Interleukin-1-mediated Stabilization of Mouse KC mRNA Depends on Sequences in both 5'- and 3'-Untranslated Regions*

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mRNA transcribed from the mouse KC chemokine gene accumulated to significantly higher levels in multiple cell types after treatment with interleukin 1α (IL-1α) as compared with tumor necrosis factor-α (TNFα). Although TNFα and IL-1α both signaled the activation of nuclear factor κB and enhanced transcription of the KC gene with equal potency, only IL-1α treatment resulted in stabilization of KC mRNA. Nucleotide sequences that confer sensitivity for IL-1α-mediated mRNA stabilization were identified within the 5'- and 3'-untranslated regions (UTRs) of KC mRNA using transient transfection of chimeric plasmids containing specific portions of KC mRNA linked to the chloramphenicol acetyltransferase (CAT) gene. When plasmids containing either the 3'- or 5'-UTR of KC mRNA were used, the half-life of CAT mRNA was unaltered either in untreated or IL-1α-stimulated cells. In contrast, CAT mRNA transcribed from plasmids that contained both the 5'- and 3'-UTRs of the KC mRNA decayed more rapidly than control CAT mRNA, and this enhanced decay was prevented in cells treated with IL-1α. A cluster of four overlapping AUUUA motifs within the 3'-UTR was required, whereas the 5'-UTR region exhibited orientation dependence. These findings indicate that cooperative function of the two nucleotide sequences involves a distinct signaling pathway used by IL-1α but not TNFα.

The development of an inflammatory response is mediated, in part, by the modulation of gene expression in multiple participating cell types (1–4). The changes in gene expression associated with inflammation are stringently controlled in response to extracellular signals encountered in the microenvironment of the inflammatory site. Among the most potent of such signals are the cytokines interleukin-1α/β (IL-1α/β)1 and tumor necrosis factor-α (TNFα). Although IL-1α and TNFα are structurally unrelated and interact with distinct receptors, they induce a very similar set of functional responses in many cell types (5–8). Indeed, some components of the intracellular signaling pathways that mediate cellular response to TNFα and IL-1α are shared (9–13). These signaling pathways lead to alterations in gene transcription, in mRNA stability, and in mRNA translation (10, 13–16).

Members of the chemoattractant cytokine or chemokine gene families are recognized as important targets of TNFα/IL-1α during inflammation (17–19). The products of these genes serve to recruit select subsets of inflammatory leukocytes into tissue sites and have significant impact on the magnitude and character of an inflammatory reaction. In the mouse, one of the earliest events in inflammation is the infiltration of neutrophils, a process controlled in part by members of the CXC chemokine family that includes IL-8 and GROα (17–19). Though there is no direct equivalent of IL-8 in the mouse, the GRO-α-related genes are termed KC and MIP-2 (20, 21). Expression of the mouse KC gene is stimulated by a number of inflammatory agents including lipopolysaccharide, thrombin, platelet-derived growth factor, TNFα, and IL-1α/β in a number of cell types including macrophages, fibroblasts, epithelial cells, and endothelial cells (22–26). Although KC mRNA expression requires increased KC gene transcription through the action of NFκB, IL-1α has been shown to enhance the accumulation of KC mRNA by prolonging its half-life in BALB/c 3T3 cells (27, 28).

In the present study we consider the mechanism(s) by which IL-1α can selectively stabilize KC mRNA. Although TNFα and IL-1α are both competent stimuli for the activation of NFκB and associated changes in gene transcription, only IL-1α stabilizes KC mRNA. Furthermore, both the constitutive instability of KC mRNA and the sensitivity to IL-1α depend upon two separate nucleotide sequences within the mature mRNA. Although a cluster of four overlapping AUUUA pentamers in the 3'-UTR is required for both rapid decay and IL-1α-mediated stabilization, this sequence motif is by itself insufficient and requires the 68 nucleotides composing the 5'-UTR as well.

EXPERIMENTAL PROCEDURES

Reagents—DMEM, Dulbecco’s phosphate-buffered saline, antibiotics, glucose, fungizone, guanidine isothiocyanate, and cesium chloride were obtained from Life Technologies, Inc. Acetyl-coenzyme A was purchased from Sigma (St. Louis, MO). Chloramphenicol was purchased from Sigma (St. Louis, MO). Amersham Pharmacia Biotech. NEN Life Science Products was the source of [35S]chloramphenicol, [3H]UTP, and [α-32P]dCTP. Polyacrylamide gel electrophoresis and protein assay reagents were purchased from Bio-Rad. Actinomycin-D (Act D) was purchased from Sigma.

Cell Culture—BALB/c 3T3 were obtained from the ATCC. The mouse endothelial cell line HSV was a gift from Alberto Mantovani (Mario
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Preparation of Reporter Plasmids—The following chimeric constructs were used in this study (see Fig. 4): pCAT3'-UTR, pCAT 5'-UTR, pCAT5'-ARE, pCAT5'/AREmu, and pCAT5'/rev ARE. The nucleotide numbering is based on the KC cDNA sequence as provided in the GenBank database with the addition of a 68-nucleotide 5'-UTR fragment defined previously (28). The fragments of the KC 3'-UTR were prepared by PCR. The pCAT5'/AREmu was generated by substituting nucleotides between positions 449 and 461 (wild-type ARE sequence (underlined), ATTTCGATCGAGATATCTTTA). Polymerase chain reaction products of the 3'-UTR were subcloned into pCATcontrol vector at the XbaI site immediately upstream of the CAT coding region. PCR products of the 5'-UTR (1–68) were subcloned into pCATControl vector at the NotI site immediately upstream of the CAT coding region. The nucleotide sequences of cloned fragments were determined by the Molecular Biotechnology Core Facility of the Lerner Research Institute.

Preparation of RNA, Northern Hybridization, and Ribonuclease Protection Assay (RPA)—Total cellular RNA was extracted by the guanidium thiocyanate-cesium chloride method (32). Northern hybridization analysis was done as described previously (29). Template DNA (1 μg) for KC, CAT, and β-actin were transcribed in vitro to generate an [α-32P]UTP radiolabeled, single-stranded RNA hybridization probe for RPA using the Maxiscript kit. Total cellular RNA (10 μg) from transfected cells treated with or without stimulus for the indicated times before preparation of total cell extracts and analysis of IκBα levels by immunoblotting. BALB/c 3T3 cells were untreated (NT) or stimulated with TNFα or IL-1α as indicated above for 30 min before preparation of nuclear extracts and analysis of κB DNA binding activity by electrophoretic mobility shift assay. C, BALB/c 3T3 cells were transfected with a plasmid encoding a 104 nt fragment of the KC gene promoter linked to the CAT reporter gene and 6 h later were divided into three separate cultures. After a 24-h rest, these transfected cultures were treated or not (NT) with IL-1α or TNFα for 18 h. Cytoplasmic extracts were prepared and used for determination of CAT activity. Similar results were obtained in three separate experiments.

Preparation of Nuclear Extracts and Electrophoretic Mobility Shift Assay—Nuclear extracts were prepared as described previously using a modification of the method of Dignam et al. (34). Protein concentrations were measured by the method of Bradford (35). Electrophoretic mobility shift assays were done as described previously using a double-stranded oligonucleotide containing the NFκB binding motif corresponding to positions −75 to −55 in the KC gene promoter (28).

Western Blot Analysis—Western blot analysis was done essentially as described previously using 10% denaturing polyacrylamide gel electrophoresis of total cytosolic extracts and ECL detection technology (36).

CAT Assay—CAT activity was assayed from cell extracts as described previously (28).

RESULTS

IL-1α Stimulates Enhanced KC mRNA Stability in Multiple Cell Types—Previous work demonstrated that TNFα and IL-1α could differentially stimulate expression of the KC chemokine gene in BALB/c 3T3 cells (27). To determine if this response to IL-1α is a general phenomenon, the ability of TNFα or IL-1α to stimulate KC mRNA accumulation was measured in other cell types including the mouse endothelial cell line H5V and the renal tubule epithelial cell line MCT-1. Cultures of all three cell lines were treated for 2 h with IL-1α or TNFα, and KC mRNA levels were measured by northern hybridization analysis (Fig. 1A). As previously observed, treatment of BALB/c 3T3 cells with IL-1α resulted in a significant accumulation of KC mRNA

- [Fig. 1](#): IL-1α and TNFα differentially regulate the accumulation of KC mRNA in multiple cell types. A, cultures of BALB/c 3T3, H5V, or MCT-1 were treated with nothing (NT), IL-1α (10 ng/ml), or TNFα (10 ng/ml) for 2 h before preparation of total RNA and analysis of KC, IP-10, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels by northern hybridization. B, H5V or BALB/c 3T3 cells were treated with nothing (NT), IL-1α (10 ng/ml), or TNFα (10 ng/ml) alone or in combination as indicated for 2 h before analysis of KC mRNA levels by northern hybridization. Similar results were obtained in two separate experiments.

- [Fig. 2](#): IL-1α and TNFα are equipotent stimuli for activation of NFκB and NFκB dependent gene transcription. A, BALB/c 3T3 cells were treated with nothing (NT), IL-1α (10 ng/ml), or TNFα (10 ng/ml) for the indicated times before preparation of total cell extracts and analysis of IκBα levels by immunoblotting. B, BALB/c 3T3 cells were untreated (NT) or stimulated with TNFα or IL-1α as indicated above for 30 min before preparation of nuclear extracts and analysis of κB DNA binding activity by electrophoretic mobility shift assay. C, BALB/c 3T3 cells were transfected with a plasmid encoding a 104 nt fragment of the KC gene promoter linked to the CAT reporter gene and 6 h later were divided into three separate cultures. After a 24-h rest, these transfected cultures were treated or not (NT) with IL-1α or TNFα for 18 h. Cytoplasmic extracts were prepared and used for determination of CAT activity. Similar results were obtained in three separate experiments.

Negri Institute, Milan, Italy. The MCT-1 cells were derived from renal proximal tubule cells and were a gift from Dr. Peter Heger (Case Western Reserve University Medical School). All three cell lines were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum, penicillin, and streptomycin in humidified 5% CO₂.

Preparation of Plasmid DNA—The plasmids encoding the genes for KC, IP-10, and glyceraldehyde-3-phosphate dehydrogenase were as described previously (24, 29, 30). Methods for plasmid preparation were as described by Maniatis and co-workers (31).

Preparation of RNA, Northern Hybridization, and Ribonuclease Protection Assay (RPA)—Total cellular RNA was extracted by the guanidium thiocyanate-cesium chloride method (32). Northern hybridization analysis was done as described previously (29). Template DNA (1 μg) for KC, CAT, and β-actin were transcribed in vitro to generate an [α-32P]UTP radiolabeled, single-stranded RNA hybridization probe for RPA using the Maxiscript kit. Total cellular RNA (10 μg) from transfected cells treated with or without stimulus for the indicated times before hybridization with radiolabeled cRNA (5 × 10⁶ cpm) following the manufacturer’s instructions. Protected fragments were electrophoresed on a 5% denaturing polyacrylamide gel containing 8% urea in 1× TBE buffer (90 mM Tris, 64.6 mM boric acid, and 2.5 mM EDTA (pH 8.3)). Gels were exposed to x-ray film and quantified by phosphorescence analysis as described previously (33).

Transfection—Reporter plasmids were transiently transfected into BALB/c 3T3 or H5V cells using the Transfekt transfection reagent following the manufacturer’s instructions.
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Fig. 3. IL-1α but not TNFα stabilizes KC mRNA in H5V and MCT-1 cells. A, H5V cells were treated with nothing (NT), IL-1α (10 ng/ml), or TNFα (10 ng/ml) for 2 h in medium containing 1% fetal calf serum. Each culture was subsequently treated with Act D (5 μg/ml), and incubation was continued for the indicated times (untreated cultures were harvested before the addition of Act D). Total RNA was prepared and used in RPA to detect β-actin or KC mRNAs. The gels were quantified by Phospholimager, and the ratio of KC to β-actin in each sample was calculated and used to determine the relative amount of specific mRNA remaining in each sample. Similar results were obtained in two separate experiments.

IL-1α and TNFα Are Equivocative in Signaling Activation of NFκB and Transcription from the KC Gene Promoter—Though previous work indicated that transcriptional activation of the KC gene in BALB/c 3T3 cells was comparably stimulated by both TNFα and IL-1α (27), we wished to further explore the primary signaling pathways used by these agents. Three separate experimental strategies were employed that focused on the NFκB transcription factor family known to be a major signaling end point for IL-1α and TNFα (10, 12, 13) and central to transcriptional activation of the KC gene (28). IκBα, a major regulator of NFκB activity in the cytosol, undergoes rapid, stimulus-induced phosphorylation, ubiquitination, and proteosome-mediated degradation, resulting in the release of NFκB dimers (37). In BALB/c 3T3 cells, both IL-1α and TNFα stimulation resulted in comparable degradation of IκBα within 15 min; IκBα re-expression was observed within 30 min (Fig. 2A). Consistent with this observation, DNA binding activity specific for a κB sequence motif from the KC gene promoter was markedly elevated in cells stimulated with either agent (Fig. 2B). Finally, when BALB/c 3T3 cells were transfected with a plasmid containing the CAT gene linked to a 104-base pair fragment from the KC gene promoter (28), both TNFα and IL-1α produced substantial and comparable expression of reporter gene activity (Fig. 2C). These three experimental results provide definitive support for the equivalent sensitivity of BALB/c 3T3 cells to both stimuli and confirm that both produce similar transcriptional stimulation of the KC gene. Furthermore, they clearly indicate that the differential response to IL-1α for the accumulation of KC mRNA involves signaling events distinct from those leading to the activation of NFκB.

IL-1α Stabilizes KC mRNA Expression—Previous work has demonstrated that the half-life of KC mRNA in IL-1α-treated BALB/c 3T3 cells was prolonged relative to the half-life in TNFα-treated cells (27), and this finding was confirmed in the mouse endothelial cell line H5V (Fig. 3A). H5V cells were treated with IL-1α or TNFα for 2 h before treatment with Act D to block transcription. After further incubation for the indicated times, levels of KC and β-actin mRNA were assayed by RPA. After 2 h of stimulation with TNFα, KC mRNA levels were low in comparison to IL-1α-treated cells, and the mRNA exhibited a half-life of approximately 30 min. In contrast, the level of KC mRNA in IL-1α-treated cells was substantially greater, and the rate of mRNA decay was markedly reduced (half-life estimated to be ≥3 h). In this experiment, the mRNA concentrations at the time of addition of Act D varied markedly between cell cultures stimulated with either TNFα or IL-1α, and this difference might significantly influence the decay kinetics. In a second experiment, the epithelial cell line MCT-1 was used to assess the impact of IL-1α on TNFα on decay of KC mRNA that had been induced by an unrelated stimulus (serum) (Fig. 3B). MCT-1 cells were cultured in 10% serum and treated with Act D and either IL-1α or TNFα for the indicated times before analysis of mRNA levels by RPA. Starting levels of KC mRNA were comparable; in the presence of TNFα, KC mRNA decayed with a half-life of approximately 30 min,
whereas in IL-1α-treated cells, the half-life was estimated to be >4 h. Thus IL-1α can stabilize KC mRNA in the absence of transcriptional stimulation.

Multiple Regions within KC mRNA Are Necessary for Constitutive Instability and IL-1α-induced mRNA Stability—The stability of a specific mRNA is determined by nucleotide motifs within the primary sequence of the mRNA molecule (38, 39). Although sequences within the 3′-UTR are most frequently linked with regulation of mRNA stability, the 5′-UTR and coding region have also been implicated. To localize the cis-acting sequence elements responsible for IL-1α-induced KC mRNA stabilization, a set of plasmids was constructed in which sequences from the 5′-UTR and 3′-UTR of the KC mRNA were inserted within the transcription unit of the CAT reporter gene using pCATcontrol as the backbone plasmid (Fig. 4). H5V cells were transiently transfected with the indicated constructs and treated with Act D either alone or with IL-1α, and levels of β-actin and CAT mRNA were measured by RPA at the indicated times (Fig. 5). In this experiment, CAT mRNA transcribed from pCATcontrol plasmid exhibited a half-life of approximately 4 h, and this behavior was not significantly altered in cultures treated with IL-1α. In contrast, CAT mRNA derived from pCAT5′-3′-UTR plasmid decayed with a half-life of approximately 90 min and could be stabilized by treatment with IL-1α. Although the decay of KC mRNA is more rapid than that of the modified CAT mRNA (KC half-life = 30 min, CAT5′-3′-UTR half-life = 90 min), the introduction of KC mRNA sequences clearly modifies the metabolism of CAT mRNA, indicating that such a sequence may be an important determinant of IL-1-dependent control of specific mRNA levels.

To determine the relative contribution of the 5′- and 3′-UTR KC mRNA sequences in mediating both constitutive instability and IL-1α-enhanced stability of CAT mRNA, H5V cells were transfected with pCATcontrol, pCAT5′-3′-UTR, pCAT3′-UTR, or pCAT5′-UTR plasmids, and the stability of corresponding CAT mRNAs was determined in the presence or absence of IL-1α (Fig. 6). Only CAT mRNA containing both the 5′- and 3′-UTR regions of KC mRNA was unstable in untreated cells and markedly stabilized in cells treated with IL-1α. CAT mRNA from cells transfected with pCATcontrol, pCAT5′-UTR, or pCAT3′-UTR plasmids showed little or no decay, and treatment with IL-1α neither increased nor decreased the rate of CAT mRNA degradation. Thus, a combination of sequences within the KC 5′-UTR and the full-length 3′-UTR is apparently required to confer both constitutive instability and sensitivity to IL-1α-mediated stabilization.

AU-rich motifs have been shown to be responsible for the

![Fig. 4. Schematic outline of CAT mRNA reporter plasmids.](http://www.jbc.org/)

![Fig. 5. KC mRNA stability is determined by sequences in the 5′- and 3′-UTRs.](http://www.jbc.org/)
short half-life of many growth factors and cytokine mRNAs (38, 40, 41). KC mRNA contains several AU-rich segments in its 3′-UTR, including a cluster of four overlapping AUUUA pentamers. To determine whether this clustered ARE is necessary for constitutive instability and/or sensitivity to IL-1α-mediated stabilization, two plasmid constructs were prepared and analyzed (see Fig. 4). The first plasmid contained a 116-nt fragment (nt 408–524 from the KC mRNA 3′-UTR containing the ARE cluster) placed in the 3′-UTR of the CAT reporter and a 68-nucleotide fragment (nt 1–68 from the KC 5′-UTR) placed 5′ to the CAT coding sequence and termed pCAT5′/ARE. The second plasmid contained the 68-nucleotide KC 5′-UTR and the full-length KC 3′-UTR sequence (nt 357–952), in which the ARE cluster was mutated by nucleotide substitution at positions 449–461 and was termed pCAT5′/AREmu. H5V cells were transiently transfected with these plasmids and treated with Act D with or without IL-1α for the indicated times (Fig. 7). mRNA transcribed from pCATcontrol plasmids decayed modestly over the experimental time period (t1/2. 4 h), and this was not altered by IL-1α treatment. Furthermore, CAT mRNA transcribed from the plasmid pCAT5′-UTR exhibited a half-life that varied between 90 min and 2 h in untreated cells and was stabilized by IL-1α treatment, as expected from prior findings (See Figs. 5 and 6). CAT mRNA derived from pCAT5′/ARE was also destabilized in untreated cells as compared with control CAT mRNA and was stabilized in cells treated with IL-1α. These results indicate that the ARE cluster is likely to be the important region of the KC 3′-UTR. CAT mRNA containing the full KC 3′-UTR sequence but in which the ARE cluster motif had been mutated exhibited a half-life comparable with that of control CAT mRNA in untreated cells, and this was not altered in cells treated with IL-1α. Thus the ARE sequence motif is necessary for both the constitutive instability of reporter mRNA and for conferring sensitivity to IL-1α-mediated stabilization.

As a test of the nucleotide sequence specificity of the 68-nt
5′-UTR fragment, H5V cells were transfected with a plasmid construct containing the 116-nt ARE-containing fragment placed in the 3′-UTR of the reporter gene but in which the 5′-UTR region was inserted in the opposite orientation (pCAT5′-rev/ARE) (Fig. 8). mRNA encoded by pCAT5′-UTR was predictably destabilized in untreated cells (t1/2 < 90 min) and was stabilized by IL-1α treatment as expected. CAT mRNA transcribed from pCAT5′-rev/ARE demonstrated a half-life ≥4 h and showed no difference in cells treated with IL-1α. Thus the sequence of the 68-nt 5′-UTR fragment is orientation-dependent and is required, along with the ARE cluster region in the KC mRNA 3′-UTR, for constitutive instability and for sensitivity to IL-1α-mediated mRNA stabilization.

**DISCUSSION**

Chemokines are now believed to be critical players in the development and resolution of inflammatory reactions (17–19). The overlapping target cell specificity and receptor utilization of many chemokines, however, suggest that the control of chemokine expression in vivo may be an important determinant of their distinct functions (19). The expression of many chemokine genes is known to be controlled at the level of transcription, and the mechanisms involved are well studied (27, 28, 42–45). It is likely, however, that post-transcriptional mechanisms are also important. Indeed, prior work from this and other laboratories has demonstrated that stimulus-dependent changes in specific chemokine mRNA stability can be an important and even critical determinant of the level of specific chemokine gene expression (27, 46–48). In the present study, we have explored the IL-1α-mediated post-transcriptional regulation of mouse KC gene expression. The results of these experiments support the following conclusions. 1) IL-1α-mediated stabilization of KC mRNA is a general phenomenon that can be detected in fibroblast, epithelial, and endothelial cell types. 2) The IL-1α-initiated intracellular signaling pathway leading to the activation of NFκB is not sufficient for inducing alterations in KC mRNA stability. 3) Nucleotide sequences in the 5′-UTR and 3′-UTR of KC mRNA are both required for destabilizing the message and for conferring sensitivity to IL-1α for mRNA stabilization.

IL-1α/β and TNFα are known to exhibit broadly overlapping functional activities that include the ability to modulate proinflammatory gene expression in a wide array of cell types (5–8). Not surprisingly, these agents also share many intracellular signaling components (9–13). For example, both TNFα and IL-1 are known to stimulate the activation of NFκB, and data presented here demonstrate that, under the experimental conditions employed, both agents were equipotent stimuli for the induced degradation of IκBα, the activation of κB sequence-specific DNA binding activity, and the stimulation of NFκB-dependent gene transcription. Receptor occupancy by either IL-1α or TNFα leads to a series of sequential protein-protein interactions that are distinct for each ligand receptor pair (10, 12, 13). Both pathways, however, converge with involvement of TRAF6 and share in common the downstream components NIK, the IκB kinase complex, and finally the release and nuclear translocation of NFκB. The finding that IL-1α but not TNFα can stimulate the stabilization of KC mRNA clearly demonstrates that IL-1α is able to activate signaling events that are not shared with TNFα. In this regard, TNFα and IL-1 have been reported to produce differential effects in some cell types and/or to use nonidentical signaling pathways to achieve the same biologic outcomes (14, 16, 49). At least a portion of this diversity is likely to involve the contribution of the stress-activated/mitogen-activated protein kinase signaling pathways (14, 16, 49), and recent reports link these signaling pathways with regulation of mRNA stability (50, 51).
IL-1-mediated modulation of stability is a property of all AREs or is restricted to a subset at present not known.

Furthermore, there have been many reports identifying RNA-binding proteins that exhibit sequence specificity for AREs (57–61). At least two families of ARE-binding proteins have been well characterized. The Elav family (embryonic lethal abnormal vision) contains at least four members (elr A-D), one of which, termed HuR or elr A, is widely expressed and has been clearly demonstrated to bind AREs and regulate the stability of ARE-containing mRNAs (62–64). A second well-characterized RNA-binding protein is termed AUF1 and is a member of the heterogeneous nuclear ribonucleoprotein family (65). The binding of the HuR protein with an ARE containing mRNA is correlated with mRNA stabilization, while interaction with AUF1 appears to destabilize the target mRNA (62–64, 66, 67). Which, if either, of these proteins participates in the mechanism of IL-1α-mediated KC mRNA stabilization will be the object of future studies.

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