Molecular Cloning of F4/80, a Murine Macrophage-restricted Cell Surface Glycoprotein with Homology to the G-protein-linked Transmembrane 7 Hormone Receptor Family*

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F4/80 is a monoclonal antibody that recognizes a murine macrophage-restricted cell surface glycoprotein and has been extensively used to characterize macrophage populations in a wide range of immunological studies. Apart from the tightly regulated pattern of expression of the F4/80 antigen, little is known about its possible role in macrophage differentiation and function. We have sought to characterize the molecule at the molecular level, through the isolation of cDNA clones, and now describe the sequence of the F4/80 protein. The primary amino acid sequence demonstrates homology to two protein superfamilies. The NH2-terminal region consists of seven epidermal growth factor-like domains, separated by approximately 300 amino acids from a COOH-terminal region that shows homology to members of the seven transmembrane-spanning family of hormone receptors. The potential role of these distinct domains is discussed with respect to the possible function of the F4/80 molecule.

Macrophages play a crucial role in the initiation and effector stages of both innate and adaptive immune responses. A number of specialized cell surface molecules expressed by macrophages participate in these responses, such as macrophage mannose receptor, macrophage scavenger receptor, complement receptor 3 (CD11b/CD18), and opsonic Fc receptors for mannose receptor, macrophage scavenger receptor, complement receptors 1 and 3. F4/80 expression on macrophages is defined by the antigen-specific immunoglobulins. One of the most highly restricted macrophage membrane molecules is defined by the monoclonal antibody F4/80, which recognizes a 160-kDa glycoprotein on the surface of most mouse macrophage populations. The F4/80 molecule is known to be down-regulated by interferon-γ and in response to Bacille Calmette-Guérin infection, as well as being absent from macrophages localized within T cell areas of lymph nodes and spleen. This further suggests that T cells, or a T cell-derived product, may play a role in the regulation of F4/80 expression. The lack of F4/80 expression on migrating veiled cells, derived from F4/80-/- Langerhans cells within the skin epidermis, and the low level of expression on blood monocytes (6, 9) would suggest that the molecule is in some way involved in cell adhesion within certain tissues. As a means of delineating the physiologic role of F4/80 on mature macrophages, we have successfully isolated F4/80 cDNA clones. Herein we report that the primary amino acid sequence of F4/80 shows a degree of homology to two protein superfamilies: the extracellular NH2-terminal region contains seven EGF-like repeats, while the final third of the molecule shows homology to members of the seven transmembrane (Tm7) hormone receptor family.

MATERIALS AND METHODS

Antibodies and Cell Lines—The mAbs F4/80 (rat IgG2b), SC1 (rat IgG1), anti-mouse F4/80, CAMPATH-9 (rat IgG2b; anti-human CD4; a kind gift of Dr. Steve Cobbold, Sir William Dunn School of Pathology), and MRG OX-20 (rat IgG1; anti-mouse IgG; a kind gift of Mike Puklavec, Cellular Immunology Unit, Sir William Dunn School of Pathology) were used in the form of purified IgG or as hybridoma supernatant. The rabbit anti-mouse F4/80 antiserum was raised against purified F4/80 antigen and has been described elsewhere (10). A number of murine cell lines were used: J774.A1 (macrophage), RAW 264.7 (macrophage), N50 (myeloma), NIH-3T3 (fibroblast), L929 (fibroblast), P1G19 (melanoma), BW5147 (thymoma), WEHI-231 (B cell lymphoma), CTL-2 (IL-2-dependent T cell), J558 (lymphoma), and MEL 707 (erythroleukemia). CHO-K1 cells were used in transfection assays.

Peptide Sequencing and cDNA Cloning—F4/80 antigen was purified by Triton X-100 lysis from the J774.A1 cell line, grown as a tumor in the peritoneal cavity of BALB/c mice. The pelleted tumor mass was homogenized on a Polytron tissue grinder in a solution consisting of 10 mM Tris-Cl, pH 7.4, 10 mM NaCl, 3 mM MgCl2, 3 mM iodoacetamide, 1 mM phenylmethylsulfonyl fluoride, and 5 μM of pepstatin. The homogenate was centrifuged at 70,000 g for 7 min to remove the nuclear pellet, which was discarded, and at 100,000 × g for 30 min to collect the membrane-rich fraction. The sample was then extracted with lysis buffer containing 1% Triton X-100, 10 mM EDTA, 5 mM Na2SO4, and the protease inhibitors at 4 °C for 30 min, before spinning at 100,000 × g for 30 min. The supernatant was collected and stored at −70 °C. Before use, the extracts were thawed, and, after the addition of 1 μM disopropyl fluorophosphate, they were pre-cleared at 100,000 × g for 30 min before passing sequentially through a PD-10 column (Pharmacia Biotech Inc.) and a bovine IgG-Sepharose CL4B precolumn followed by a SC1-Sepharose CL4B affinity column equilibrated with lysis buffer. After washing, the SC1 column was eluted with 50 mM diethylamine, pH 11.5, and fractions containing the majority of the protein, as assessed by absorbance at 280 nm, were neutralized with 2 M glycine, pH 2.0, and pooled. The sample was then passed over a second SC1 affinity column, washed, and eluted as before, and the eluate was concentrated over a 100-kDa cut-off SpectraPor membrane (Pierce and Warriner, Chester, UK), filtered through a 0.2-μm filter, and stored at 4 °C. Minor contaminants were removed by preparative SDS-polyacrylamide gel electrophoresis incorporating excision of the antigen band and electroelution. On analytical SDS-polyacrylamide gel electrophoresis, the final antigen preparation...
Sequence of Mouse F4/80

A

B

FIG. 1. A, deduced amino acid sequence of F4/80. The region comprising seven EGF-like repeats (residues 32–367) is indicated by horizontal arrows, and the seven putative transmembrane-spanning regions are underlined. Three potential protein kinase C phosphorylation sites, located intracellularly, are highlighted by asterisks. The F4/80 cDNA sequence is available from EMBL/GenBank/DDBJ under accession number X93328. B, diagrammatic representation of the F4/80 protein structure. EGF-like domains (triangles), N-linked glycosylation sites (lozenges), and the seven transmembrane segments are shown.

Displayed a major homogeneous band, and a minor one possibly corresponding to the precursor form of the molecule. The antigen was recovered, alkylated, and digested with trypsin, from which peptides were subjected to amino acid sequence analysis by gas-phase sequencing. A cDNA library was constructed in the λZAPII vector (Stratagene Ltd., Cambridge, UK) using oligo(dT)-primed cDNA from the J774.2 cell line. Approximately 1 × 10⁶ plaques were screened with rabbit anti-mouse F4/80 polyclonal antiserum and detected with alkaline phosphatase-conjugated goat anti-rabbit IgG. Positive plaques were enriched following two further rounds of screening, resulting in 10 independent clones that were isolated in pBluescriptII-SK(--). The clone containing the largest insert, pF4/80(12.2), was sequenced to obtain unambiguous overlapping readings from both strands. 5'-rapid amplification of cDNA ends PCR, using oligonucleotide-anchored spleen cDNA template, in the presence of an anchor-specific primer and (primary PCR) ends nested PCR using oligonucleotide-anchored spleen cDNA template was performed to characterize the 5' fragment of the F4/80 cDNA. The PCR conditions were as follows: 100 mM dNTP, 10 μM each primer, 2.5 units of Taq polymerase (New England Biolabs, Beverly MA), 100 ng of pF4/80(12.2) as a template, using the following cycling parameters 94°C/1 min, 55°C/1 min, 75°C/3 min for a total of 35 cycles. The amplified fragment was subcloned into HindIII-XbaI-digested pcDNA3 (Invitrogen, San Diego, CA), and the construct was stably transfected into CHO-K1 cells by the calcium phosphate precipitation technique (11). Following transfection, cells were dispersed into 96-well flat bottomed microtitre plates, and clones selected with 250 μg/ml Geneticin (Life Technologies, Inc.). A control construct, pcDNA3/ji-galactosidase, was kindly provided by Dr. David Greaves, Sir William Dunn School of Pathology.

RESULTS AND DISCUSSION

The macrophage cell line J 774.2 has been shown previously to express high levels of the F4/80 antigen (1, 10), and, as such, an amplified cDNA library was constructed with poly(A)⁺ RNA from this source in the AZAPII vector and screened using rabbit polyclonal antisera raised against purified F4/80 antigen. Following a further two rounds of screening, 10 positive clones were isolated and characterized by restriction enzyme analysis and sequencing. None of the clones appeared to contain a full-length cDNA coding sequence, as witnessed by the lack of an in-frame ATG at their 5' end. A 5'-rapid amplification of cDNA ends PCR strategy was therefore applied, utilizing antisense oligonucleotide primers specific for internal sequence within clone pF4/80(12.2) to amplify a cDNA fragment that overlapped pF4/80(12.2) and encoded 46 bp of novel 5' sequence including the ATG initiation codon. The overall composite sequence consists of 3286 bp, including a stretch of 49 adenines corresponding to the poly(A) tail and an upstream AATAAA motif. The open reading frame encodes a precursor of 931 amino acids with a predicted signal peptide of 27 residues, resulting in a mature protein of 904 amino acids with a predicted mass of 98.9 kDa (Fig. 1A). On SDS-polyacrylamide gel electrophoresis analysis, F4/80 appears as a smear of approximately 160 kDa, which, together with the mass differential from the deduced sequence, suggests extensive glycosylation of the molecule. The presence of 10 potential N-glycosylation sites (Asn-X-Ser/Thr) and a region highly rich in Ser and Thr residues (Fig. 1A, amino acids 399–462) suggests that the protein is heavily N- and O-glycosylated in agreement with earlier...
Control pcDNA3/ β-galactosidase construct are shown in panels a and b. Cells transfected with a control pcDNA3/β-galactosidase construct were transfected with a full-length expression construct in the pcDNA3 vector. Following selection with Geneticin, cells were amplified to yield micromolar concentrations of F4/80 messenger RNA (mRNA) expression using the noncompetitive mAbs F4/80 and 5C1 (Fig. 3). The 5C1 mAb was raised against purified F4/80 antigen and has not been described previously. Compared with cells transfected with a control pcDNA3/β-galactosidase construct, the pcDNA3/F4/80 transfectants demonstrated detectable surface expression of the F4/80 antigen.

As further evidence of the identity of the cDNA, CHO-K1 cells transfected with a control pcDNA3/β-galactosidase construct were transfected with a full-length expression construct in the pcDNA3 vector. Following selection with Geneticin, cells were amplified to yield micromolar concentrations of F4/80 messenger RNA (mRNA) expression using the noncompetitive mAbs F4/80 and 5C1 (Fig. 3). The 5C1 mAb was raised against purified F4/80 antigen and has not been described previously. Compared with cells transfected with a control pcDNA3/β-galactosidase construct, the pcDNA3/F4/80 transfectants demonstrated detectable surface expression of the F4/80 antigen.

Northern blot analysis of F4/80 mRNA expression in mouse cell lines. 15 μg of total RNA from each cell line was electrophoresed across a GeneScreen Plus membrane and probed with a 757-bp fragment from pF4/80(12.2) (top panel). Ethidium bromide staining of the gel (bottom panel) demonstrates equal loading of the samples. The relative position of RNA markers are shown.

The primary amino acid sequence of F4/80 demonstrates a high degree of homology to members of two independent protein superfamilies. First, the NH₂-terminal region of the protein contains seven tandem EGF-like domains (13). These repeats of approximately 50 amino acids are characterized by the spatial arrangement of six cysteine residues that form three disulfide bonds within each domain, thereby generating a tightly folded structure. A search of the SwissProt and NBRF-PIR databases with the F4/80 sequence identified a high degree of homology to a number of proteins containing EGF repeats, with the highest scores between F4/80 and connective tissue components such as fibrillin 1 (14) and fibulin 2 (15). As well as the six invariant cysteines, five of the EGF-like domains contain consensus motifs implicated in Ca²⁺ binding (16), which may play a role in stabilizing the conformation required for ligand interaction. Preliminary analysis of the mouse F4/80 gene demonstrates that each separate EGF-like domain is encoded by a single exon as described for the genomic organization of other EGF superfamily members. A role for EGF-like domains in numerous protein-protein interactions has been proposed, such as the critical requirement of two EGF repeats in the neurogenic Drosophila protein Notch for its interaction with the Delta and Serrate proteins (17).

The second region of homology identified between F4/80 and members of a protein superfamily is located at the COOH-terminal region of the F4/80 protein. A hydropathy profile of the F4/80 sequence (18) demonstrated an abundance of hydrophobic residues within a region of approximately 250 COOH-terminal amino acids (Fig. 4), suggesting that the molecule may span the cell membrane a number of times. Protein database searches identified significant homology scores between F4/80 and members of the Tm7 hormone receptor family, including the receptors for peptide hormones such as parathyroid hormone, calcitonin, vasoactive intestinal peptide, glucagon, and secretin (19). This recently described receptor family shares a common overall topology with an extracellular NH₂ terminus, an intracellular COOH terminus, and a central region consisting of seven transmembrane segments, which re-

Fig. 3. Fluorescence-activated cell sorting analysis of pcDNA3/F4/80 transfected CHO-K1 cells, stained with F4/80 (c) and SC1 (d) shown as solid lines. CAMPATH-9 and MRC-0X20 control staining are shown as dashed lines. Cells transfected with a control pcDNA3/β-galactosidase construct are shown in panels a and b.

studies. The predicted amino acid sequence also contained four tryptic peptides obtained from the purified protein, ranging from 64 to 96% similarity (Table I). To confirm that the cloned cDNA encoded the F4/80 protein, Northern blot analysis was performed using RNA from a range of mouse cell lines and screened with a 757-bp probe from clone pF4/80(12.2). Fig. 2 demonstrates that the transcript recognized by this probe is expressed exclusively in cells of the macrophage lineage, in accordance with the well documented macrophage-specific expression pattern of F4/80. The level of mRNA expression in J 774.2 cells is also higher than in RAW 264.7 cells, which correlates with the increased level of F4/80 surface expression on the J 774.2 line. The approximate size of the mRNA species (3.2 kb) also correlated well with the size of the cloned cDNA. As further evidence of the identity of the cDNA, CHO-K1 cells were transfected with a full-length expression construct in the pcDNA3 vector. Following selection with Geneticin, cells were amplified to yield micromolar concentrations of F4/80 messenger RNA (mRNA) expression using the noncompetitive mAbs F4/80 and 5C1 (Fig. 3). The 5C1 mAb was raised against purified F4/80 antigen and has not been described previously. Compared with cells transfected with a control pcDNA3/β-galactosidase construct, the pcDNA3/F4/80 transfectants demonstrated detectable surface expression of the F4/80 antigen.

Fig. 2. Northern blot analysis of F4/80 mRNA expression in mouse cell lines. 15 μg of total RNA from each cell line was electrophoresed through a 1.2% denaturing agarose gel, transferred to a Genescreen Plus membrane and probed with a 757-bp fragment from pF4/80(12.2) (top panel). Ethidium bromide staining of the gel (bottom panel) demonstrates equal loading of the samples. The relative position of RNA markers are shown.

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results in three external loops and three internal loops. Characteristic residues were found to be conserved between F4/80 and the members of this particular subset of Tm7 receptors in the transmembrane segments (with the exception of Tm6), the three intracellular loops and the cytoplasmic tail immediately following Tm7. In addition, F4/80, in common with the other members of the family, contains a cysteine residue in each of the first and second extracellular loops. The formation of a disulfide bridge between these cysteines is believed to be crucial to the overall tertiary structure of the receptors. The Tm7 receptors interact with heterotrimeric α-β-γ G-proteins, on the cytosolic surface of the membrane, which are involved in signal transduction following ligand binding to the extracellular loops of the Tm7 molecule (20). The F4/80 ligand, and function, remains unknown, and its identification will determine whether F4/80 serves as a receptor for a hormone involved in macrophage differentiation and function. The presence of seven EGF-like repeats in the NH2-terminal region of F4/80 is an unusual divergence for Tm7 molecules which, with a limited number of exceptions (20, 21), have relatively short NH2-termini with no defined protein superfamily domains. We suggest that F4/80 possibly interacts with two separate ligands, via the EGF-like domains and an extracellular portion of the Tm7 multispans region, respectively. This notion is strengthened by the presence of an Arg-Gly-Asp motif (Fig. 1A; amino acids 506–508), often found in matrix proteins with multiple EGF repeats, which could play a role in cell adhesion following recognition by an integrin molecule (22). Based upon the structural elements and macrophage-restricted expression pattern of the molecule, we propose that F4/80 is involved in macrophage adhesion within tissues combined with receptor signaling following its interaction with a peptide ligand, possibly resulting in the activation of adenylate cyclase and increased intracellular cAMP levels (19). This receptor activity may therefore influence macrophage responses within a defined tissue microenvironment.

A recent report has described the cloning of a cell surface molecule (designated EMR1) from a human neuroectodermal cDNA library, which shows an extremely high degree of similarity to the F4/80 sequence described here (23). This sequence shows 68% overall identity to F4/80 and contains six EGF-repeats and seven postulated transmembrane segments. Reverse transcriptase PCR analysis suggests that expression of the EMR1 molecule is not as tightly regulated as F4/80 is in mice, although increased levels of EMR1 transcripts appear to be expressed in peripheral blood mononuclear cells. The wide distribution of EMR1 expression, in comparison with the restricted pattern of F4/80 expression, is intriguing. The development of mAbs directed to the human protein will aid greatly in defining the localization of cells expressing this molecule, as will in situ hybridization studies on normal human tissue sections. The deduced structure of the F4/80 and EMR1 proteins suggests a role in the cellular response to an undefined hormone or an interaction, possibly through the EGF-like repeats, with an alternative protein ligand. The identification of the F4/80 ligand(s) will help to elucidate the function of this specialized molecule in macrophage physiology.

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