibition of NF-kappaB-mediated transcription in TNF-tolerant cells and suggest that this is caused by
blockade of p65 phosphorylation. These results define a new molecular mechanism responsible for
TNF tolerance in monocytic cells that may contribute to the unresponsiveness seen in patients with
sepsis.