MOLECULAR AND CELLULAR BIOLOGY, Jan. 1990, p. 418–421
0270-7306/90/010418-04$02.00/0

Vol. 10, No. 1

A Gene That Encodes a Protein Consisting Solely of Zinc Finger Domains Is Preferentially Expressed in Transformed Mouse Cells

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Received 25 July 1989/Accepted 5 October 1989

We describe the cloning and characterization of the mouse *MOK-2* gene, a new member of the Krüppel family of zinc finger proteins. Sequencing of both cDNA and genomic clones showed that the predicted MOK-2 protein consists of seven zinc finger domains with only five additional amino acids. The finger domains of MOK-2 are highly homologous to one another but not to those of other zinc finger proteins. *MOK-2* is preferentially expressed in transformed cell lines, brain tissue, and testis tissue. Its possible role in cellular transformation is discussed.

Many specific nucleic acid-binding proteins are built around common structural motifs. One such well-known motif is the zinc finger domain which was first described in the *Xenopus laevis* transcription factor TFIIIA involved in transcription and storage of 5S RNA (1, 10, 31–33). This protein contains nine imperfect tandem repeats of approximately 30 amino acids, and each repeat contains two cysteines and two histidines at invariant positions (2, 13, 23). It was proposed that each of these units folds as an independant domain centered on a zinc ion coordinated by the cysteines and histidines and interacts with about five nucleotides on the DNA molecule (2, 23, 27). Subsequently, zinc finger domains have been found in many other genes from a wide variety of species (11, 19). The *Drosophila* Krüppel gene (*Kr*) encodes a zinc finger protein that is involved in segmentation control in embryos. This gene has been used as a probe to isolate related zinc finger genes from frogs (29), mice (3, 6), and humans (30). The Krüppel family of zinc finger proteins is distinguished by a high degree of conservation of the H/C link sequence which connects the final histidine of one finger with the first cysteine of the next finger (35). The amino acid sequence of the H/C link is HT GEKP(Y/F)XC, in which X can be any amino acid.

Here we report the isolation and characterization of *MOK-2*, a new member of the Krüppel family from mice. Surprisingly, seven highly repetitive zinc finger domains account for 97.5% of the deduced MOK-2 protein. Transcription studies show that *MOK-2* is preferentially expressed in several different transformed cell lines compared with the parental untransformed cell lines. It is also expressed in a tissue-specific manner in mice.

Isolation and sequences of mouse *MOK-2* and genomic clones. To select Krüppel-related murine cDNA clones, a cDNA library constructed by Okayama (unpublished data) with mRNA from MCA16 cells (C3H1OT1/2 mouse cells transformed by 3-methylcholanthrene; 36) was screened at low stringency with a synthetic oligonucleotide, 5′ GCATC GAATGGCCGTTCACCAGTGTG 3′, which encodes the Drosophila Krüppel H/C link (35), and with the 562-base-pair *Eco*RI fragment containing the finger region of mouse gene *mkr1* (6). Five plasmids which hybridized to both probes were isolated after screening of 10^5 colonies. Partial sequencing revealed the presence of zinc finger structures in four plasmids called *MOK-1*, *MOK-2*, *MOK-3*, and *MOK-4* (data not shown). The complete sequence and the predicted amino acid sequence of the *MOK-2* cDNA clone are shown in Fig. 1. The sequence is 2,343 nucleotides long and terminates with a stretch of 24 adenine residues but does not contain a canonical AATAAA polyadenylation signal (12) in the 3′ untranslated region. On the basis of the estimated size of the *MOK-2* mRNA [approximately 3,000 nucleotides, including the poly(A) tail (see below)], *MOK-2* cDNA is probably nearly complete. This clone revealed a single extended open reading frame of 603 nucleotides, beginning at an ATG codon (position 878) and extending to a TAA termination codon (position 1481). The reading frame encodes a polypeptide of 201 amino acids with a calculated molecular mass of 22,812 daltons. This coding sequence is preceded within the cDNA by a 5′-flanking region of 877 nucleotides containing numerous stop codons in all three reading frames. Surprisingly, 97.5% of this predicted protein sequence consists of seven zinc finger domains.

To ensure that the *MOK-2* cDNA clone did not undergo rearrangements or recombination during construction of the library, we isolated and analyzed the corresponding genomic DNA. An EMBL4 mouse genomic DNA library was screened under stringent conditions with a 1,452-base-pair *Hin*dIII fragment of *MOK-2* cDNA, and two recombinant bacteriophages, *G11MOK-2* and *G12MOK-2*, were isolated after screening of 10^6 recombinants. Phage DNA was isolated from each clone, digested with different restriction enzymes, and compared with the *MOK-2* cDNA clone by Southern blotting with the 5′ untranslated *Hin*dIII-*Xho*I fragment (nucleotides 482 to 930) of the cDNA as a probe. Phages *G11MOK-2* and *G12MOK-2* contain approximately 15 kilobases of mouse DNA. The partial restriction maps show that the 5′ and 3′ termini of the inserts are different (Fig. 2, digestion by *Bam*HI and *Xho*I; data not shown). However, in the region corresponding to *MOK-2* cDNA, the same bands were detected by the probe when the genomic DNA and *MOK-2* cDNA were digested by *Hin*dIII and *Bam*HI or *Hin*dIII and *Xho*I. This suggests that there was no gross rearrangement of this region during cDNA cloning. To confirm that the genomic DNA and *MOK-2* cDNAs are identical, we sequenced the complete cDNA region of phage *G11MOK-2* after subcloning it into M13 vectors. The ge-

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   1 CACCTCCATCAGGACCATACTGGCATGTGCTGCACAGGCATCCTTGCAGGCAAAACACTTAACACGTGAA
  71 ATAAAAATCTTTAAAGTGAGAGAAAGAGAAAAGACTTCAGGATTTTTCCTAGTGGCTGATTTTGAAAGAA
 141 ATGGCCAGTCAGTAGCTGGAAGTTGAGTTTATATTGTGAATCTTCAAGAGGTACACACCAATACTGAAGT
 211 AGATTGCTGTCAAAAGTGGGGAGAAGTGTCTTGCCATATTTCCCAAAACCACAGATTTCGGTGACTCTTT
 281 AAAGTTATTTCACCAACATTGAAAGTGGAAAAAAAATTTTTTATCTTTGAAATCCTAAGCCAAATAACCA
 351 ACAGGTCTCCTCTGAAATGTGTGTGTGTGTGGGGGGGGGGGGAGTCTCTCTGCAACTAGAAGAAAGAGGG
 421 AGAGAAAAGGAATAAGGGAGAGTTTCATCCCACACACCACTGTTGAGAGACTGGTCAAGTCAAGCTTCCA
 491 GGTGATGTGACAGAACTGGCACCTCCAACATTCTCTGCTGAGACAATGCGCCAAAAATGTCTCCTTTGAC
 561 TGTAACAGTAAGGACATTTTTATAGGGACGTCACCATTAGTCACTTGGAGTCTTCAAAGAGAGACGCACAC
 631 AGAGGAATCCGGTGACTGGTGATTCCTAGGAGATGCTTATCACCAACCCAGATGGTCACCTCTTCAAGAA
 701 AATCCCCACTTCAGAACAACTGTGCACGCGTGATCGGTGTAGTGAGGATTTCATTCAGAGCTCAGAACTG
 771 ATGAGTCATCAGAGAGACCACCTGAAAGAAAAAGCCTGCGGGCGGGAGCATTGTGGCAGGGCCTTCACTG
 841 GCCAATCAAGTCCCGTTTCCGCATCAGGCAGTCCAC ATG GCT GAG AAA CCT TAC AAA TGC
   1                                      M   A   E   K   P   Y   K   C
 901 GAC AAG TGC GGG AAG GGT TTC ACC AGG AGC TCG AGT CTG CTT GTC CAT CAT TCC
   9 D   K   C   G   K   G   F   T   R   S   S   S   L   L   V   H   H   S
 955 CTC CAT ACC GGT GAG AAA CCT TTC AAG TGT GAC AGG TGT GGG AAG GGC TTC AGC
  27 L   H   T   G   E   K   P   F   K   C   D   R   C   G   K   G   F   S
1009 CAG AGC TCA AAG CTC CAC ATC CAC AAG AGA GTC CAC ACC GGT GAG AAG CCG TAT
  45 Q   S   S   K   L   H   I   H   K   R   V   H   T   G   E   K   P   Y
1063 GCG TGC GAG GAG TGC GGT ATG AGC TTC AGT CAG CGA TCC AAC CTG CAC ATC CAC
  63 A   C   E   E   C   G   M   S   F   S   Q   R   S   N   L   H   I   H
1117 CAA CGT GTC CAC ACC GGA GAG AGG CCC TAC AAG TGT GGG GAG TGC GGA AAA GGC
  81 Q   R   V   H   T   G   E   R   P   Y   K   C   G   E   C   G   K   G
1171 TTC AGC CAG AGC TCG AAC CTC CAC ATC CAC CGG TGC ACC CAC ACG GGA GAG AAG
  99 F   S   Q   S   S   N   L   H   I   H   R   C   T   H   T   G   E   K
1225 CCG TAC CAG TGT TAC GAA TGT GGG AAA GGC TTC AGC CAG AGT TCA GAC CTT CGG
 117 P   Y   Q   C   Y   E   C   G   K   G   F   S   Q   S   S   D   L   R
1279 ATC CAC CTC CGA GTA CAC ACC GGG GAA AAG CCC TAC CAC TGC GGC AAG TGT GGG
 135 I   H   L   R   V   H   T   G   E   K   P   Y   H   C   G   K   C   G
1333 CAG GGC TTC AGC CAG AGC TCC AAA CTC CTC ATC CAT CAG AGA GTT CAC ACG GGT
 153 Q   G   F   S   Q   S   S   K   L   L   I   H   Q   R   V   H   T   G
1387 GAG AAG CCG TAT GAG TGC AGC AAG TGT GGC AAG GGC TTC AGC CAG AGC TCG AAC
 171 E   K   P   Y   E   C   S   K   C   G   K   G   F   S   Q   S   S   N
1441 CTC CAC ATC CAC CAG CGG GTT CAC CGC AAG GAG CTT CAC TAA GTAACATGAGCCCAC
 189 L   H   I   H   Q   R   V   H   R   K   E   L   H   *
1499 TCAGAAGACTTTTATTGTAAAGATAAATATTTTTCACGACCGAGTGTGCATATCAGAGGTAGCATGCTTGC
1570 CTAGCATGTATCAGTCCCTGAGTTTGAGCCCTGATACGCCCCCACCCACACACACACACACACGGTTTCCA
1641 GCTTATTAATACTTTGTGCATGTTAGGAATGTGTGTTCATGCAGAGAGGGGTATGTGTGTTGTCTGGTGT
1712 GTGCATGTATGTGTGCACGCACGTGTGTGGACGTCTGAGGATATCTCAGATACTACATTCTGTATGTGAGA
1783 CTAGGCATCTGTCTGTCACACATGGTGTGTAATGTCACCAAGTAAGCCAGGCCAGAGTCCCATGGATCTAA
1854 CTGTCTCCACTTCCCAGCTCACCGTGGCTAGGGTTGCGGATGTGTGCCACCACATCCAACCTTTTTAGTGG
1925 ATTCTGTCTCAAGCTTTCTAGACAAGAGCTTTGCTGCCTAAGCTATGTCCCAGGGCTCCAGTTTAATACTT
1996 TAAACTCTTACGTTTGAATTCCTCAAAGGAAAGGAAAGAAATAGTTAAGGGTTATTCCGATATAGCCCCTC
2067 ACAGAAGAAATCAATCCGAGTACTCAGCACATTTTATGTTATACAGTGAATGGGTTACTCTGGTTTCTCAT
2138 ATGGGTAGAGTGTCTAATGCAATTCTGCCAGTGTTTGTTAGAATTATATTCTACATTTTTTAACTGCAAGAA
2209 CTCTGTATTTTCCAAGCACAGCATGGTTCCCTTCATTCATATTCTCTGAGAAATTGGAATTCATGTTTCC
2280 TCTGAAATTATGTGCCTTGTTTTTCATATTCCATTTAAGTCCTAAATAGCTCTCTTTAAACTGTAAAAAAA
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FIG. 1. The nucleotide sequence of *MOK-2* cDNA and the predicted amino acid sequence of the encoded protein. Note that 17 A residues at the 3′ terminus are omitted. The amino acid sequence is numbered from the first ATG codon, and the termination codon is marked with an asterisk. Exactly the same sequence was found for genomic DNA. The cDNA clone *MOK-2* and the genomic clone *G11MOK-2* were sequenced by using a combination of specific oligonucleotide priming and cloning of overlapping restriction fragments into M13 vectors. Sequencing was performed by the dideoxynucleotide chain termination method (34) with Sequenase (U.S. Biochemical Corp.).

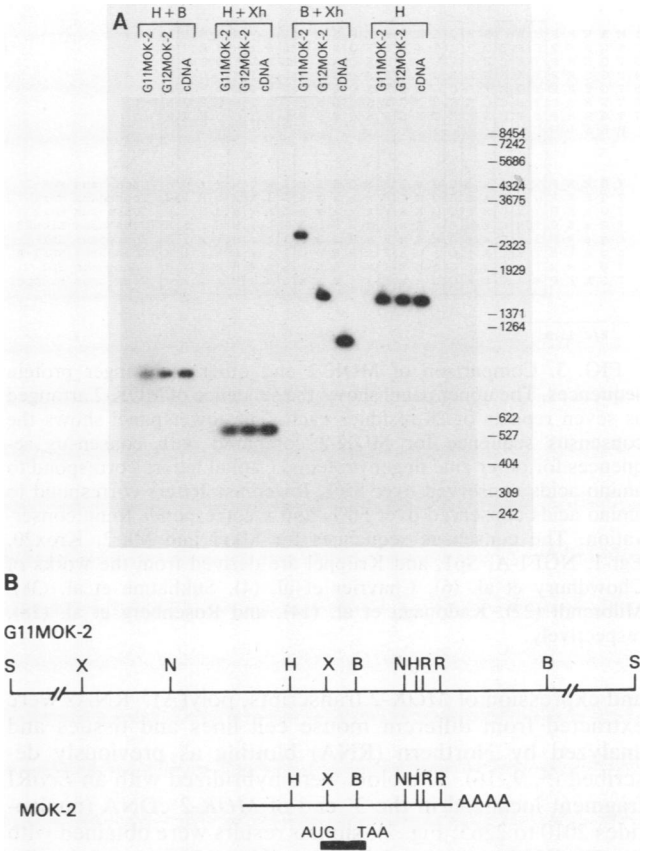

FIG. 2. (A) Southern blot analysis of genomic clones. Genomic phage DNAs (*G11MOK-2* and *G12MOK-2*) and *MOK-2* cDNA were digested with the indicated restriction enzymes and electrophoresed through a 1% agarose gel. The gel was blotted and hybridized to a 5′-untranslated *Hin*dIII-*Xho*I fragment (nucleotides 482 to 939) by standard methods (21). (B) Partial restriction maps of genomic DNA (*G11MOK-2*) and *MOK-2* cDNA. In the *MOK-2* cDNA map, the stretch of A residues represents the poly(A) tail. The black box represents the MOK-2 open reading frame. Abbreviations: B, *Bam*HI; H, *Hin*dIII; N, *Nco*I; R, *Eco*RI; S, *Sal*I; X, *Xho*I.

nomic DNA has exactly the same sequence as *MOK-2* cDNA (Fig. 1). Although no intron was found within the *MOK-2* gene, we cannot exclude the existence of introns in 5′ untranslated sequences missing from the cDNA clone. These studies confirm that the *MOK-2* gene encodes a protein of 23 kilodaltons which consists almost exclusively of zinc finger domains. Other zinc finger proteins contain extensive nonfinger regions, and in TFIIIA (37) and Sp1 (8, 15), these are known to be important for transcriptional activation. Although the function of MOK-2 is unknown, two obvious possibilities suggested by its unusual structure are a transcriptional repressor or a chromatin component.

Zinc finger structures. The predicted MOK-2 protein is highly basic (estimated pI, 10.96) and contain seven almost perfect tandem repeats of 28 amino acid residues (Fig. 3, top). Only the five carboxy-terminal residues are obviously out of the finger region. A comparison of the MOK-2 consensus sequence with the consensus sequences for Krüppel and several mammalian zinc finger proteins is shown in the bottom of Fig. 3. The cysteine, phenylalanine, leucine, and histidine amino acid residues are localized at their characteristic positions in each finger. In addition, as expected on the basis of the work of Schuh et al. (35), the six-amino-acid H/C link sequence is also highly conserved. According to the model of Miller et al. (23), the crucial amino acids that define the specificity of recognition of the target DNA sequence are located in a loop between Cys-11 and His-24. In this region, there is little obvious homology to the other zinc finger proteins, suggesting that if MOK-2 binds to nucleic acids, it must recognize a different target sequence. A striking feature of the MOK-2 sequence is the high degree of homology between the predicted loop sequences of the fingers. Glycine 12 and glycine 14 are found in seven and six repeats, respectively, and the sequence serine 16-glutamine 17-serine 18-serine 19 (sequence SQSS) is strictly conserved in five repeats. In addition, there are many potential DNA-binding residues (25) in the loop sequences. This raises the intriguing possibility that the MOK-2 protein binds to a repetitive nucleic acid sequence. Similar internal homology has been observed in several other zinc finger proteins, including Sp1 (14) and the rodent finger proteins Krox 20 (4), Egr1 (also known as Krox 24 and Zif/268; 7, 20), and NGF1-A (22). The latter three genes are all intermediate early genes which are rapidly and transiently activated during the G_0-to-G_1 transition and are somewhat homologous to one another, suggesting a common target site. *MOK-2* is clearly differentiated from these genes by the lack of homology in the loop region and the fact that it is not induced by serum stimulation (unpublished data).

Expression of *MOK-2* in various cell lines and adult mouse tissues. The *MOK-2* gene is preferentially expressed in transformed cells and certain tissues. To determine the size

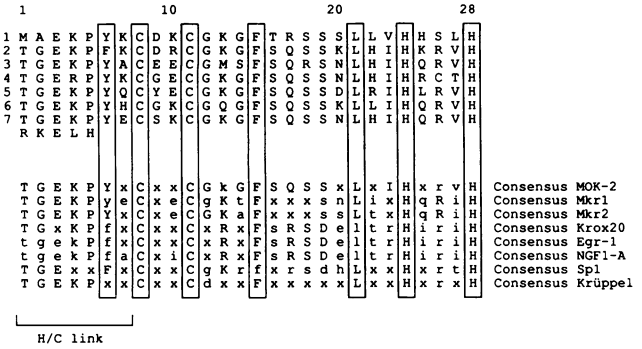

FIG. 3. Comparison of MOK-2 and other zinc finger protein sequences. The upper panel shows the sequence of MOK-2 arranged as seven repeats of 28 residues each. The lower panel shows the consensus sequence for MOK-2 compared with consensus sequences for other zinc finger proteins. Capital letters correspond to amino acids conserved over 85%, lowercase letters correspond to amino acids conserved over 50%, and x corresponds to no conservation. The consensus sequences for Mkr1 and Mkr2, Krox20, Egr-1, NGF1-A, Sp1, and Krüppel are derived from the works of Chowdhury et al. (6), Chavrier et al. (4), Sukhatme et al. (38), Milbrandt (22), Kadonaga et al. (14), and Rosenberg et al. (28), respectively.

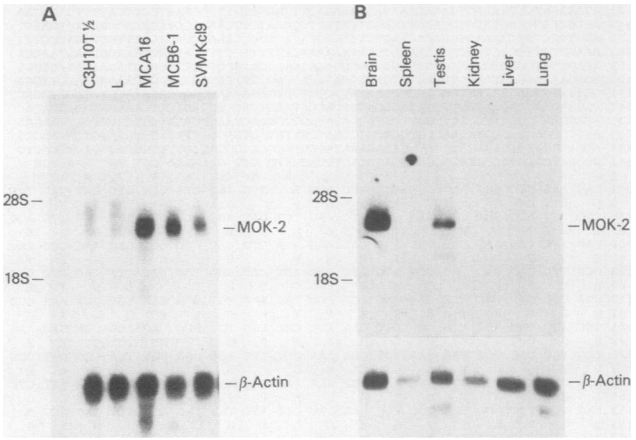

FIG. 4. Northern blot analysis of *MOK-2* mRNA. Poly(A)$^+$ RNAs (10 μg) from different mouse cell lines (panel A) and different mouse organs (panel B) were analyzed by hybridization with the *Eco*RI fragment localized in the 3′-untranslated region (nucleotides 2010 to 2265). The blot was then stripped and rehybridized with a β-actin probe.

and expression of *MOK-2* transcripts, poly(A)$^+$ RNAs were extracted from different mouse cell lines and tissues and analyzed by Northern (RNA) blotting as previously described (5, 9, 16). The blots were hybridized with an *Eco*RI fragment localized in the 3′ end of *MOK-2* cDNA (nucleotides 2010 to 2265; Fig. 2); similar results were obtained with the *Hin*dIII fragment (nucleotides 482 to 1934) containing the finger region, but this probe gives a higher background with 28S RNA (data not shown). A strongly hybridizing 3-kilobase mRNA was detectable in cells transformed by 3-methylcholanthrene (MCA16 and MCB6-1 cells; 26, 36) or simian virus 40 (SVMKcl9; 39) but was weakly, if at all, detectable in the corresponding untransformed cells (C3H10T1/2, L, and kidney cells) (Fig. 4A). Rehybridization of the filters with a β-actin gene probe confirmed that similar amounts of poly(A)$^+$ RNA were present in the different lanes. Expression of *MOK-2* was also examined in different adult mouse organs. The data presented in Fig. 4B and in several other Northern blot experiments (data not shown) showed that the *MOK-2* gene is expressed at a high level in brain tissue and at a moderate level in testis tissue. All other tissues, including spleen, pancreas, liver, lung, and kidney, do not contain detectable levels of *MOK-2* transcripts (with spleen tissue, the RNA sample gave a low β-actin signal, and no *MOK-2* RNA was observed, even after long exposure of the autoradiogram). These results show that expression of the *MOK-2* gene is restricted to certain cell types and tissues.

Two other zinc finger proteins have recently been implicated in neoplastic transformation. The *Evi-1* gene is activated in several retrovirus-transformed myeloid leukemia cell lines (24). The *GLI* gene was identified by virtue of its amplification in a subset of human brain tumors (17, 18). The *GLI* gene is expressed in two embryonal cells but not in any of the tissues examined. In contrast, *MOK-2* is expressed in at least in two adult tissues, brain and testis. The possible role(s) of these genes in the initiation, maintenance, or regulation of transformation is unknown. Our current efforts with *MOK-2* are focused on determining its target nucleic acid sequence and ability to act as an oncogene.

We thank P. Gruss for the gift of the *mkr1* probe, H. Okayama for the mouse cDNA library, and M. Cochet for the mouse genomic library. Many thanks are due to Peter Fürst and Jean Imbert for stimulating and useful discussions.

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