Molecular Mechanism of Human CD38 Gene Expression by Retinoic Acid

IDENTIFICATION OF RETINOIC ACID RESPONSE ELEMENT IN THE FIRST INTRON

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CD38 is a nonlineage-restricted type II transmembrane glycoprotein possessing ecto-NAD\(^+\) glycohydrolase activity. Because of its unique expression pattern in lymphocyte differentiation, it appears to function as an immunoregulatory molecule. We previously reported that CD38 was specifically induced by all-trans-retinoic acid (RA) in human promyelocytic leukemia HL-60 cells. Here we studied the molecular mechanism of the RA-dependent induction of human CD38. The expression of CD38 mRNA by RA appeared to be caused by the transcriptional stimulation of the gene, since it was blocked by an RNA synthesis inhibitor, but not by a protein synthesis inhibitor. In search of the RA response element (RARE) possibly present in human CD38 gene promoter, we isolated and sequenced the genomic DNA covering the 5'-flanking region, exon 1, and partial intron 1. Transient transfection experiments revealed that the responsiveness to RA was conferred through an RARE consisting of two direct repeat TGACCT-like hexamer motifs with a 5-nucleotide spacer, which was located in the first intron rather than the 5'-flanking region of the CD38 gene. This RARE interacted with heterodimer composed of RA receptor and retinoid X receptor in vitro. Thus, the RA-induced expression of the human CD38 gene was demonstrated to be mediated through the RARE located in the first intron.

The human cell surface antigen CD38 is a 46-kDa type II glycoprotein with a short amino-terminal cytoplasmic domain and a long carboxyl-terminal extracellular domain (1). The expression pattern of CD38 has been widely investigated after the cell surface antigen was first identified as T10 by means of monoclonal antibodies directed against human T lymphocytes (2). Using these antibodies, CD38 was found to have a rather unique distribution pattern. It is strongly expressed on lymphocyte precursors, weakly expressed on peripheral B and T lymphocytes, up-regulated on activated lymphocytes and mature plasma cells, and also displayed on resting natural killer cells, monocytes, and granulocytes (2–8). Because of this curious pattern of the distribution in lymphocyte differentiation, CD38 expression seems to be regulated by a complex mechanism.

Besides the unique distribution pattern of CD38, interest in the cell surface molecule has grown recently after the finding that CD38 has an amino acid sequence similar to Aplysia ADP-ribosyl cyclase (9), an enzyme that catalyzes the formation of cyclic ADP-ribose from NAD\(^+\) (10) and that it indeed acts as a multifunctional enzyme catalyzing the formation and hydrolysis of the cyclic nucleotide (11–15). Cyclic ADP-ribose has been expected to be a novel candidate for the mediator or modulator of intracellular Ca\(^{2+}\) mobilization. In addition to these enzyme activities, CD38 has the ability to bind hyaluronate, which is a large glycosaminoglycan existing in the extracellular matrix and on the cell surface (16). Moreover, CD38 is considered to be an important regulatory molecule in the immune system, as inferred from the observation that CD38 ligation by its monoclonal antibodies induces various cell responses including cell proliferation, lymphopoiensis, apoptosis, adhesion, cytokine production, and tyrosine phosphorylation of cellular proteins (17–23).

In human promyelocytic leukemia HL-60 cells, differentiation into granulocytic cells by RA was accompanied with the induction of an ecto-enzyme of NAD\(^+\) glycohydrolase (24). We previously determined that the ecto-NAD\(^+\) glycohydrolase activity was due to the extracellular domain of CD38 (25). CD38 is not expressed when HL-60 cells were treated with other inducers of granulocytic maturation, such as dimethyl sulfoxide, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor (26). Although the induction of CD38 appeared to be rather specific for RA-induced granulocytic differentiation (26) and was mediated by RAR\(\alpha\) (27), 1,25-dihydroxy vitamin D\(3\), which also acts through nuclear receptors, was recently reported to increase CD38 expression in activated tonsillar B cells, peripheral T cells, and also in HL-60 cells (28). Quite recently, it has been reported that transgenic mice expressing an antisense construct of RAR\(\alpha\) lacked or produced very low levels of CD38 in various tissues (29). This finding suggests that RA also plays an important role in the transcriptional regulation of CD38 gene in vivo. In the present study, we investigated the molecular mechanism by which RA induces CD38 gene expression and found that a...
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EXPERIMENTAL PROCEDURES

Isolation of Total RNA from HL-60 Cells and Northern Blot Analysis—HL-60 cells were cultured for the indicated times in RPMI 1640 medium supplemented with 10% fetal calf serum (25), and total RNA was prepared from the cells using TRizol (Life Technologies, Inc.). Total RNA (30 μg) was separated by 1.2% agarose-formaldehyde gel electrophoresis and blotted onto a nitrocellulose membrane. The BamHI-ClaI fragment of human CD38 cDNA was labeled with [32P]dCTP by random priming. Hybridization was carried out at 42 °C for 24 h in 5 × SSC (1 × SSC = 0.15 M NaCl, 15 mM sodium citrate), 50% formamide, 0.2 mg/ml salmon sperm DNA, 3 × Denhardt’s solution (1 × Denhardt’s solution = 0.002% Ficoll, 0.02% bovine serum albumin, 0.02% polyvinylpyrrolidon), and 50 mM sodium phosphate (pH 6.8). The plasmid carrying cDNA sequence for elongation factor 1α (PAN7) was kind gift from Dr. Yoshito Kaziro, Tokyo Institute of Technology, Yokohama, and was used for the hybridization probe as a control.

Isolation of Human CD38 Genomic DNA—pCDM-CD38 containing human CD38 cDNA was kindly supplied from Dr. David G. Jackson, Institute of Molecular Medicine, University of Oxford, United Kingdom (1). A recombinant λ phage which contained 11 kbp of human CD38 genomic sequence covering 6 kbp of the upstream region (CG11) was isolated from a human genomic λ EMBL3 library using a PCR-amplified 180-bp fragment including 69 bp of noncoding and 111 bp of coding regions of human CD38 cDNA as a probe.

Construction of Plasmids—The 11-kbp BamHI fragment from CG11, which contained the 5′-flanking region of CD38 promoter, exon 1, and intron 1, was subcloned into a pUC18 cloning vector (pCD11) for sequencing. pCDP1.7-CAT was constructed by inserting a Ncol-BglII fragment (CDP1.7; −1639 to +37) of pCD11 into a XbaI site upstream of the coding sequence for CAT in the reporter plasmid of pCAT-Basic (Promega). pCAT-Control harboring SV40 promoter and enhancer was purchased from Promega. pCDP1.7-CAT-I1.4 was constructed by inserting a PCR-amplified fragment (I1.4; +73 to +1492 bp) of pCD11 into a BamHI site of pcDP1.7-CAT.

The pG.CAT plasmids containing a series of various fragments of the intron 1 (I1.4) were constructed as follows. Various fragments of I1.4 as shown in Figs. 3 and 4 were amplified by a PCR reaction using primers having an additional sequence for BamHI digestion. The PCR-amplified fragments were digested with BamHI and inserted into a BamHI site upstream of the rabbit β-globin short promoter of pG.CAT (30). Synthetic oligonucleotides were also used for the construction of another deletion (+741/+765) and mutation (MUT1–3) plasmids. All constructions were verified by sequencing. DR5-G.CAT plasmid was described previously (31).

Cell Transfection and CAT Assay—For the transfection into HL-60 cells, the growing cells were washed twice with phosphate-buffered saline and suspended in opti-MEM I medium (Life Technologies Inc.) at the concentration of 5 × 10⁶ cells/ml. Reporter plasmids (20 μg of DNA) were transfected into the cells by electroporation using a Bio-Rad Gene Pulser (Bio-Rad) at a voltage of 200 V and a capacitance of 960 μF and supplemented with RPMI 1640 containing 10% fetal calf serum. The transfected cells were further cultured with or without 1 μM RA at 37 °C for 36 h. Cell extracts were prepared by freeze-thawing and subjected for CAT assay after normalizing to the total amount of protein, which was determined by the Bradford assay (Bio-Rad).

For the transfection into COS-7 cells, the cells were cultured in Dulbecco’s modified Eagle’s medium containing 5% fetal calf serum, which had been treated with dextran-coated charcoal, in the absence of phenol red. Reporter pG.CAT plasmids (10 μg) harboring the various constructs of CD38 and the rabbit β-globin promoter, together with 0.5 μg of each expression vector for mouse RARα and RXRa (31), were transfected into the cells at 40–60% confluence in 9-cm Petri dishes by means of calcium phosphate coprecipitation. pSV-β-galactosidase (3 μg, Promega) was also co-transfected as an internal control to normalize for variations in transfection efficiency. pUC18 was used as a carrier to adjust the total amount of DNA to 20 μg. The transfected cells were maintained with the calcium phosphate-precipitated DNA at 37 °C for 1 h and cultured with or without 1 μM RA for 19 h. The cells were washed with fresh medium and further

![Fig. 1. Effects of protein and RNA syntheses inhibitors on RA-induced expression of CD38 mRNA in HL-60 cells. Exponentially growing HL-60 cells were cultured with or without 5 nM RA for 4 h in the presence or absence of cycloheximide (1 mg/ml) or actinomycin D (0.1 mg/ml). Total RNA was isolated from the cells and subjected to Northern blot analysis. Relative abundance of CD38 mRNA (6.3 kbp) was calculated by densitometric scanning of the Northern blot (panel A). The relative values shown were normalized to the amount of elongation factor 1α (EF1α) transcript (1.9 kbp, panel B). Molecular size calculated from the position of 28 S (4.7 kbp) and 18 S (1.9 kbp) rRNAs are indicated on the right.](http://www.jbc.org/)

![Fig. 2. Structure and function of human CD38 gene promoter and intron 1. The structure of cloned human CD38 gene (CG11) is schematically shown (upper left). CG11 contained 6 kbp of the 5′-flanking region, 309 bp of exon 1, and 5 kbp of partial intron 1. CAT reporter plasmids containing 1.7-kbp CD38 promoter alone (pCDP1.7-CAT) and the promoter plus 1.4-kbp intron 1 (pCDP1.7-CAT-I1.4) are illustrated. The CAT reporter plasmids and cultured for 36 h in the presence (closed bars) or absence (hatched bars) of 1 μM RA (right panel). The cells were harvested and subjected to CAT assay. Transcriptional activities normalized for protein quantity are expressed as mean values with standard errors from five independent experiments. The fold inductions by RA, which were calculated by dividing CAT activity determined in extracts from RA-treated cells by that in untreated control cells, are shown in open boxes. The activity of pCAT-Control harboring SV40 promoter and enhancer is taken as value of 1 in each experiment.](http://www.jbc.org/)
cultured for 20–24 h. Cell extracts were prepared by freeze-thawing and subjected for CAT assay after normalizing for  

\[ \beta\text{-galactosidase activity} \] as described previously (30).

Gel Retardation Assay—Gel retardation assay was carried out as described before (30). Partially purified histidine-tagged mouse RARa and RXRa lacking the AB region (32) were incubated at 0 °C for 15 min in 10 mM Tris-HCl (pH 7.5), 150 mM KCl, 0.1 mg/ml of double-stranded poly(dI-dC), 1 mM dithiothreitol, 1 mM EDTA, and 10% glycerol. The binding reaction was initiated by adding synthesized oligonucleotides (10,000 cpm) that had been 5'-end-labeled with \([\gamma-32P]ATP\) and T4 polynucleotide kinase, and the mixture was incubated at 20 °C for 20 min. Samples were analyzed on 5% polyacrylamide gel as described previously (30).

RESULTS AND DISCUSSION

Transcriptional Control of CD38 Gene by RA in Intact HL-60 cells—When HL-60 cells were cultured with RA and analyzed by reverse transcription-PCR analysis, CD38 mRNA was significantly detected within 3 h and reached to a maximum level at 18–24 h (25). To determine the mechanism whereby RA induced the expression of CD38 mRNA, effects of RNA and protein synthesis inhibitors, actinomycin D and cycloheximide, respectively, were examined. Northern blot analysis was performed with total RNA prepared from HL-60 cells that had been cultured for 4 h in the presence or absence of RA and the inhibitors (Fig. 1). While actinomycin D strongly inhibited the induction of CD38 mRNA, cycloheximide did not have such an inhibitory effect, implying a transcriptional effect in the RA-induced expression of CD38 mRNA.

Isolation of the CD38 Gene Promoter—A PCR-amplified 180-bp cDNA probe was used to screen a human genomic DNA library. Two positive clones were obtained after screening 1.2310^6 phage plaques. By PCR analysis, we found that one clone (CG11) includes 6 kbp of 5'-flanking region, 0.3 kbp of exon 1, and partial intron 1 spanning 5 kbp (Fig. 2). A BamHI fragment from CG11 was subcloned into a pUC18 cloning vector for further analysis. A BgII fragment consisting of 1.7 kbp of the 5'-flanking region, exon 1, and 1.2 kbp of intron 1 was obtained from the clone and sequenced. In the 5'-flanking region of the CD38 gene, there were several putative cis-elements for transcription factors which may function in hematopoietic cells. Such included MZF-1, a hematopoietic cell-specific zinc finger protein (33, 34), LyF-1, a transcriptional regulator for lymphocyte-specific genes (35), and C/EBPβ, a myeloid-specific transcription factor (36). However, no consensus sequence of the expected RARE was found throughout the 5'-flanking region sequenced.

Recently, Nata et al. (37) reported the genomic structure of human CD38, together with the transcription start site and the partial nucleotide sequence. The nucleotide sequence of the 5'-flanking region reported by them was perfectly identical to that of our clone. To check the transcription start site again in HL-60 cells, primer extension analysis was performed using 1 μM RA (right panel). The cells were harvested and subjected for CAT assay. Transcriptional activities normalized for β-galactosidase activity are expressed as mean values with standard errors from three independent experiments. The RA-induced c-DR5 activity is taken as 100% in each experiment.

FIG. 3. First intron is responsible for RA-induced expression of human CD38 gene. The pG.CAT reporter plasmids containing different regions of human CD38 gene (from 73 to 1456) or consensus DR5 (DR5; GGAGGTCACCGAAAGGTCACTC) (31) in front of rabbit β-globin short promoter (+109/+10) are illustrated in the left panel. COS-7 cells were transfected with the pG.CAT reporter plasmids, together with expression vectors for mouse RARa/RXRa and β-galactosidase. The cells were cultured for 40–44 h in the presence (closed bars) or absence (hatched bars) of 1 μM RA (right panel). The cells were harvested and subjected for CAT assay. Transcriptional activities normalized for β-galactosidase activity are expressed as mean values with standard errors from three independent experiments. The RA-induced c-DR5 activity is taken as 100% in each experiment.

FIG. 4. DNA sequence of the exon 1 and partial intron 1 of human CD38 gene. DNA sequence (from −35 to +1491) covering the exon 1 and partial intron 1 of human CD38 gene is illustrated. The transcription start site is located at +1 bp (arrow). The degenerative DR5 (CD38-DR5) and putative Sp-1 (Sp-1) motifs are boxed.
mRNA from RA-treated HL-60 cells (data not shown). In accordance with the previous report (36), multiple transcription start points were also suggested, but the major one was located about 75 bp upstream of the first ATG (see Fig. 4).

**First Intron of Human CD38 Gene Confers RA Responsiveness**—Although there was no consensus RARE in the sequenced 5′-flanking region, Northern blot analysis in Fig. 1 suggested the existence of an RARE-mediating transcriptional activation by RA in the CD38 gene. To explore the RARE, we analyzed CD38 promoter using a transient transfection assay with the CAT reporter gene. A series of CAT vectors containing various length of the 5′-flanking regions was transfected into

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**FIG. 5. Characterization of RARE in the first intron of human CD38 gene.** 

A, the pG.CAT reporter plasmids containing different regions of the CD38 intron 1 (from +691 to +793) or c-DR5 in front of the rabbit β-globin short promoter are illustrated in the left panel. Transcriptional activities of the plasmids were measured as described in Fig. 3. B, CD38-DR5 sequences of the wild type (WT) and its 2-base mutants (MUT1, MUT2, and MUT3) are illustrated (middle panel). The pG.CAT reporter plasmids containing the wild-type and mutant CD38-DR5 were subjected for measuring the transcriptional activities. The RA-induced c-DR5 activity is taken as 100% in each experiment.

**FIG. 6. Specific binding of RAR/RXR heterodimer to RARE in the first intron of human CD38 gene.** Gel-shift assay was performed with radiolabeled probes consisting of DR5, CD38-DR5 (+741/+765), or its mutants (MUT1, MUT2, and MUT3; see the sequences in Fig. 5B) in the presence (+) or absence of partially purified RARα (RAR) and/or RXRα (RXR). A, an anti-RARα or RXRα monoclonal antibody was also added in the reaction mixture as indicated. B, indicated oligonucleotides at either 10-, 50-, or 100-fold molar excess to the probes were added to the reaction mixture as competitors. Closed arrowheads point to the position of RAR/RXR-DNA complexes, and open arrowheads point to the complex obtained by antibody-induced supershift.
HL-60 cells, and the cells were cultured with or without RA for 36 h. As shown in Fig. 2, pCDP1.7-CAT harboring 1.7 kbp of 5′-flanking region had strong transcriptional activity in HL-60 cells even in the absence of RA, but did not confer RA responsiveness. CAT vectors constructed with longer 5′-flanking regions (2.3 and 6 kbp) also failed to respond to RA (data not shown), suggesting that RARE exists out of the 5′-flanking region tested here. Therefore, we analyzed the first intron of the CD38 gene and found that pCDP1.7-CAT-I.4 covering the 1.2 kbp of intron 1 confers RA responsiveness.

Identification of RARE in the First Intron of Human CD38 Gene—To define the RARE possibly located in the 1.2-kbp partial intron 1, we used COS-7 cells because of the low efficiency in the transfection to HL-60 cells. The CD38 promoter was also replaced with the rabbit short β-globin promoter (−109/+10) to construct a pG.CAT plasmid because of the weakness of the CD38 promoter activity in COS-7 cells. The pG.CAT plasmids constructed with various regions of the intron 1 (from +73 to +1456) were co-transfected with expression vectors for mouse RARα and mouse RXRα into COS-7 cells, and the cells were incubated with or without RA for 40–44 h.

As shown in Fig. 3, the transcriptional activity of pG.CAT (−73/+1456) was increased only 3.6-fold by RA. pG.CAT (+551/+1456) was still induced 2.5-fold by RA. However, the inducibility in pG.CAT (+73/+1097), (+73/+778), and (+691/+1456) were greatly increased to 14−, 86−, and 18-fold, respectively, by RA, although neither pG.CAT (+73/+696) nor (+787/+1456) was induced. These findings indicated that an RARE is located in the region from +691 to +778 and also suggested that there are repressor elements in the regions from +778 to +1097, +1097 to +1456, and +551 to +691, which may function in COS-7 cells. Indeed, the transcriptional activity of pG.CAT (+691/+778) was markedly (220-fold) stimulated by RA (see Fig. 5A).

Directly repeated PuGGTCA hexamer motifs separated by 5′-spaces (DR5; PuGGTCA(N)5PuGGTCA) have been to constitute a consensus RARE which is recognized by RAR/RXR heterodimer and mediates RA-induced gene expression (38). DNA sequence (−35/+1491) covering the exon 1 and partial intron 1 of human CD38 gene is illustrated in Fig. 4. There are DR5-like motifs in the region from +745 to +761; TGACCCgaaagTGC-CCC. This sequence is complementary orientation for CCC. This sequence is complementary orientation for GGGGACtttGGGGTC which has one nucleotide mismatch compared with the consensus DR5 sequence, and this mismatch is similar to that of RARE (AGGTTGACtgctAGGGCA) localized in the promoter regions of complement factor H gene (38). In addition, a putative Sp-1 motif (+731/+738) is present in the upstream of the DR5 motif. Further analysis with pG.CAT plasmids containing the putative Sp-1 plus DR5-like motif (+725/+778) and DR5-like motif alone (+745/+765) suggested that this DR5-like motif, henceforth referred to as CD38-DR5, confers the RA responsiveness by itself (Fig. 5A).

The mutations of 2 bases in each half-site motif within box A and B (pG.CAT (MUT1) and (MUT2)) or both of them (pG.CAT (MUT3)) clearly impaired the ligand inducibility (Fig. 6B), suggesting that the RAR/RXR heterodimer has higher affinity for the consensus DR5 than for CD38-DR5. Mutations in each motif within box A and B or both of them abolished binding of the RAR/RXR heterodimer (Fig. 6C). These results, together with the transcriptional analysis, demonstrated that the DR5 present in the CD38 intron 1 indeed functions as an RARE.

The Existence of Various Cis-elements in the Intron 1 of Human CD38 Gene—In this report, we found that a DR5-like element is present in the intron 1 (+741/+765) of the human CD38 gene. Using deletion and site-directed mutagenesis, this element was demonstrated to act as a functional RARE in both CAT-reporter gene assay and gel-retardation assay. In addition, the 5′-flanking region (−1639/+37) of the CD38 gene had transcriptional activity in HL-60 cells, which was much higher than that of SV40 promoter and enhancer (Fig. 2). There were also repressor elements in intron 1 both upstream and downstream of the RARE upon analysis in COS-7 cells (Fig. 3), although they have not been fully elucidated in the present study. Thus, various cis-elements located in intron 1 appeared to play important roles in the transcriptional regulation of the human CD38 gene.

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