A constitutive decay element promotes tumor necrosis factor alpha mRNA degradation via an AU-rich element-independent pathway

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Tumor necrosis factor alpha (TNF-alpha) expression is regulated by transcriptional as well as posttranscriptional mechanisms, the latter including the control of mRNA decay through an AU-rich element (ARE) in the 3' untranslated region (UTR). Using two mutant cell lines deficient for ARE-mediated mRNA decay, we provide evidence for a second element, the constitutive decay element (CDE), which is also located in the 3' UTR of TNF-alpha. In stably transfected RAW 264.7 macrophages stimulated with lipopolysaccharide (LPS), the CDE continues to target a reporter transcript for rapid decay, whereas ARE-mediated decay is blocked. Similarly, the activation of p38 kinase and phosphatidylinositol 3-kinase in NIH 3T3 cells inhibits ARE-mediated but not CDE-mediated mRNA decay. The CDE was mapped to an 80-nucleotide (nt) segment downstream of the ARE, and point mutation analysis identified within the CDE a conserved sequence of 15 nt that is required for decay activity. We propose that the CDE represses TNF-alpha expression by maintaining the mRNA short-lived, thereby preventing excessive induction of TNF-alpha after LPS stimulation. Thus, CDE-mediated mRNA decay is likely to be an important mechanism limiting LPS-induced pathologic processes.

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