-308 tumor necrosis factor (TNF) polymorphism is not associated with survival in severe sepsis and is unrelated to lipopolysaccharide inducibility of the human TNF promoter.

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Abstract
Tumor necrosis factor (TNF) is recognized as a central mediator of sepsis, septic shock, and multiple organ failure. These host reactions are associated with increased TNF levels in circulation, presumably due to increased TNF production. A previously described nucleotide variation at position -308 in the promoter region of the human TNF gene was shown to be associated with the clinical outcome of malaria. In this study we addressed the relevance of the -308 polymorphism for expression of the human TNF gene in response to bacterial endotoxin in vivo and in vitro. First, we typed 80 patients suffering from severe sepsis and 153 healthy individuals and found no association of the -308 variation with incidence of the disease. In contrast, the NcoI marker in the closely linked lymphotoxin-alpha (LT-alpha) gene showed association with survival. This discrepancy can be explained by the linkage of the TNFB2(NcoI) allele to the common TNF1 (-308) allele. Second, we generated reporter gene constructs with the promoter deletions and with both -308 variation in the context of the extended human TNF promoter region. Although such constructs were highly inducible by lipopolysaccharide (LPS) in transient transfections into a macrophage cell line, the -308 variation had no significant effect on transcription, consistent with the promoter deletion study. We conclude that the functional consequence of the -308 polymorphism may be unrelated to transcriptional response of the TNF gene to bacterial endotoxin.