Inhibition of NAD\textsuperscript{+} Glycohydrolase and ADP-ribosyl Cyclase Activities of Leukocyte Cell Surface Antigen CD38 by Gangliosides*

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Miki Hara-Yokoyama*, Iwao Kukimoto†, Hiroshi Nishina‡, Kenji Kontani§, Yoshiro Hirabayashi**, Fumitoshi Irie**, Hiroshi Sugiyata†, Shunsuke Furuyama*, and Toshiaki Katada¶

From the Department of Physiology, Nihon University School of Dentistry at Matsudo, 2-870-1 Sakae-cho Nishi, Matsudo, Chiba 271, the Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo, Hongo, Bunkyo-ku, Tokyo 113, the Department of Life Science, Tokyo Institute of Technology, Midori-ku, Yokohama, Kanagawa 227, and the Laboratory for Glyco-Cell Biology, Frontier Research Program, The Institute of Physical and Chemical Research (Riken), 2-1 Hirosawa, Wako, Saitama 351-01, Japan

We have recently reported that gangliosides act as inhibitors of ADP-ribosyltransferases and NAD\textsuperscript{+} glycohydrolases (NADase) of pertussis toxin and the C3 exoenzyme from Clostridium botulinum (Hara-Yokoyama, M., Hirabayashi, Y., Irie, F., Syuto, B., Morishita, K., Sugiyama, H., and Furuyama, S. (1995) J. Biol. Chem. 270, 8115–8121). Here, we investigated the effect of gangliosides on the enzymatic activity of leukocyte cell surface antigen CD38, which is identified as an ecto-NADase (Kontani, K., Nishina, H., Ohoka, Y., Takahashi, K., and Katada, T. (1993) J. Biol. Chem. 268, 16895–16898). Gangliosides G\textsubscript{M3} and G\textsubscript{M1} inhibited the NADase activity in the immunoprecipitate of anti-CD38 antibody from the membrane extract of retinoic acid-treated human leukemic HL-60 cells. Gangliosides also inhibited the NADase activity of the extracellular domain of CD38 antigen, which was deprived of the transmembrane domain and was expressed in Escherichia coli as a fusion protein with maltose-binding protein (MBP-CD38). The order of the inhibitory effect of purified ganglioside species on the NADase activity on MBP-CD38 was as follows: G\textsubscript{Q1b} > G\textsubscript{D1b} > G\textsubscript{D3} > G\textsubscript{M1b} > G\textsubscript{M2b} > G\textsubscript{M1d} > G\textsubscript{D3} > G\textsubscript{M3} > G\textsubscript{Q1b}. Inhibited the NADase activity of MBP-CD38 in a non-selective manner versus NAD\textsuperscript{+} with a K\textsubscript{c} value of about 0.3 μM. Neither ceramide nor the oligosaccharide moiety of G\textsubscript{Q1b} had an effect on the NADase activity. G\textsubscript{D3b}, G\textsubscript{T1b}, and G\textsubscript{Q1b} also efficiently inhibited the ADP-ribosyl cyclase activity of MBP-CD38. At present, gangliosides are the only endogenous species that can block the enzymatic activity of CD38 antigen. The present results suggest a potential role of gangliosides as inhibitors of the ecto-NADases.

Gangliosides are sialic acid-containing glycolipids mainly present on the outer surface of cell membranes and are considered to be involved in the cell to cell recognition or adhesion processes. On the other hand, recent results suggest that gangliosides modulate the entry of signal into the signal transduction pathway. For example, 2,3-sialylparagloboside, G\textsubscript{M3} and G\textsubscript{M1} regulate the tyrosine kinase activities of insulin (1), epidermal growth factor (2), and nerve growth factor (3) receptors, respectively. However, the structural bases for such interactions have not been elucidated.

We have reported for the first time that gangliosides act as an inhibitor of the ADP-ribosylation using pertussis toxin and C3 exoenzyme from Clostridium botulinum (4). The inhibition is not due to the interaction of gangliosides with the carboxylic acid recognition domain of the proteins, a general motif for the ganglioside-protein interactions. In the case of pertussis toxin, ganglioside G\textsubscript{Q1b} is the most potent inhibitor, and its tandem sialic acid residues linked to the internal galactose residue are crucial for inhibition. Because the inhibition by G\textsubscript{Q1b}, is competitive versus NAD\textsuperscript{+}, we have proposed that a negative charge cluster, formed by the two carboxyl groups in the tandem sialic acid residues, mimics the diphospho moieties of NAD\textsuperscript{+}. Based on our speculation, it is expected that gangliosides with the tandem sialic acid residues also inhibit other enzymes that use NAD\textsuperscript{+} as a substrate.

Leukocyte cell surface antigen CD38 is a type II membrane protein present on the surface of multiple cell lineages of hematopoietic origin predominantly in early and activated phenotypes (5). The expression of CD38 antigen mRNA was also reported in the rat brain, duodenum, heart, and pancreatic islets (6). Ligation of CD38 antigen with specific antibodies has a stimulatory effect on cultured lymphocytes (7), prevents apoptosis of human germinal center B cells (8, 9), or suppresses stroma cell-supported lymphopoiesis of human B cells (10). These results suggest that CD38 antigen positively or negatively modulates the activation signal for lymphocytes. Recently, CD38 antigen is identified as an ecto-enzyme of NAD\textsuperscript{+} glycohydrolase (NADase) (11). CD38 antigen also catalyzes a conversion of NAD\textsuperscript{+} to cyclic ADP-ribose (cADPR), a Ca\textsuperscript{2+}-mobilizing factor from inositol 1,4,5-trisphosphate-insensitive Ca\textsuperscript{2+} stores (12).

To verify the potential role of ganglioside as an inhibitor of the NAD\textsuperscript{+} metabolizing enzymes, we investigated the effect of gangliosides on the NADase and ADP-ribosyl cyclase activities of CD38 antigen in the present study. The results clearly demonstrated that both activities of MBP-CD38 were inhibited by gangliosides, especially by G\textsubscript{T1b}, G\textsubscript{Q1b}, and G\textsubscript{Q2b}. These data

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† To whom correspondence should be addressed. Tel.: 81-473-68-6111; Fax: 81-473-68-6295.

1 The abbreviations for gangliosides are according to Svennerholm nomenclature (36) and our previous publications (15, 37).

2 The abbreviations used are: NADase, NAD\textsuperscript{+} glycohydrolase; cyclic ADP-ribose, MBP, maltose-binding protein; Chaps, 3-(3-cholamidopropyldimethylammonio)-1-propanesulfonic acid; GPI, glycosylphosphatidylinositol.
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**EXPERIMENTAL PROCEDURES**

**Materials**—[carbonyl-14C]NAD$^+$ (25-40 Ci/mmol) was purchased from DuPont NEN. Endoglycoceramidase was from Seikagaku Kogyo (Japan). Ceramide from bovine brain sphingomyelin (type III) was purchased from Sigma. Mouse anti-CD38 monoclonal antibody (IgG$_1$) was purchased from Cosmo Bio (code IO86).

Purification of the MBP-CD38 Fusion Protein and Preparation of the Immunoprecipitate—The extracellular domain of human CD38 cDNA was obtained by reverse transcriptase-mediated polymerase chain reaction from mRNA of human leukemic HL-60 cells that had been differentiated by retinoic acid. Construction of plasmid that encodes a fusion of maltose-binding protein (MBP) to the extracellular domain of CD38 antigen and subsequent purification of the fusion protein were previously described (13). The purified MBP-CD38 was treated with 8 μg guanidine hydrochloride, dialyzed, and stored in 20 mM Tris-HCl, pH 8.0, 100 mM NaCl, and 1% Chaps. The immunoprecipitate of anti-CD38 antibody was prepared from the membrane extract of retinoic acid-treated human leukemic HL-60 cells as described previously (11).

Purification of ADP-ribosyl cyclase from Aplysia ovotestis—ADP-ribosyl cyclase was purified from the cytosolic fraction of ovotestis of Aplysia kurodai as described previously (13).

Preparation of Individual Gangliosides—Total bovine brain gangliosides were applied to a Q-Sepharose column and fractionated into 23 fractions as described previously (14). GM$_1$-a, GM$_1$-b, GD$_1$-a, GD$_1$-b, GT$_1$-a, GT$_1$-b, and GQ$_1$-b were purified from the fractions. GM$_1$, GT$_1$, and GQ$_1$ were purified as described previously (15, 16).

**Assay of Enzyme Activity**—To measure the NADase activity of MBP-CD38, the reaction mixture (10 μl) containing 50 mM MBP-CD38 in Buffer A (50 mM Tris-HCl, pH 8.0, 1 mM EDTA) was preincubated for 10 min at 37°C. Then the reaction was started by the addition of 10 μl of 4.6 μM [carbonyl-14C]NAD$^+$ (2.5 nCi/assay) in Buffer A. After 10 min incubation at 37°C, the reaction mixture was mixed with 5 μl of 50 mM NAD$^+$ and 10 mM nicotinamide and was spotted onto Whatman 3MM paper. The paper was developed by 1 M AcONH$_4$, pH 5.0, 95% EtOH (3.7, v/v) as described previously (17), and NAD$^+$ and nicotinamide were detected under UV light. The radioactivities in these spots were measured. The release of [14C]nicotinamide from [14C]NAD$^+$ was linear up to 15 min of incubation. Because the stock solution of MBP-CD38 contained 1% Chaps, the final concentration of Chaps in the reaction mixture was 18 μM. We noticed that the specific activity of NADase and the extent of the inhibition by gangliosides depend on the concentration of Chaps in the reaction mixture. The specific activity was 30 and 60 nmol/min/mg in the presence of 18 and 90 μM Chaps, respectively. The apparent K$_i$ value of gangliosides in the presence of 90 μM Chaps were about 10-fold greater than those in the presence of 18 μM Chaps (data not shown). For the assay of the NADase activity in the immunoprecipitates, the immunocomplexes were suspended in Buffer A and preincubated for 10 min. The subsequent procedures are according to that for MBP-CD38.

As for the ADP-ribosyl cyclase activity of MBP-CD38, the reaction mixture (10 μl) containing 250 mM MBP-CD38 in Buffer A was preincubated, and the reaction was started by the addition of 10 μl of 200 μM NAD$^+$ in Buffer A. The amount of cyclic ADP-ribose produced after 10 min of incubation at 37°C was measured using radiomunoassay system as described previously (18).

For the assay of Aplysia ADP-ribosyl cyclase activity, the release of nicotinamide from NAD$^+$ was measured, because the release of nicotinamide and production of cyclic ADP-ribose are almost equal (19). The reaction mixture was composed of 20 mM Tris-Hepes, pH 7.4, 1 mM EDTA, 2 mM MgCl$_2$, 30 mM KCl, 50 μM [carbonyl-14C]NAD$^+$, and 0.8 mM Aplysia ADP-ribosyl cyclase. The reaction mixture without [14C]NAD$^+$ was preincubated for 2 min and further incubated with [14C]NAD$^+$ for 2 min. The linearity of the generation of cyclic ADP-ribose or release of nicotinamide versus time was confirmed in the case of ADP-ribosyl cyclase activity of MBP-CD38 or Aplysia enzyme, respectively. In all cases, enzyme was omitted from the reaction mixtures to obtain the background level. The value in the absence of other additions was used as the control. After subtracting the background, the relative values to the control were indicated.

Preparation of the Oligosaccharide Moity of G$_{O1b}$,—G$_{O1b}$ (50 μg) was dissolved in buffer (30 μl) containing 100 mM sodium acetate, pH 6.0, and 1 mg/ml sodium taurocholate, and endoglycoceramidase (0.75 milliunits). After incubation for 14 h at 37°C, the reaction mixture was applied to a C18 Sep-Pak cartridge (Waters) previously washed with methanol and subsequently with water. The oligosaccharide moiety (6 μg) passed through the cartridge as eluted with water, whereas G$_{O1b}$ remained. The oligosaccharide moiety was completely separated from G$_{M1a}$, as checked by thin-layer chromatography.

**RESULTS**

Inhibition of the CD38 Antigen-catalyzed NAD$^+$ Glycohydrolysis by Gangliosides—In human leukemic HL-60 cells, the expression of CD38 antigen is induced by retinoic acid (11). The NADase activity in the immunoprecipitate was inhibited by either G$_{M1a}$ or G$_{Q1b}$, G$_{Q1b}$ inhibited more effectively than G$_{M1a}$, suggesting the specificity of the gangliosides in the inhibition.

Inhibitory Effect of Gangliosides on the NAD$^+$ Glycohydrolysis Catalyzed by MBP-CD38—CD38 antigen is type II integral membrane protein composed of the large extracellular domain with the 256 amino acid residues in the C-terminal region, the transmembrane domain with the 23 amino acid residues, and the small cytoplasmic domain with the 21 amino acid residues in the N-terminal region (20). The extracellular domain of CD38 antigen is an NAD$^+$ glycohydrolase (11). To investigate whether the transmembrane domain of CD38 antigen is involved in the inhibitory effect of gangliosides, the extracellular domain of CD38 antigen was expressed in Escherichia coli as a fusion protein with maltose-binding protein (MBP-CD38). As shown in Fig. 2, the MBP-CD38 catalyzed NAD$^+$ glycohydrolysis was inhibited by gangliosides. Thus, the transmembrane domain is not required for the inhibitory effect of gangliosides. The potency of the inhibitory effect was clearly different among the ganglioside species. G$_{Q1b}$, most effectively inhibited the NAD$^+$ glycohydrolysis. By contrast, G$_{T1b}$, up to 1 μM did not have such an inhibitory effect. G$_{Q1b}$ inhibited the NADase of MBP-CD38 in a noncompetitive manner versus NAD$^+$ with a Ki value of about 0.3 μM (Fig. 3). G$_{Q1b}$ and G$_{T1b}$ were also more effective than the other gangliosides, G$_{O1b}$, G$_{D1b}$, G$_{M1b}$, G$_{M3}$, and G$_{O3}$, G$_{Q1b}$, G$_{Q1b}$, and G$_{Q1b}$ belong to the b-series ganglioside group containing tandem sialic acid residues linked to the internal galactose residue.

Requirement of Both Oligosaccharide and Ceramide Moiety of G$_{Q1b}$ on the Inhibition of NAD$^+$ Glycohydrolysis—The oligosaccharide moiety of G$_{Q1b}$, was prepared by cleaving G$_{Q1b}$ with endoglycoceramidase. As shown in Fig. 4, neither the oligosaccharide moiety nor the ceramide alone was effective in the inhibition. It should be noted that the inhibitory effect of...
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The NAD$^+$ glycohydrolysis catalyzed by MBP-CD38 was measured in the presence of GQ1b (●), the ganglioside moiety of GD3β (△), or ceramide (□) as described under “Experimental Procedures.” The effect of GQ1b was observed either in the absence (○) or the presence (●) of 170 μM ceramide. The values are means from duplicate assays. The values in the absence of other additions was 39.0 nmol/min/mg.

Discussion

Inhibition of the Enzymatic Activities of CD38 Antigen and Aplysia ADP-ribosyl Cyclase by Gangliosides—The present study demonstrates that gangliosides inhibit the NADase and ADP-ribosyl cyclase activities of MBP-CD38. GQ1b, GQ1b, and GT1b were more effective in the NADase inhibition than the other gangliosides. Because the IC$^{50}$ values of these gangliosides (less than 1 μM) were much lower than the critical micelle concentrations (about 100 μM according to Ref. 22), the multivalency of ganglioside micelles is not required for the inhibition. GQ1b, GQ1b, and GT1b were also effective in the inhibition of ADP-ribosyl cyclase activity of MBP-CD38. Furthermore, GQ1b and GT1b inhibited the activity of Aplysia ADP-ribosyl cyclase. In the previous paper, we showed the inhibitory effect of gangliosides on the ADP-ribosyltransferase and NADase activities of pertussis toxin and C3 exoenzyme (4). Here, we confirmed the inhibitory effect of gangliosides on the endogenous NADases.

The physiological role of the NADase or ADP-ribosyl cyclase activity of CD38 antigen is controversial, probably because antibodies of CD38 antigen that inhibit the enzymatic activity have not been obtained. Gangliosides are the first species that are found to block the enzymatic activity of CD38 antigen.
Depletion of gangliosides by inhibitors of glycolipid biosynthesis or overexpression of gangliosides may be helpful to investigate the physiological role of the enzymatic activity of CD38 antigen.

The Importance of the Tandem Sialic Acid Residues—G_{Q1b} and G_{T1b} were more effective in the NADase inhibition of MBP-CD38 than G_{T1a}, and G_{Q1a} respectively, indicating that the tandem sialic acid residues linked to the internal galactose residue are important for the inhibition. To investigate whether the negative charges in the carboxyl groups of the sialic acid residues are involved in the inhibition, we blocked the negative charges by the lactonization of gangliosides (23). The lactonization of G_{T1b} greatly diminished the inhibitory effect (data not shown). Thus, the negative charges in the carboxyl groups are probably involved in the inhibition. Mimicking the diphosphate moiety of NAD by the two carboxyl groups of the tandem sialic acid residues can explain the inhibitory effect of gangliosides, as we have proposed in our previous paper (4). Information on the recognition of the sialic acid residue by proteins so far elucidated has been restricted to that of one sialic acid residue either α2→3 or α2→6 linked. For example, the α2→3 linked sialic acid residue is recognized by selectins (24), and the α2→6 linked sialic acid residue is recognized by CD22 antigen (25). However, the recognition of tandem sialic acid residues has not been reported. The importance of the tandem sialic acid residues in the inhibition of the NAD⁺-involving reaction, ADP-ribosylation, NAD⁺ glycohydrolysis, or generation of cGMP-ADP-ribose, would be a new aspect to elucidate the physiological role of b-series gangliosides.

Among the b-series gangliosides, G_{Q1b} was the most potent inhibitor in the case of the ADP-ribosyltransferase of pertussis toxin (4) or the NADase of MBP-CD38, whereas the inhibitory effect of G_{T1b} prevailed against that of G_{Q1b} for the NADase of C3 exoenzyme (4) or Aplysia ADP-ribosyl cyclase. Although the presence of the tandem sialic acid residues is a basic motif of the inhibition, the specificity of the inhibition is also determined by the other part of ganglioside structure. The sialic acid residue linked to the GaINAc residue facilitates the inhibition of the NADase of MBP-CD38. By contrast, the absence of the sialic acid residue linked to the GaINAc residue is necessary for the inhibition of C3 exoenzyme or Aplysia ADP-ribosyl cyclase. The difference of the specificity in the inhibition suggests the variety of the interaction between b-series gangliosides and the enzymes.

Possible Interaction of Gangliosides with CD38 Antigen—The tandem sialic acid residues of gangliosides are important for the inhibition of the NADase activity of MBP-CD38. However, the oligosaccharide moiety of G_{Q1b} did not have the inhibitory effect. Thus, the remaining part of G_{Q1b}, the ceramide moiety, is also required for the inhibition. The decrease of the inhibitory effect of G_{Q1b} in the presence of excess amount of ceramide suggests that the ceramide moiety is involved in the binding of G_{Q1b} to MBP-CD38. The binding of ceramide moiety is considered to be a prerequisite for the inhibition. Such binding of the ceramide moiety probably do not compete with that of NAD⁺, causing the noncomprehensive type inhibition of G_{Q1b} versus NAD⁺.

MBP-CD38 does not contain the hydrophobic transmembrane region of CD38 antigen. Although the hydrophobic region is not predicted in the primary structure (20), the binding of 8-anilino-1-naphthalenesulfonate to MBP-CD38 suggests the presence of hydrophobic area on the surface of MBP-CD38. Such hydrophobic area on MBP-CD38 probably interacts with the ceramide moiety. If a similar interaction occurs between native CD38 antigen and gangliosides, gangliosides may induce the internalization of the extracellular domain of CD38 antigen, because the ceramide moiety is usually embedded in the lipid bilayer.

Biological Implication—CD38 antigen is supposed to modulate the onset of signals for lymphocyte activation (5, 7–10). So far, the natural ligands of CD38 antigen have not been definitely identified. The present result raised a possibility that gangliosides interact with CD38 antigen in vivo.

In lymphocytes, the association of glycosylphosphatidylinositol (GPI)-anchored proteins and nonreceptor type tyrosine kinases has been reported (26–28). Although a GPI-anchored protein Thy-1 is present in detergent-insoluble glycolipid microdomains, neither cavelin nor the caveola-like structure is present in lymphocytes (29). There may be another type of core structure consisting of glycolipids and membrane-spanning proteins to connect the GPI-anchored proteins to the tyrosine kinases in lymphocytes. CD38 antigen is an integral membrane protein and probably linked to the tyrosine kinases, because ligation of CD38 antigen induces the tyrosine phosphorylation of proteins (30). Recently, we identified one of the tyrosine-phosphorylated proteins stimulated by anti-CD38 monoclonal antibody as c-cbl proto-oncogene product (p120⁺c-cbl) (31). Accordingly, the association of b-series gangliosides with CD38 antigen, if occurring in vivo, is a candidate for the transmembrane core. It is speculated that diverse effects of CD38 ligation (5, 7–10) are due to the stabilization or disruption of the CD38-mediated membrane machinery.

Several ecto-NADase or ecto-ADP-ribosyltransferases have been identified in addition to CD38 antigen. BST-1 is a stromal cell-derived GPI-anchored protein that facilitates pre-B-cell growth (32). BST-1 is homologous to CD38 antigen and has an activity of NADase and ADP-ribosyl cyclase (33). The rat alloanogen RT6 is a GPI-anchored ecto-ADP-ribosyltransferase expressed on lymphocytes (34, 35). RT6 may regulate the activity of cytotoxic T cells (34). The present study provides an idea that b-series gangliosides interact with the ecto-NADase molecules. Further study should be required to verify the in vivo interactions between b-series gangliosides and ecto-NADase molecules.

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