Self Glycosphingolipids: New Antigens Recognized by Autoreactive T Lymphocytes

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T cells may recognize glycolipids and lipids of bacterial and self origin associated with the CD1 antigen-presenting molecules. Understanding the mechanisms governing CD1-self glycolipid interaction will provide information on the molecular rules of glycolipid presentation and suggest new approaches to immunotherapy.

T lymphocytes play a central role in the immune response. They provide important defense mechanisms by killing virus-infected or transformed cells and releasing proinflammatory cytokines that amplify the immune response during infection. T cells may also help B lymphocytes to mature and produce antibodies or play regulatory and inhibitory roles. This is accomplished by the presence of highly specialized T cell subpopulations.

Fundamental for T cell function is the specific recognition of antigens, achieved through a clonally distributed T cell receptor (TCR) that is a heterodimer composed of α- and β- or γ- and δ-chains. T lymphocytes recognize a variety of antigens such as short peptides, phosphorylated metabolites, and glycolipids. A unique characteristic of T cells is that recognition occurs when the antigen associates with a dedicated antigen-presenting molecule, thus forming a complex that by interacting with the TCR initiates T cell activation. Peptides associate with classical major histocompatibility complex (MHC) molecules, which are classified into class I and class II, according with their structure.

Phosphorylated metabolites represent a type of ligand that exclusively stimulates T cells expressing the TCR-γδ. These antigens are produced either by prokaryotic or eukaryotic cells and represent intermediate products during polysaccharide or isoprene synthesis (5). It is likely that phosphorylated metabolites are also presented to T cells by appropriate antigen-presenting molecules. These molecules have not been identified so far.

Glycolipids represent a third type of T cell-stimulatory antigen. Several studies have shown that glycolipids bearing a variety of sugars linked to different types of lipid tails may stimulate T cells expressing the TCR-αβ or γδ. Glycolipids are presented by dedicated antigen-presenting molecules, which belong to the CD1 family. In the human genome there are five CD1 genes, of which only four give rise to protein products expressed on the cell surface and present glycolipids to T cells (4).

TCR recognition of CD1-glycolipid complexes resembles that of MHC-peptide complexes, thus explaining why the TCRs expressed by T cells recognizing peptides or glycolipids are made by the same families of TCR-α and -β genes. In this review, we first describe the CD1 antigen presentation system and then present the insights obtained by studying recognition of self glycosphingolipids by autoreactive T cells. The potential implications of these reactivities in autoimmune diseases are also discussed.

CD1 genes and proteins

Five different CD1 genes, called CD1A, B, C, D, and E exist in humans. These genes are located on chromosome 1, a cluster on the q22 arm, a region paralogous to the MHC locus on chromosome 6.

CD1 proteins show a moderate degree of homology (~30%), and, despite the fact that they are likely derived from an ancestral common gene, they appear to be quite different from each other. Whereas the first four CD1 genes give rise to surface and functional proteins, CD1E is spliced into different variants and transcribed into proteins that remain intracellular. Surface CD1 molecules are conventionally separated into two groups according to their similarities. Group I is composed of CD1a, CD1b, and CD1c, whereas group II consists only of CD1d. All of them are predicted to resemble classical MHC class I molecules. Indeed, all CD1 molecules expressed on the cell surface are heterodimers formed by a heavy chain encoded by the CD1 gene, associated with a light chain encoded by the β2-microglobulin gene.

CD1 molecules also show a transmembrane region and a short intracellular tail. The intracytoplasmic part differs among different CD1 members. In CD1b, CD1c, and CD1d tails, tyrosine-based motif directs CD1 recycling to late endosomes. CD1a molecules lack this motif and recycle in early endosomes. This might be of great importance to present microbial antigens localized in different cellular organelles as a result of preferential bacterial tropism. This feature may also help to explain the duplication and diversification of CD1 genes.

The most important feature of CD1 genes is that they are not polymorphic, this being the main difference from the MHC genes encoding the peptide-presenting molecules. Although minor differences have been found in the CD1 genes among individuals, these polymorphisms are silent or do not seem to lead to main differences with functional relevance. When polymorphism is analyzed in MHC molecules, strikingly it is mainly concentrated in the peptide-binding regions of these proteins and directly participates in the selection of immune responsiveness against protein antigens. An explanation for
this main difference between the MHC and CD1 families is not obvious. One possibility is that the nature of the bound antigens, peptides vs. glycolipids, has represented the driving force stabilizing polymorphism in MHC and not in CD1 molecules. Therefore, the TCR makes cognate interactions with residues in the α1 and α2 domains, which are also capable of binding glycolipids. Between the two α-helices is located a narrow groove, resembling that present in MHC molecules. The CD1 groove is much narrower and deeper than the MHC groove. Furthermore, it is delimited by a series of nonpolar amino acids, which form pockets, ideal for binding hydrophobic molecules such as the lipid tails of glycolipids. The pockets are interconnected and communicate with the external part of the groove through a single small opening placed at the base of the groove.

The pockets are compatible with insertion of the glycolipid hydrophobic tails, thus allowing their anchoring to CD1. Figure 1 illustrates a model of a CD1a-sulfatide complex. This model also predicts that the sugar moieties of the glycolipids are exposed on the external part of CD1 between and/or above the two α-helices. Such a positioning of the hydrophilic part of bound antigens facilitates the cognate interaction with the TCR. This is also the best arrangement, allowing the TCR to discriminate among glycolipids that share the lipid tail but differ in their carbohydrate part.

T cells recognizing CD1-glycolipid complexes

Restriction by CD1 molecules was initially described for two autoreactive T cell clones stimulated by CD1a and CD1c, respectively, without any requirement for exogenous antigens (10). Human T cell lines specific for microbial ligands and restricted by CD1b were later isolated and characterized (12). These cells, which showed a CD8+ or CD4-CD8 double-negative phenotype and expressed apparently random TCR-γδ, recognized the mycobacterial mycolic acid (1), thus demonstrating for the first time that CD1-lipid complexes are stimulatory for T cells. Because phenotypic analyses did not reveal unique surface markers, it is commonly accepted that these cells resemble peptide-specific T cells, being different only in their antigen specificity and, perhaps, type of thymic selection.

At the same time another subset of T cells expressing unique features was described in humans and later also in the mouse (2, 11). Because these cells express the murine natural killer (NK) marker NK1.1 or its homologous human protein NKR-P1.1, they were named NKT cells. More importantly, these cells express a semi-invariant TCR composed of a fixed...
TCR Vα-chain (Vα14 in the mouse and Vα24 in humans) rearranged without N nucleotides to a fixed Jα (murine Jα281 and human JαQ). The Vβ repertoire is also limited, although it is not as invariant as the Vα one. NKT cells are CD4+ or CD4-CD8 double negative and are restricted by CD1d (3).

Antigens recognized by CD1-restricted T cells

The glycolipid antigens identified up until now can be divided into two groups according to their microbial or eukaryotic origin. They are represented by phospholipids, mycolates, and glycosphingolipids. Figure 2 shows the structure of self and bacterial glycolipids known to bind to CD1 molecules and to stimulate specific T cells.

For simplicity, we will discuss glycolipid antigens according to the presenting CD1 family. CD1d presents a variety of endogenous ligands to NKT cells. The structures of these self ligands are not known, and indirect evidence suggests that they bind to CD1d in different cellular compartments and are not present in some cell types.

The glycolipids with a known structure that are presented by CD1d to NKT cells still form a small group. These are α-glucosylceramides that stimulate both human and mouse NKT cells. These molecules are constituted by a ceramide tail, to which a monosaccharide or a disaccharide with an α-anomeric glycosidic bond are attached. Among these ligands, α-galactosylceramide is the most active and is produced by sponges but not mammalian cells (7). Synthetic α-galactosylceramide very efficiently stimulates NKT cells by inducing their expansion in vitro and activation in vivo.

On the contrary, a large variety of glycolipid antigens associate with group I CD1 molecules (9). Several antigens do not contain ceramide and may have one long lipid tail, as in the case of mycolic acid, lipoarabinomannan, hexosyl-1-phosphoisoferooids, and the structurally related mannosyl-1-phosphodolichols, or may have two acyl chains, as does γ-Galactosylgalactosylceramide.

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cose monomycolate. Most of these ligands have been isolated from Mycobacterium tuberculosis, which is very rich in glycolipids. It is likely that other bacteria produce glycolipids capable of binding to CD1 molecules and stimulating CD1-restricted T cell responses.

Another class of CD1 ligands is represented by self glycosphingolipids. These molecules show a structure very similar to that of α-galactosylceramide, because they are made of a ceramide tail attached to different sugars (13). However, in all antigens of this type, the β-anomeric bond is present, thus differentiating them from α-galactosylceramide.

**T cells recognizing self glycosphingolipids in autoimmune diseases**

The discovery that self glycosphingolipids are CD1 ligands has opened new perspectives in the field of T cell response during autoimmune diseases. Human T cells specific for different self glycosphingolipids and restricted by all types of CD1 molecules have been identified and studied (13). These cells were isolated from the peripheral blood of patients with multiple sclerosis (MS), an autoimmune disease characterized by the presence of inflammatory plaques of demyelination in the brain and local accumulation of T cells. Functional tests showed that the clones release large amounts of IFN-γ and TNF-α, thus suggesting their participation in inflammatory reactions in vivo. ELISPOT assays also revealed that the frequency of T cells that react against self glycosphingolipids is higher in MS patients than in control subjects.

Glycosphingolipids such as GM1 ganglioside, sulfatide,galactosylceramide, and sphingomyelin may stimulate individual T cells, thus demonstrating that several self glycolipid ligands may activate autoreactive T lymphocytes. Importantly, T cell clones specific for the same ligands and restricted by all CD1 molecules were also isolated. Thus individual CD1 molecules, although different in their structures, bind the same set of self ligands. These findings suggest that self ligands play important roles in T cell stimulation and perhaps also in CD1 stabilization, intracellular maturation, and surface recycling.

**“...glycosphingolipids bound to CD1 molecules can be readily displaced by other glycosphingolipids.”**

Phenotypic and molecular studies showed that the autoreactive T cell clones express TCRs with different TCR Vα- and Vβ-chains and with TCR CDR3 junctional regions of variable length. Furthermore, immunofluorescence studies revealed a CD4 or a CD8 phenotype and a lack of the NKRPI.1 marker, usually expressed by NKT cells. Thus these T cells resemble classical peptide-specific T cells and do not use the typical semi-invariant TCR of NKT cells.

**Antigen presentation of self glycosphingolipids**

Because glycosphingolipids are self antigens able to elicit an autoreactive T cell response, it is important to understand the mechanisms allowing presentation of these antigens to T cells. Presentation of self glycosphingolipids appears to be quite different from presentation of mycobacterial glycolipids. Glycosphingolipids are presented to T cells without being internalized by the antigen-presenting cell (APC) and bind to intact CD1 molecules on the cell surface (14). On the contrary, mycobacterial ligands require internalization in late endosomes, perhaps because they bind only to partially unfolded CD1 molecules (6). Binding of self glycosphingolipids to CD1a and CD1b molecules has been confirmed by using in vitro refolded soluble CD1 molecules, which also efficiently stimulate specific T cells (14, 15). Thus CD1 molecules bind self glycosphingolipids at physiological pH and in the absence of dedicated chaperones.

Kinetic analysis of antigen loading revealed that CD1 molecules on the APC surface are loaded and were already immunogenic 5 min after pulsing with the appropriate glycosphingolipid. This is true also for recombinant soluble CD1a and CD1b molecules. On the other hand, when the same glycosphingolipids (GM1 and sulfatide) were analyzed for their capacity to remain stably bound to CD1 molecules, they showed a prolonged persistence on the surface of living APC, which varied from 24 h to up to 144 h when tested with recombinant CD1. Thus the on rate of these ligands is slow (on the order of a few minutes), although it is not possible to make a precise calculation due to the tendency of glycolipids to form micelles, which do not allow enumeration of individual ligands. The off rate is instead very long, on the order of several days in vitro. In vivo it is shorter, likely because it is influenced by the half-life of CD1 molecules and by recycling intracellular compartments with low pH where the complexes may be disassembled.

A second important characteristic is that glycosphingolipids bound to CD1 molecules can be readily displaced by other glycosphingolipids. This was shown by using either fixed or recombinant CD1 molecules. Surprisingly, in both experimental systems displacement occurs in <2 h. Thus an apparent paradox is that, whereas the off rate constant is on the order of days, displacement and binding of new ligands occurs in a much shorter time. This paradox is explained by the fact that the CD1 molecules bind more than two hydrophobic tails at the same time and if binding of a third acyl chain belonging to a second ligand induces the displacement of the first ligand. A possible way of testing this hypothesis is to assess whether ligands with three acyl chains also bind to CD1: in this case, it would be possible to predict that this type of ligand will not be displaced as readily as glycosphingolipids with two acyl chains. The crystal structures of type I CD1 molecules will reveal whether this prediction is correct.

What is the physiological implication of this unusual capacity to displace glycosphingolipids that are already bound to CD1 molecules? We prefer the hypothesis that this system confers upon CD1 molecules the possibility to continuously exchange their ligands with those present in the extracellular milieu. Thus the repertoire of bound glycolipids will constantly reflect the repertoire of the most abundant glycolipids in the serum and those that are available for CD1 binding. Any modification of the relative abundance of these glycolipids...
will influence the number of individual CD1-glycolipid complexes and thus might directly influence the response of specific T cells.

Recognition of large carbohydrates and model of CD1b-GM1 interaction

The fine glycosphingolipid specificity of T cells has been studied using a large number of ganglioside molecules that differ from GM1 in the number of carbohydrates present in the polar head (14). These studies showed that GM1 contains the minimal epitope recognized by these T cells, because gangliosides composed of a head smaller than that of GM1 were not stimulatory. Gangliosides with bigger heads were instead fully activatory without being processed, suggesting that they contain the same GM1 epitope still available for interaction with the TCR. This is in agreement with the known GM1 and GD1a conformations, detected by NMR, which show a high degree of three-dimensional similarity in both molecules. Modeling and superimposition of GM1, GalNAc-GD1a, GT1b, and GQ1b gangliosides (one example is shown Fig. 3) shows that the region important for TCR stimulation composed by galactose IV and GalNAc III residues (shown in red in the figure) is always exposed in the same direction. Furthermore, the irrelevant residues represented by the additional sialic acids or GalNAc sugars (shown in blue in the figure) point in different directions, far from the antigenic epitope.

Because recognition of GM1 requires the presence of five sugars, it remains to clarify how all of these sugars stimulate the same T cell. The TCR of these clones makes cognate interactions with several residues of the CD1b molecule (8). Therefore, it is predicted that a small space remains between the TCR and CD1b. Most likely, the five sugars of GM1 cannot accommodate between the TCR and CD1α-helices, as suggested for recognition of MHC class II-restricted glycopeptides (16). One possibility is that the terminal sugars present in GM1 and other stimulatory gangliosides lie out of the CD1b-binding groove (14). According to this model, the additional negatively charged carbohydrates do not hinder antigen recognition because they protrude out of the CD1b-binding groove (14).

The structure of the lipid tails also affects recognition by T cells. Indeed, glycosphingolipids with fatty acids of variable length show different levels of T cell stimulation (14). Also, the rigidity of the sphingosine base is important, as shown by the finding that when the double bond is abolished and thus sphinganine is present, a marked reduction of T cell activation was detected. These findings show that the structure of the acyl chains confers the CD1-binding capacities and also affects TCR recognition, likely by influencing the orientation assumed by the glycolipid sugars between the CD1 α-helices.

Function of T cells reacting against self glycosphingolipids

The direct evidence of the role of T cells reacting against self glycosphingolipids during autoimmune responses is not easily extrapolated in human diseases. A series of indirect evidence suggests that they might have important functions. An important finding is that these cells are more abundant in patients with MS than in normal donors. An increased number of precursor T cells reacting with self glycosphingolipids was described in the peripheral blood of patients with different forms of MS. These experiments were performed by using a mixture of brain glycosphingolipids. More recent studies conducted with individual glycosphingolipids have shown that some ligands are much more immunogenic than others in MS patients, thus suggesting that T cell reactivity is selectively directed against some molecules (our unpublished data). The reason for this discriminating immune response is not clear, and several explanations may apply, such as the large difference in the relative amounts of individual glycosphingolipids in brain tissue, their distribution in the inflammatory plaque or a different tolerogenic capacity. Furthermore, it is conceivable that the most immunogenic glycosphingolipids are those with the capacity to form very stable complexes with CD1. A last possibility, which deserves careful consideration, is antigenic mimicry. Indeed, some of these molecules share carbohydrate epitopes with bacterial products. For example, some gangliosides such as GM1 and GD1a express the same terminal sugars as LPS from different strains of Campylobacter jejuni. Importantly, antibodies against these LPS are associated with Guillain-Barré syndrome, a peripheral neuropathy characterized by autoantibodies against gangliosides and exacerbated by infections with Campylobacter strains expressing LPS with ganglioside-mimicking structures. Because these autoantibodies are of the IgG isotype, it is possible that glycolipid-specific T helper cells are present in these patients.
Functional studies showed that CD1-restricted and self glycosphingolipid-reactive T cells may be classified as Th1, Th2, or Th0 cells. Indeed, they may release large amounts of IL-4 or IFN-γ and TNF-α cytokines. Interestingly, this was also found when a panel of T cell clones reacting against the same ligand and isolated from the same donor were studied. These findings suggest two important conclusions. First, these cells may behave as proinflammatory or regulatory cells, thus resembling classical peptide-specific T cells. Second, the specificity against one particular glycolipid is not associated with only one functional phenotype, suggesting that these autoimmune responses are the outcome of balanced effector and regulatory mechanisms.

Conclusions and perspectives

Discovery of glycolipid recognition by T cells has provided a further proof of the enormous flexibility of the immune system to recognize a variety of antigenic molecules. It has also shown that the rule of TCR recognition of a complex formed by the antigen and dedicated antigen-presenting molecules applies also to hydrophobic molecules such as glycolipids. Importantly, this recognition is mediated by the same TCR to which applies also to hydrophobic molecules such as glycolipids.

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