The Human Semaphorin-like Leukocyte Cell Surface Molecule CD100 Associates with a Serine Kinase Activity*

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CD100 is a 150-kDa homodimeric glycoprotein broadly expressed on the surface of human hematopoietic cells. CD100 has been recently identified as the first lymphoid gene that belongs to the semaphorin gene family. Semaphorins function as chemorepellent molecules in the nervous system, but the function of CD100 remains poorly understood. In lymphoid cells, it has been suggested to play a role in homotypic cell adhesion and in T cell activation. We demonstrate that in T cells and natural killer cells a serine kinase activity is immunoprecipitated with CD100. Distinct epitopes of CD100 have been defined with specific monoclonal antibodies, mediating opposite effects at the functional level, especially in T cells. The kinase activity is retained only with an antibody against a particular epitope of CD100. Additionally, a fusion protein containing the cytoplasmic domain of the molecule retains the kinase activity in cellular lysates, and CD100 itself is presumably a favorite substrate of the kinase. These findings suggest that a serine kinase pathway may participate in the different functional effects triggered through the distinct epitopes of CD100 and is likely involved in the biological effects of this semaphorin-like leukocyte cell surface molecule.

CD100 is a 150-kDa homodimeric human lymphocyte surface antigen initially identified using two different specific monoclonal antibodies (mAb), namely mAb BB18 and BD16, raised in mice immunized with human T cell clones (1, 2). BB18 and BD16 are directed against two different epitopes of the CD100 molecule (3). CD100 is expressed by various cell types, in particular all T cell subsets (3). It is also expressed by B cells, natural killer (NK) cells, and myeloid cells (3). In the human, CD100 appears therefore to be a broadly distributed cell surface antigen in cells from hematopoietic origin. The recent cloning of CD100 has permitted the classification of the molecule into the semaphorin family, since it contains in its extracellular region a semaphorin-like domain (4, 5). CD100 is the first known receptor in hematopoietic cells that belongs to this large and phylogenetically conserved family of cell surface and secreted proteins. Semaphorins have mainly been described in the nervous system as mediators of repulsive growth cone guidance and are critical for the organization of the nervous system (6–8). The semaphorins are structurally defined by a conserved 500-amino acid extracellular domain with 16 conserved cysteines, the so-called sema domain, often followed by an Ig-like domain, as is found in the CD100 molecule. CD100 also contains an additional 104-residue stretch C-terminal to the Ig domain, a transmembrane domain, and a 110-residue cytoplasmic domain with no significant homology with the intracellular part of other semaphorins (4, 5).

So far, nothing is known about the identity of semaphorin receptors, including that of CD100. However, the use of specific mAbs as ligands has permitted the classification of CD100 into the family of T cell activation molecules (2, 9–11). We previously reported that mAbs BB18 and BD16 had distinct effects depending on the activating system used to trigger T cell activation, but both clearly had an agonistic effect. T cell stimulation through various cell surface activation molecules frequently involves a partnership with enzymatical activities, especially kinases and phosphatases, that are proximal elements able to trigger complex intracellular biochemical cascades (12–14). Investigating the status of CD100 associations in human T cells, we recently discovered that CD100 was linked to the phosphatase CD45 (15), a key membrane molecule in the T cell receptor activation process (16). In the present report, to further document the signaling pathway associated with CD100, we determined whether a protein kinase might also be associated with this semaphorin-like leukocyte cell surface structure. We find that a cellular kinase activity can physically associate with the cytoplasmic domain of CD100. We show that CD100 itself is presumably a favorite substrate of this kinase, and we also provide arguments that a differential participation of the kinase may account for the distinct functional effects triggered by the different epitopes of CD100.

EXPERIMENTAL PROCEDURES

Cells and Antibodies—The human leukemic T cell line Jurkat and the human CD25-negative NK line YT22C2 were propagated in RPMI 1640 medium supplemented with 10% fetal calf serum, 2 mM l-glutamine, 1% sodium-pyruvate, and antibiotics. Peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteer donors by Ficoll centrifugation. To obtain activated T cells, PBMC were cultured for 4 days in the same medium as above supplemented with 1 mg/ml phytohemagglutinin (PHA; Difco). CD100-specific mAbs BD16 (IgG1) and BB18 (IgG1) were obtained as described previously (1, 17). They were produced as ascitic fluid and purified by affinity chromatography on a protein A- or G-Sepharose
were grown at 37 °C and induced with 100 μM buffer containing 50 mM Pipes, pH 6.8, 10 mM MnCl₂, 10 mM MgCl₂. Fusion protein complexes, prepared as described above, were washed with the fusion protein coupled to glutathione beads.

Binding assays, Nonidet P-40 cell lysates were incubated for 1 hour at 4°C in the presence of phosphate-buffered saline containing 0.1% SDS followed by protein was recovered by heating the beads 10 min at 90 °C in the Sepharose CL-4B before immunoprecipitation with 10 μg of the appropriate mAb and protein A-Sepharose. Immune complexes were eluted from the beads by boiling the samples in a Laemmli sample buffer for 3 min. Solubilized proteins were separated by SDS-PAGE and electro-transferred onto nitrocellulose membranes. Blots were probed using horseradish peroxidase-conjugated streptavidin, and an enhanced chemiluminescence detection system (Amersham Life Science, Inc.) on x-ray film (DuPont).

Glutathione S-Transferase (GST) Fusion Protein of the Intracellular Domain of CD100 (GST-CD100)—cDNA encoding the intracellular domain of human CD100 (amino acids 754–863, Fig. 1 and Ref. 4) was expressed as a GST fusion protein. The recombinant plasmid was used to transform Escherichia coli protease-deficient strain BL21. Cultures grown at 37 °C and induced with isopropyl-β-D-thiogalactopyranoside for 1 h. Cells were harvested by centrifugation. The pellet was washed once in 50 mM Tris, pH 7.5, 150 mM NaCl, 1 mM EDTA, 1 mM sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride, 50 units/ml aprotinin, and 1 mM leupeptin for 30 min at 4 °C. After a centrifugation at 12,000 × g to remove cellular debris, the lysates were precleared with protein A-sepharose CL-4B before immunoprecipitation with 10 μg of the anti-CD100 monoclonal antibody (BB18, kindly provided by Dr. M. Y. de Genet, Meudon, France). After 5 min at 30 °C, the reaction was started by the addition of the beads of 30 μl of phosphorylation buffer supplemented with 1 μCi of [γ-32P]ATP (4000 Ci/mmol, ICN Biomedicals France, Orsay, France). When indicated, 1 μg of myelin basic protein (Sigma) was added as an exogenous substrate. In some experiments we used a recombinant wild-type form of the Src tyrosine kinase p56lck expressed in SF9 insect cells (0.5 μl of a crude cell lysate) and kindly provided by Dr. S. Fisher (INSERM U 363, Institut Cochin de Génétique Moleculaire, Paris, France). After 5 min at 30 °C, the reaction was stopped by the addition of 40 μl of SDS-PAGE sample buffer and boiling for 3 min. The beads were separated by 10% SDS-PAGE and the gel was then washed with 1 M KOH at 55 °C for 2 h. Assays were performed with inhibitors of protein kinases (see “Results”) obtained from Calbiochem (France Biochem, Meudon, France) to determine their effect on the cellular kinase activity retained by the GST-CD100 fusion protein. Quantification of radioactivity was achieved by transferring the dried gel to a high resolution β-imager (Biospace, Paris, France), allowing us to obtain a digital autoradiogram and quantitate signals by direct measurement of numerical images obtained from actual counting of β-particles emitted.

For phosphoamino acid analysis, phosphoproteins were revealed by autoradiography of the undried gel then excised and digested with 5.9 μl of HCl for 1 h at 110 °C. The digested material was then dried in a speedvac apparatus, and the pellets were resuspended in 20 μl of a buffer containing 2.2% formic acid and 1.38 mM acetic acid, pH 1.9. Samples were analyzed by two-dimensional thin layer chromatography on nitrocellulose-coated plates (Merck, Darmstadt, Germany) using the pH 1.9 buffer for the first dimension (900 V for 90 min) and a buffer containing 5% acetic acid and 0.5% pyridine, pH 3.5, for the second dimension (900 V for 45 min). Standard phosphoamino acids (phosphothreonine, phosphoserine, and phosphothreonine; Sigma) were run in parallel and visualized by spraying the plates with a 1% ninhydrin solution and heating at 80 °C before autoradiography.

RESULTS

CD100 Is Associated with a Kinase Activity in Jurkat T Cells—The T cell stimulating properties of two CD100 mAbs, BB18 and BD16, which recognize different epitopes of CD100, have been previously reported (2, 9–11). Since protein kinases are frequently essential elements of receptor-triggered signaling events leading to T cell activation, we performed in vitro kinase assay experiments using CD100 immunoprecipitates obtained from Jurkat T cell lysates. As shown in Fig. 2, panel A, different phosphoproteins can be observed in the BB18 immunoprecipitate. They include two bands migrating with an apparent molecular mass of 150 and 120 kDa (see also panel B) and additional phosphorylated proteins in the 80-, 55–60-, and 33-kDa regions of the gel. The results were not different with Jurkat cells previously activated with anti-CD3 (not shown). The phosphoprotein patterns obtained with the CD2-specific mAb 0275 used as a positive control of kinase-associated receptor (19) and with an IgG1 irrelevant mAb (referred to as control in Fig. 2 and in all subsequent experiments) are also shown. The kinase activity was indifferent to the lysis conditions, since the same pattern could be obtained when using Nonidet P-40 instead of Brij-58-based lysates (Fig. 2B). Intriguingly, as shown in Fig. 2, A and B, we found that the CD100-specific BD16 mAb failed to precipitate a detectable amount of phosphoproteins.
only CD100-specific mAb BB18 Immunoprecipitates the Kinase Activity—To further investigate this point, we used Jurkat cell lysates previously labeled with biotin to perform CD100 immunoprecipitations followed by parallel Western blot analysis and in vitro kinase assays. As shown in Fig. 3A, BD16 (lane 2) and BB18 (lane 3) mAbs immunoprecipitated almost equal amounts of biotinylated CD100. However, in the in vitro kinase assay shown in Fig. 3B, only BB18 (lane 3) retained the kinase activity as compared with BD16 (lane 2) or a control antibody (lane 1). We also show in the same experiment that immunodepletion with BD16 totally removes the kinase activity immunoprecipitated with BB18 (lane 4), excluding that BB18 and BD16 recognize distinct populations of CD100. Preliminary experiments showed that the kinase activity was likely of the serine kinase nature (see Fig. 5 below). Thus, in vitro kinase assay experiments were also conducted using myelin basic protein, an exogeneous serine kinase substrate. As shown in Fig. 3, lower panel, using increasing amounts of Jurkat cell lysate, BB18, strongly retained the kinase activity. Only a faint phosphorylation of myelin basic protein was seen with BD16 immunoprecipitates.

The CD100-associated Kinase Phosphorylates CD100 and a 120-kDa Protein in Various CD100-positive Cells—CD100 is an homodimeric glycoprotein that usually migrates in reducing conditions as a unique band around 150 kDa (3). However, after labeling with biotin, we frequently observed an additional protein migrating with an apparent molecular mass of 120 kDa in CD100 immunoprecipitates. This is shown in Fig. 4A, where we analyzed Jurkat T cells, the CD100 highly positive YT2C2 NK cell line, unstimulated PBMC, and PHA blasts. An additional biotinylated 120-kDa band is clearly observable in the BB18 immunoprecipitates from YT2C2 cells and PHA-activated T cells. This band was always less evident in Jurkat cells and especially in freshly isolated PBMC. In vitro kinase assays were performed in parallel with the same cell lysates. Fig. 4B shows the results obtained with mAb BD16 and BB18. With BB18, two phosphorylated bands with the same molecular mass as the biotinylated proteins observed in Fig. 4A could be detected in YT2C2 cells and PHA blasts. In Jurkat cells, together with the major phosphoprotein of 150 kDa, the additional band around 120 kDa was weakly labeled, confirming the results obtained in Fig. 2. No bands were detected with unstimulated PBMC in this experiment, but we observed a faint labeling of the 150-kDa band with some donors (not shown). Several conclusions can be drawn from these results. They first demonstrate that the kinase activity is associated with CD100 in the different cell types, including normal T cells. They also strongly suggest that in BB18 immunoprecipitates, the 150-kDa phosphoprotein is CD100, and the 120-kDa band is an additional form of CD100 or a CD100-associated membrane protein highly expressed in YT2C2 and activated PBMC (see “Discussion”). Finally, they confirm that BD16 immunoprecipitates do not retain the kinase activity whatever the cell type.

CD100 Is Phosphorylated on Serine Residues—We further investigated whether the 150- and 120-kDa phosphoproteins were phosphorylated on tyrosine or on serine/threonine residues. YT2C2 cell lysates were immunoprecipitated with mAb BB18, an in vitro kinase assay was performed, and the phosphorylated protein was separated by SDS-PAGE (Fig. 5A). The 150- and 120-kDa phosphoproteins were then subjected to phosphoamino acid analysis (Fig. 5B). The majority of the radioactive phosphate was on serine residues in both phosphoproteins. The 150-kDa band was slightly labeled on threonine residues. No phosphotyrosine could be detected.

A Cellular Serine Kinase Activity Is Specifically Retained by the Intracellular Domain of CD100—Human CD100 has been recently cloned (4), and we constructed a GST fusion protein of its intracellular domain (GST-CD100i) to investigate if it could retain a kinase activity. As shown in Fig. 6B, after Coomassie Blue staining, the fusion protein migrates with an apparent molecular mass of 40 kDa. Various amounts of glutathione-Sepharose-bound GST or GST-CD100i fusion proteins were incubated with a Jurkat cell lysate then washed and subjected to in vitro phosphorylation, and the proteins were separated by SDS-PAGE. As shown in Fig. 6A, a kinase activity can be retained by the polypeptide corresponding to the intracellular...
Human CD100 Molecule Associates with a Serine Kinase

A cellular kinase activity is specifically retained by the intracellular domain of CD100. A. Nonidet P-40 Jurkat cell lysates \((5 \times 10^6 \text{ cells})\) were incubated with increasing amounts of GST or GST-CD100i recombinant fusion proteins immobilized on Sepharose beads. After washing, the beads were subjected to \(\textit{in vitro}\) kinase assays. For the GST precipitates, 1 \(\mu\text{g}\) of soluble GST-CD100i was used as an additional control substrate added just before the kinase assay. B. Coomassie Blue staining of the gel shown in \(A\). Ipp, immunoprecipitates.

DISCUSSION

A broad range of serine/threonine kinases have been identified in lymphoid cells. But only a few of these activities have been found to be directly associated with cell membrane receptors. In B cells, for instance, an association of immunoglobulin with a casein-kinase-like serine/threonine kinase has been reported (26). Immunoprecipitates of the B cell-specific membrane proteins CD19 and CD20 also contain a serine kinase activity (27, 28). In T cells it is noteworthy to mention the case of Raf-1, a serine/threonine kinase associated with the CD3 \(\delta\) and \(\gamma\) chains and with the CD4-p56\(^{ck}\) complex (29, 30) and of a serine kinase activity associated with CD5 in T cells (31). We report in the present study the immediate association of the CD100 activation molecule with a serine kinase activity, a finding that may be an essential step in the elucidation of downstream signals mediated by the engagement of this new class of hematopoietic receptors.

We initially suspected that the enzymatic activity found in CD100 immunoprecipitates would be endowed by the CD100 molecule itself. Our very recent knowledge of the CD100 amino acid sequence reveals none of the particular consensus sequences found in protein kinases; thus, this possibility can now
be excluded. Nevertheless, our experiments with the GST-CD100i recombinant protein suggest a close and maybe constitutive interaction between the intracellular domain of the molecule and a cellular serine kinase. They also show that the cytoplasmic tail of CD100 is a very good substrate for the associated kinase, in good agreement with its sequence, which contains numerous potential serine/threonine phosphorylation sites (Fig. 1). We can thus speculate that in vivo one major target of the kinase detected in BB18 immunoprecipitates is the intracellular domain of CD100. Consistent with this, we have been able to precipitate CD100 as a 150-kDa phosphoprotein in some human T cell clones labeled in vivo with $^{32}$P. However, this was not consistently reproduced using transformed cell lines (not shown). In vitro phosphorylation of CD100 always appeared undetectable or very low in resting T cells compared with PHA-activated cells. This suggests either a link between the state of activation of the cell and CD100 association with the kinase or an increase in the kinase activity after cell stimulation. This point is under investigation. If true, it would be reminiscent of what has been shown after T cell antigen receptor or CD5 activation for the serine kinase activity associated with CD5 (31). However, the level of CD100 expression by T cells, which is increased by activation (2), may also be partly responsible. Besides CD100, a 120-kDa protein was usually found in CD100 immunoprecipitates and was phosphorylated in in vitro kinase assays (Figs. 2 and 4). Preliminary data suggest that it may arise from cleavage in the intracellular domain of one chain of a 150-kDa homodimer, resulting in a truncated form of CD100 associated with the integral CD100 membrane protein.

Multipotipotopic characterization of cell surface antigens using different specific mAbs is often a fruitful approach, particularly when one can distinguish these mAbs by their capacities to induce different functional effects. This is the case with mAbs BD16 and BB18, which differentially influence CD5- or CD2-induced proliferation of PBMC and purified T cells (9, 11). We report here the different behavior of these two CD100 mAbs at a biochemical level, although they clearly have similar binding capacities as attested by immunoprecipitation experiments. One puzzling observation in the present work concerned the effect of BD16 epitope ligation on the CD100-associated kinase activity, since we were unable to measure a significant kinase activity in CD100 immunoprecipitates. The most likely hypothesis is that perturbation of the BD16 epitope induces a direct conformational change of the molecule thereby altering its association with the intracellular kinase.

In our recent and parallel work in human T cells, a physical link between CD100 and the phosphatase CD45 was observed (15). It is noteworthy that before the discovery of CD100, the association of CD45 with an unknown 150-kDa protein was already reported in human peripheral blood lymphocytes (32). Such a finding suggested a functional association between the two molecules at the cell surface. Stover and Walsh (33) recently showed that the protein-tyrosine phosphatase activity of CD45 in vitro was enhanced after sequential phosphorylations on tyrosine and serine residues (33). Regulation of CD45 by the CD100-associated serine kinase is thus quite possible. Moreover, we previously published that mAb to CD100 and CD45 gave similar effects on CD2-triggered PBMC proliferation (3). Altogether, these findings suggest a close relationship between the two molecules, an important result since CD45 plays a key role in regulating the T cell activation process through receptor-associated tyrosine kinases (34–38).

Signaling molecules with either attractive or repulsive effects might be involved in guiding lymphoid cells to their appropriate destinations. In the nervous system, proteins of the semaphorin family contribute to this phenomenon, since they appear to control axonal pathfinding during neural development by inhibiting growth cone extension and reorientation (6–8). The finding that CD100 is homologous to the semaphorin gene family, which includes both transmembrane and secreted proteins (39), is therefore of the highest interest. Furuyama et al. (5) cloned the murine homologue of CD100, termed M-semaG. The sema domain has 88% amino acid identity to human CD100 and the cytoplasmic domain has 94% identity, implying a highly conserved signaling function. Inagaki et al. (40) also identified an additional transmembrane semaphorin in mouse brain that contains in its extracellular region a semaphorin-like domain followed by a single Ig-like domain. Interestingly, the intracellular domain of this molecule, although very different from the corresponding part of CD100, also has several consensus serine/threonine phosphorylation sites. Therefore, despite the fact that the mechanism of semaphorin action in growth cone collapse is poorly understood, an intracellular signaling cascade is likely involved (40, 41). Whether phosphorylation events are implicated in this process is unknown and does not permit generalizations about signaling by transmembrane semaphorins. Nevertheless, our present results reveal that a serine kinase pathway is likely associated with the CD100 semaphorin. This may help to understand whether CD100 is also a positive and/or a negative guidance membrane receptor for lymphoid cells.

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Human CD100 Molecule Associates with a Serine Kinase

**FIG. 8.** Src kinase p56$^{lck}$ does not phosphorylate GST-CD100i in vitro. Left panel GST (lane 1) or GST-CD100i (lane 2) recombinant fusion proteins (3 μg) bound to glutathione-Sepharose beads were subjected to in vitro kinase assay in the presence of a recombinant form of p56$^{lck}$. Precipitates from Nonidet P-40 Jurkat cell lysates (5×10$^6$ cells) with GST (lane 3) or GST-CD100i (lane 4) immobilized on Sepharose beads were subjected to in vitro kinase assays as in Fig. 6 and run in parallel. Right panel, the same experiment but after KOH treatment of the gel.
Human CD100 Molecule Associates with a Serine Kinase

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