Direct Evidence for Involvement of NF-κB in Transcriptional Activation of Tumor Necrosis Factor by a Spirochetal Lipoprotein

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Louse-borne relapsing fever (LBRF) caused by the spirochete Borrelia recurrentis provides one of the clearest examples of the causal role of tumor necrosis factor (TNF) in the pathogenesis of fever in humans. When patients with LBRF are treated with antibiotics such as penicillin, a significant proportion develop an exacerbation of fever and other clinical symptoms. This phenomenon, known as the Jarisch-Herxheimer (J-H) reaction (12), can be suppressed by administration of anti-TNF antibody prior to antibiotic therapy (3). Using a (J-H) reaction (12), can be suppressed by administration of...
some practical importance, particularly in the tropics. Many parts of Africa have a high incidence of tick-borne relapsing fever, and epidemics of potentially fatal LBRF are prone to occur when populations are displaced (1). Several investigations have demonstrated the proinflammatory properties of membrane lipoproteins expressed by borrelial species and other spirochetes (6, 10, 11, 14, 17), and it has recently been demonstrated that these lipoproteins can stimulate macrophages through TLR 2 (5).

Here we focus on VmpA1, a variable major lipoprotein

activity was then measured according to the Promega protocol. Stimulation of these cells with VmpA1 resulted in a 60% decrease in the level of inducible luciferase activity compared to control cells (Fig. 3). Overexpression of the degradation-deficient IκBα S32/36A mutant (18) resulted in an even greater reduction (80% decrease of the original induced level). From these results, we conclude that NF-κB complexes have an essential role in up-regulation of transcription of the TNF gene in MonoMac 6 cells stimulated with VmpA1.

The pathogenesis of borrelial relapsing fever is a problem of some practical importance, particularly in the tropics. Many parts of Africa have a high incidence of tick-borne relapsing fever, and epidemics of potentially fatal LBRF are prone to occur when populations are displaced (1). Several investigations have demonstrated the proinflammatory properties of membrane lipoproteins expressed by borrelial species and other spirochetes (6, 10, 11, 14, 17), and it has recently been demonstrated that these lipoproteins can stimulate macrophages through TLR 2 (5).

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which we have previously shown to be the major TNF-stimulating component of clinical isolate A1 of *B. recurrentis*, the agent of LBRF (16). In the human monocyte-like cell line MonoMac 6, we find that TNF mRNA is synthesized within 30 min and disappears within 4 h of stimulation with VmpA1. mRNA for IL-1β and IL-12 p40, other proinflammatory cytokines, appears later (2 h), and levels remain elevated for longer (8 h). These findings are consistent with the clinical observation that TNF is the first cytokine to appear in the circulation following antibiotic treatment of LBRF is TNF (7).

Several studies have implicated the transcription factor NF-κB in the TNF response to borrelial infection (8, 19), but there is little direct evidence that it plays a causal role. The latter question is of interest because whereas NF-κB is known to be of importance in murine TNF regulation, its role as a principal TNF-inducing factor of louse-borne relapsing fever. Lancet 1:58–62.


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REFERENCES


