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Immunological Cells and Functions in Gaucher Disease

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Abstract

The macrophage (MΦ) has been the focus of causality, research, and therapy of Gaucher disease, but recent evidence casts doubt its solitary role in the disease pathogenesis. The excess of glucosylceramide (GC) in such cells accounts for some of the disease manifestations. Evidence of increased expression of C-C and C-X-C chemokines (i.e., CCL2, CXCL1, CXCL8) in Gaucher disease could be critical for monocytes (MOs) transformation to inflammatory subsets of (MΦs) and dendritic cells (DCs) as well as neutrophil (PMNs) recruitment to visceral organs. These immune responses could be essential for activation of T- and B-cell subsets, and the induction of numerous cytokines and chemokines that participate in the initiation and propagation of the molecular pathogenesis of Gaucher disease. The association of Gaucher disease with a variety of cellular and humoral immune responses is reviewed here to provide a potential foundation for expanding the complex pathophysiology of Gaucher disease.

Keywords

Monocyte (MO); Macrophage (MΦ); Neutrophil (PMN); Dendritic cell (DC); T cell; B cell; Cytokine; Chemokine; Antibody

I. INTRODUCTION

Gaucher disease results from mutations in the glucosidase, beta, acid1 (*GBA1*) that cause functional disruption of the encoded lysosomal enzyme, acid β-glucosidase (β-D-glucosyl-N-acylsphingosine glucosylhydrolase (EC 4.2.1.25; GCase). The consequent excess accumulation of glucosylceramide (GC) and glucosylsphingosine (GS) in lysosomes is central to the disease pathogenesis, with classical involvement of macrophage (MΦ) lineage cells of visceral organs, bone, and brain of humans and other vertebrates with Gaucher disease.^{1–8} The clinical classification, epidemiology, and other aspects of Gaucher disease are available in detailed reviews.^{6,8} All variants of Gaucher disease have shown involvement of monocytes (MOs),⁹ macrophages (MΦs),¹⁰ dendritic cells (DCs)¹¹, T cells,^{9,11} and B cells. Also, B-cell or plasma cell malignancies have increased frequencies in affected individuals as do hypergammaglobulinemia (IgA, IgM, and IgG) and plasmacytosis.^{10,12} In addition, many cytokines and chemokines are increased (Table 1). Here, the spectrum of immunological cell types and molecules involved in Gaucher disease is presented as a basis for understanding the complex evolution of the disease phenotypes (Figure 1).

II. MONOCYTES (MOS)

MOs are blood mononuclear cells with bean-shaped nuclei that are present in the blood, bone marrow, and spleen; they do not proliferate in a steady state.^{13,14} Upon activation, they migrate from blood into tissues, elaborate inflammatory cytokines, and differentiate into inflammatory DCs or MΦs.^{13,15} MOs are defined by the expression of CD11b, CD11c, and CD14 in humans and by CD11b and F4/80 in mice. They lack markers of B-cells, T-cells, NK cells, and DCs.^{16,17}

Based on differential expression of Gr1/Ly6C, MOs are classified into Gr1⁻/Ly-6C^{low} and Gr1⁺/Ly-6C^{high} subsets. Gr1⁻/Ly-6C^{low} MOs represent a functionally distinct subset, which is characterized by CX3CR1^{high} LFA-1^{high} CCR2⁻L, and causes angiogenesis.¹⁷⁻¹⁹ The Gr1⁺/Ly-6C^{high} MOs are characterized by CX3CR1^{low} CCR2⁺ and are considered as inflammatory. They differentiate into MΦ and DC subsets that are critical for immune responses.^{15,20-22}

Circulatory MOs in patients with Gaucher disease showed significant suppression of superoxide generation upon stimulation with phorbol 12-myristate 13-acetate (PMA), opsonized zymosan, and formyl-methionyl-leucylphenylalanine (FMLP) as well as diminished potential for staphylococcal killing, and phagocytosis.²³ In contrast, up-regulation of the major histocompatibility complex-II (MHCII) and CD1d molecules in Gaucher disease MOs cause increased activation of CD4⁺T cells.^{9,24} GCase treatment improved some of these MOs functional activities and reduced the numbers of peripheral blood CD4⁺ T-cells in patients with Gaucher disease^{24,25} and verified a contribution to its pathophysiology.^{23,25} Significant increases in gene and protein expression of MOs chemo-attracting protein-1 (MCP-1) or CC-chemokine ligand 2 (CCL2) were found in the lung tissue of *Gba1* point-mutated mice²⁶ and other models as well as patients with Gaucher disease (Table 1). These could be critical for tissue recruitment of inflammatory MOs and their differentiation into DCs and classically activated MΦs.^{21,22,27-29} However, combining FACS staining with antibodies to Gr1, Ly-6C, CX3CR1, and CCR2 could reveal, with further investigation, clear subset identification and specific functions in Gaucher disease. Additionally, IFNγ, IL-4, and MCSF (Table 1), which are critical for differentiation of MOs to MΦ and DC subsets,^{17,30-32} had increased expression and could facilitate the MOs transformation to inflammatory subsets of MΦs and DCs in Gaucher disease.

III. MACROPHAGES (MΦS)

Elie Metchnikoff classified phagocytes into MΦs (large eaters) and microphages (a smaller type of phagocytic cell), and the polymorphonuclear leukocyte now known as granulocytes. He argued that both types of phagocytes played an important role in host resistance against infections.³³

Metchnikoff also recognized the close relationship between mononuclear phagocytic cells in the spleen, lymph nodes, bone marrow, and connective tissues, leading him to introduce the term MΦ system.³⁴ Karl Albert Ludwig Aschoff, a German physician and pathologist, developed this concept further and grouped several cell types into the reticuloendothelial system and, subsequently, the reticulo-histiocyte system. This system encompassed the reticular cells or fixed MΦs of the spleen and lymph nodes, endothelial cells of the lymph and blood sinuses, MOs, and histiocytes, (a term used for “tissue wandering” as opposed to “fixed” MΦs). In addition to these tissues, MΦs also populate the brain as infiltrating microglial cells. MΦ functions shared by most tissues include high phagocytic function and degradative potential, allowing them to clear foreign and damaged cells.²⁷ MΦs also participate in the induction of innate immunity in response to tissue infection, which plays a critical role in the killing of micro-organisms and processing their pathogenic factors.²⁷

MΦs also load extracellular antigens in MHC class II compartments, but primarily interact with effector CD4⁺ T-cells and are less efficient than DCs at priming naïve T-cells.

MΦs have been classified into two main groups, M1 and M2. M1 MΦs are characterized by increased expression of interleukins IL-12 and IL-23, with decreased expression of IL-10, reactive oxygen species (ROS), nitrogen species, and other Th1-type inflammatory cytokines. M1 MΦs are critical for the clearance of microbial infections and necrotic cell death remnants.^{13,35} M2 MΦs have increased expression of IL-1ra, decoy IL-1 type II receptor, IL-4, IL-10, IL-13, scavenger receptors, and mannose and galactose-type receptors, immune complexes, gluco-corticoid hormones, arginase I, resistin-like molecule alpha (RELMα), and Ym1/2, a chitinase. M2 MΦs have decreased expression of IL-1β, caspase 1, IL-12, and IL-23. M2 MΦs are involved in T-helper 2 (Th2) response immunoregulatory functions, encapsulation and containment of parasites, tissue repair, remodeling, and tumor progression.^{36–39} Inflammatory reactions involving M2 MΦ, e.g., a response to parasitic or helminth invasion, “type 2” inflammation, results in the accumulation of large numbers of these cells in the affected tissues.^{13,39–43}

The delineation of tissue-specific MΦ cell markers make this classification inadequate for understanding the functional differences among and between MΦs from various organs or regions. Several of these MΦ populations in different organs are detailed in Table 2. Clearly, the multitude of differences among MΦs in tissues highlights the need to examine their differential functions that lead their specific involvement in Gaucher disease.

MΦs express a broad range of pathogen-recognition receptors induced within the microbial and cytokine milieu, which drives them to specialized and polarized functions.^{36,44,45} Interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF-α), and microbial products (lipopolysaccharide) elicit a M1 MΦ activation to trigger extensive pro-inflammatory responses required to kill intracellular pathogens.

In Gaucher disease, MΦs have been functionally and numerically assigned as the dominant disease effectors. These cells, which become engorged with un-degraded GC, are present in nearly all visceral tissues,^{26,46} and are termed Gaucher cells. They contain twisted and flat layers of tubular-like structures of GC that are a hallmark of Gaucher disease. These tubular structures are bilayered membrane-like inclusions containing phospholipids and large amounts of GC.^{8,47} By immunohistochemistry, splenic Gaucher cells are positive for CD163, CD14, chitotriosidase, CD68, and HLA II, but negative for CD11b. Such cells resemble those in red pulp and in the tingible body⁴⁸ (Table 2). These findings indicate that the splenic MΦs in Gaucher disease have M2 characteristics. Also, similar MΦs were positive for Mac3, CD68, and F4/80 in several tissues of mice with *Gba1* mutations;^{7,26,49} these findings indicate their activated state in Gaucher disease.

The high degree of CD68⁺ and F4/80⁺ positive Gaucher cells in the lung tissue of *Gba1* point-mutated mice suggest that these cells are alveolar macrophages, but a more refined characterization that includes CD11b, CD169, and MHCII would facilitate subset assignment to the alveolar interstitium or airspaces (Table 2). Global gene expression profiling in the MΦs enriched lung tissue of such mice showed alterations in ~0.9–3% of all genes. The genes associated with MΦs activation and immune response were significantly enriched, e.g., INF-γ network (CCL2, CCL3, CCL9, NOS2, TNF, and IL-6) and IL-4 networks (CD163 and MMP12).²⁶ These findings implicate M1 and M2 MΦs, but in addition, storage cells were present that had characteristic markers for both M1 and M2 MΦs. Such findings suggest a disruption in the differentiation and subset formation of MΦs in Gaucher disease that may be tissue specific. The complete characterization of the tissue

specificity of the M1/M2 subsets of MΦs will require the use of purified cells and *in vitro* analyses to dissect the tissue-specific effects of Gaucher disease.

IV. NEUTROPHILS (PMNS)

PMNs or polymorphonuclear neutrophils are the most abundant white blood cells normally found in the blood, bone marrow, and areas of acute inflammation. PMNs are Gr1^{high} and CD11b⁺ cells,⁵⁰ which influence adaptive immune responses through pathogen shuttling to draining lymph nodes,^{51,52} antigen presentation,⁵³ and modulation of Th1/Th2 responses.⁵⁴ In addition to their primary role as professional phagocytes, PMNs express a variety of cytokines and chemokines in response to physiological stimuli,⁵⁵ and they play an important role in inflammatory and immune reactions.^{56–64} PMNs are classically first-responders to inflammation. They are recruited to local regions from the blood and are mobilized from bone marrow.^{65–67} Circulating PMNs are signaled to migrate into the interstitial spaces by chemo-attractants, including leukotriene B4 (LTB4), CXC chemokines, CXCL1 or KC, CXCL2 or MIP-2, IL-8 or CXCL8, C5a, IL-1, CXCL12 or stromal cell derived factor-1 (SDF-1).^{68–71}

Some studies have found increased plasma levels of C-X-C chemokines (CXCL1/KC and CXCL8/IL8), IL1α, TNFα, and MIP1α (Table 1) in Gaucher disease, which are important for activation and recruitment of PMNs.^{72–75} However, these have not been used to evaluate the chemotactic profiles of PMNs in Gaucher disease. Such studies would be important because decreased ability of PMNs migration and increased susceptibility to infection has been suggested in patients with Gaucher disease. One study reported that ~33% of affected patients had a significant decrease in *ex vivo* PMNs directed chemotaxis toward zymosan-activated serum or N-formyl-methionyl-leucyl-phenylalanine and that ~50% of patients showed defects in PMNs random migration.⁷⁶ Most of the patients with impaired PMNs chemotaxis had more severe disease manifestations. Also, 33% of patients (3/9) with impaired chemotaxis suffered from recurrent pyogenic infections, whereas this type of infection was not found in 20 patients with normal PMNs function.⁷⁶

Mean chemotaxis rates of granulocytes (which form part of the PMNs family together with basophils and eosinophils)^{77,78} were not decreased in patients with Gaucher disease, although they had normal functional assays, including superoxide generation, staphylococcal killing, and phagocytosis.^{23,25} These chemotaxis experiments used traditional Boyden chamber *ex vivo* methods⁷⁹ in which cells are placed and migrate through porous membrane (3 μM) to the chamber containing a chemotactic agent. An increase in the cell number is considered as chemotactic influence. This abnormal migration of PMNs in selected patients^{23,25,76} and could be independent of other disease manifestations. However, the relevance of these findings to clinical infection susceptibility and/or clearance in affected patients is not clearly apparent from clinical observations. Several severe infections following orthopedic procedures and recurrent pyogenic infections have been reported in severely affected patients, but such infections do not appear to be a major disease complication in the majority of patients.

V. DENDRITIC CELLS (DCS)

Steinman and Cohn identified a population of hematopoietic cells in mouse spleen that excelled at antigen presentation and T-cell stimulation; these were named DCs because of their unique morphology.^{80,81} Similar to MΦs and PMNs, DCs are antigen presenting cells (APCs) that are present in lymphoid and non-lymphoid organs.⁸² DCs derive from bone marrow and migrate as precursors through the circulation to become resident in tissues, such as Langerhans cells of the epidermis. After pathogen invasion, DCs get recruited to sites of inflammation.⁸³ DCs capture the antigen,^{8–87} migrate to the draining lymph nodes, present

extracellular antigens, and initiate tissue-specific T-cell immunity.^{88–94} During their migration from peripheral tissues to lymphoid organs, DCs undergo maturation with altered phenotypes and functions.^{90,95,96} The two DC subsets in mice are termed myeloid (mDCs) and plasmacytoid DCs (pDCs).⁹⁷ mDCs are CD11c⁺ and precursors of Langerhans cells, and dermal interstitial DCs, which express myeloid markers, intercept invading pathogens in the periphery, and then migrate to the secondary lymphoid tissue where they present pathogen-derived peptides to antigen-specific T cells.⁹⁸ In comparison, pDCs are CD11c[–], lack myeloid markers, and migrate directly from blood to the secondary lymphoid tissue, where they differentiate into cells that were originally termed plasmacytoid T cells because of their extensive endoplasmic reticuli.^{99,100} The mDCs secrete interleukin 12 (IL-12), which drives type 1 helper T-cell immune responses associated with cellular immunity.¹⁰¹ The pDCs secrete lesser amounts of IL-12 but are potent producers of interferon- α (IFN- α) and may play an important role in controlling viral infections.^{101,102} mDCs are subdivided into CD4⁺ mDCs, CD8 α ⁺ mDCs, and CD8 α [–]CD4[–]mDCs.¹⁰³ The CD4⁺ mDCs do not produce cytokines, but they effectively present antigens to CD4 T-cells.¹⁰⁴ CD8 α ⁺ mDCs perform cross-presentation of foreign antigens to CD8 T-cells and are a major producer of IL-12.^{104–107} CD8 α [–]CD4[–]cDCs produce IFN- γ .¹⁰⁴ mDCs and pDCs can be generated from their progenitor cells in BM cells *in vitro* by granulocyte macrophage colony stimulating factor (GM-CSF) and Fms-like tyrosine kinase 3 ligand (FLT3L) stimulation.^{108,109}

In untreated Gaucher disease type 1, mDCs and pDCs as well as MOs-derived DCs were decreased in the peripheral blood, but no change from healthy controls was found in the expression of the DC-associated surface molecules (i.e., CD80, CD83, CD40, HLA-DR, and CD54). Lipopolysaccharide and TNF- α stimulated immature MOs-derived DCs from patients and healthy controls had similar degrees of up-regulation of CD83, CD80, CD54 and HLA-DR, indicating an efficient maturation of MOs-derived DCs. The endocytic and allostimulatory capacities of the immature and mature MOs-derived DCs were similar to those obtained with healthy controls.

In comparison, mice with conditionally deleted *Gba1* in hematopoietic and mesenchymal cell lineages showed an increase in the inflammatory subset of mDCs [CD11b⁺CD11c⁺B220⁺CD4⁺MHCII (IA/IE)⁺cells] in thymus cells.¹¹ This could be due to infiltration of MOs due to the CCL2/MCP1 chemokine^{26,110,111} overexpression. Mature DCs of lymphoid organs are poor at antigen capture and processing, but they are markedly efficient in priming naïve T-cells^{84,87,112,113} and inducing high expression of MHC class II and B7 molecules.^{114–116} Thus, studies are needed to evaluate the relationships between MO and DC subsets and their positivity for specific activation molecules (e.g., CD40, CD80, CD86, PDL1, and PDL2) in Gaucher disease.

DCs are activated by damage-associated molecular patterns through Fc γ RI, II, III, and IV,^{117,118} CD88,^{119,120} and several TLRs.^{121,122} However, expression levels of these molecules have not been evaluated with DCs from visceral tissues of human and murine Gaucher disease.

VI. B LYMPHOCYTES

B cells are critical for humoral immune responses, and they have APC-like functions to generate T-cell-mediated immune responses.¹²³ Activated B cells express high levels of MHC class II and T-cell-activation-associated molecules that facilitate their effective antigen presentation to T cells.^{124,125} Moreover, DCs and M Φ s promote antigen specific Th1 cell differentiation as well as B-cell antigen presentation that usually induces T-cell anergy and influences naïve T-cell differentiation to the anti-inflammatory Th2

phenotype.^{126–129} Thus, B cells have dual roles in modulating T-cell immunity and potentially contributing to the maintenance of immunological homeostasis.

B lymphocytes are classified into two subtypes: B-1 and B-2. B1 cells are present in the pleural cavities, peritoneal cavities, spleen, and Peyer's patches of the intestine, whereas B2 cells are present in spleen and lymph nodes.^{130–132} B1 cells develop from self-replenishing peritoneal precursor cells and secrete natural IgM antibodies,¹³³ whereas B2 cells (conventional B cells) develop from bone-marrow precursors,^{134,135} and are distributed in lymphoid organs, where they mature and lead to immunoglobulin isotype switching and differentiation into memory B cells and plasma cells.

B1 cells are characterized by increased IgM and decreased IgD, B220, and CD11b surface expression, as compared to B2 cells.^{130,136–138} Based on the differential expression of CD5, B-1 cells are further divided into IgM^{high} IgD^{low}CD23[–]CD11b⁺CD43⁺CD5⁺B1a cells and IgM^{high}IgD^{low},CD11b⁺CD5[–]B1b cells.^{130,137,139} B1 cells often have specificities for self-antigens, such as phosphatidylcholine,¹⁴⁰ single-stranded DNA,¹⁴¹ ribonucleoprotein,¹⁴² cell-surface Thy-1 antigen,¹⁴³ and rheumatoid factor.^{144,145} The absolute numbers of B1 cells are increased in rheumatoid arthritis,¹⁴⁵ Sjogren's syndrome,¹⁴⁶ chronic inflamed gingival tissue,¹⁴⁷ and systemic lupus erythematosus.¹⁴⁸

B2 B cells express intermediate levels of IgM and IgD, as well as increased and absent cell-surface B220 and CD5, respectively. B2 cells have a major role in the pathogenesis of many inflammatory and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, atherosclerosis, thyroiditis, and autoimmune diabetes.

B1 cells can develop into B-cell chronic lymphocytic leukemia^{149–151} and Gaucher disease has been associated with B-cell and plasma cell malignancies.^{10,152–158} In addition, Gaucher disease type 1 patients develop immunoglobulin abnormalities, IgG- and IgM-specific hypergammaglobulinemia, and plasmacytosis.^{153,154,159–167}

Enzyme therapy or splenectomy decreases the IgG and IgM levels in affected patients.^{162,164,165,168} However, the effects of these interventions on the reduction of specific subsets of B cells (IgM^{high} IgD^{low}CD23[–]CD11b⁺CD43⁺CD5⁺B1a, IgM^{high}IgD^{low},CD11b⁺CD5[–]B1b, and B220^{high}CD19^{high} B2 cells) need investigation. Also, the antigens for several autoantibodies in sera of patients with Gaucher disease have been characterized as pyruvate dehydrogenase, DNA, sulfatide, and rheumatoid factor.^{155,169} The subsets of B cells that secrete these autoantibodies may have different effector functions and impacts on the disease pathogenesis in individual patients. The exact nature, source, and mechanism(s) of production of these autoantibodies, and their interaction with different FcγRs on MΦs, PMNs, and DCs could be important to the pathophysiology of Gaucher disease.

VII. T LYMPHOCYTES

T cells are classified into two major groups: CD4⁺ T-helper cells and CD8⁺ T-cytotoxic cells. CD4⁺T-helper cells are further subdivided into Th1, Th2, Th17, CD4⁺ CD25⁺ regulatory T-cells (Treg), and follicular helper T-cell (Tfh) subsets based on their cytokine production and activation by lineage-specific transcription factors: T-bet for Th1, GATA-3 for Th2, RORγt for Th17, Foxp3 for Treg, and Bcl-6 for Tfh.^{170–187} Th1 and Th2 cells produce the signature cytokines IFN-γ, IL-4, and IL-13, respectively, and are important for the elimination of microbial pathogens and intracellular microbes.¹⁷⁶ Th17 cells selectively produce IL-17 cytokines.¹⁸⁰ CD4⁺ CD25⁺ Tregs are critical for preservation of immune tolerance,^{177–179} where TGF-β plays a critical role.¹⁸⁸ Tfh cells help B cells mount antibody responses to T-cell-dependent antigens, to the development of germinal centers, and to

immunoglobulin class switching.^{182–184} CD8⁺ T-cells are critical for killing virally infected cells predominantly through the release of lytic proteins, mainly perforin and granzymes, which are secreted via exocytosis of preformed granules following recognition of infected targets.^{189–191}

T-cell lymphomas occur in Gaucher patients, for example, in a 6-year-old female with concomitant neurofibromatosis type 1¹⁹² and in a 16-year-old male. The latter individual had increased expression of CD45, CD45R0, CD3, and CD15¹⁹³ indicating a disruption of the T- and B-cell networks. T-cell deficiency and poor T-cell response to lectins were found in spleen tissue and peripheral blood of patients with Gaucher disease.^{194,195} A deficiency of CD4⁺ and CD8⁺ T-cell subsets was found in peripheral blood of 21 non-splenectomized and 10 splenectomized affected patients.¹⁹⁶ In contrast, the thymus of mice with a conditionally deleted *Gba1* gene (hematopoietic and mesenchymal cell lineage deletions) showed increased percentages of the CD4⁺T-cell subsets.¹¹ Beyond the associations of increased production of IFN γ , IL-4, IL-6, TGF- β (Table 1), the alterations in CD4⁺ T-cell subsets (Th1, Th2, Th17, Treg) and their transcription factors (T-bet, GATA -3, ROR γ t, Foxp3, and Bcl-6), which are critical for production of these cytokines,^{170–187} have not been examined in Gaucher disease.

Expression of IL-6 (Table 1) is critical for Tfh cell responses^{197,198} and is central to the development of fully matured germinal center B cells and the production of high-affinity antibodies.¹⁹⁷ The association of increased IL-6 and T-and B-cell lymphomas and hypergammaglobulinemia in patients with Gaucher disease^{26,164,192,193} suggests the need to examine Tfh cells, including their antigen specificity for CXCR5, PD-1, CD200, inducible T-cell costimulator (ICOS), as well as the potential absence of the signaling lymphocytic activation marker (SLAM) in CD4⁺ T cells.¹⁹⁷ Enhanced crosstalk between Tfh cells and B1-/B2-cell subsets could provide a mechanism for the hypergammaglobulinemia in Gaucher disease.^{182–184}

VIII. NATURAL KILLER T (NK-T) CELLS AND THE CD1 SYSTEM

In contrast to the peptide antigen associated MHC-I/II processing through CD4⁺ and CD8⁺T cells,^{199–201} NK-T cells are subsets of regulatory T cells that co-express T-cell (CD3, α / β TCRs) and NKT (NK1.1)-cell surface receptors²⁰² these T cells which recognize various lipid and glycolipid antigens through the CD1 antigen-presenting system on APCs.^{203–209} Five CD1 isoforms are present in humans and are classified into two groups based on sequence similarity; CD1a, -b, and -c constitute group I, and CD1d forms group II.²¹⁰ CD1e represents an intermediate between the two CD1 groups and acts as a chaperone to facilitate lipid transfer onto CD1b and CD1d.²¹¹ Most of the mycobacterially derived lipids (e.g., mycolic acid, glucose-monomycolate, phosphatidylinositol mannoside,²¹² lipoarabinomannan, mannosyl- β -1-phosphoisoprenoid, and mannosyl- β -1-mycoketide²¹³) bind to CD1 group I. Mice express only two homologues of CD1d: CD1d1 and CD1d2.²⁰³ CD1d presents endogenous and exogenous lipid antigens to NKT cells in humans and mice.^{207,214} The most well-known subset of CD1d-restricted NKT cells uses an invariant TCR α chain (V α 14-J α 18 in mice and V α 24-J α 18 in humans), that is, invariant NKT (iNKT) cells.²¹⁵ iNKT cells rapidly secrete IFN- γ , IL-4, IL-17, and other cytokines upon TCR stimulation.^{215–217} Activated iNKT cells in turn activate DCs, M Φ s, and NK cells, and thereby impact subsequent B- and T-cell responses.²¹⁸ These interactions highlight the critical role played by iNKT cells in bridging innate and adaptive immune responses in diseases such as cancer,²¹⁹ bacterial, viral, parasitic, and fungal infections,^{220–222} and autoimmune diseases.²²³

Up-regulation of CD1d and MHC-class II was found in MOs from patients with Gaucher disease and in *ex vivo* MOs models induced with GCase inhibitors. Based on such observations, CD1d up-regulation was postulated to be secondary to alterations in intracellular trafficking as a consequence of excess lipid accumulation. The increased expression of MHC-class II was attributed to the patient's inflammatory status.²⁴ This finding was supported by the decreased chitotriosidase activity and surface presence of MHC-class II in MOs of patients with Gaucher disease who had received enzyme therapy, suggesting up-regulation of MHC-class II expression by *ex vivo* MOs of Gaucher patients.^{9,24}

Sphingolipid activator proteins (SAPs) are ~10-kDa glycoproteins that have differential affinity for various glycosphingolipids. They have been postulated to facilitate membrane extraction and/or membrane structure of specific glycosphingolipids to enhance their degradation.²²⁴ In addition, of the four SAPs (A, B, C, D) that derive from a common precursor, prosaposin, SAP B has a significant ability to transfer lipids to CD1d molecules.²²⁵ Also, prosaposin-deficient mice fail to develop or stimulate invariant NKT cells,^{226,227} suggesting that SAPs are critical for the development of NK-T cells. The excess SAPs present in Gaucher disease have not yet been implicated in its disease-related immune system defects. Curiously, decreased numbers of NK cells are found in Gaucher disease.¹⁹⁴

IX. CYTOKINES

Each of the CD4+T-effector lymphocytes are characterized by their production of specific cytokines that drive their effector functions.²²⁸ In addition to their signature effector cytokines (e.g., IFN- γ (Th1), IL-4 (Th2),^{229,230} IL-17 (Th17),^{172,231} IL-35, and TGF- β (Treg), IL-6 and IL-21 (Tfh)^{198,232}), all helper T-cell subsets can produce IL-10, a cytokine with broad immunoregulatory properties.²³³ Th1 cells produce IFN- γ , IL-2, and TNF- α to clear intracellular pathogens and evoke cell-mediated immunity, whereas Th2 cells produce IL-4, IL-5 and IL-13 to clear extracellular organisms and evoke strong allergic responses.^{229,234–237} In contrast to Th1 and Th2 cell differentiation, which depends on their respective effector cytokines (IFN- γ and IL-4), Th17 cell differentiation does not require IL-17, but has a critical need for TGF- β and IL-6.^{238,239} IL-17 cytokines are highly concentrated in collagen-induced arthritis, multiple sclerosis, and rheumatoid arthritis.²⁴⁰ T (reg) cells produce IL-10, IL-35, and TGF- β to cause immune tolerance and inhibit IFN- γ synthesis²⁴¹ as well as blocking T-helper cell differentiation of naïve T-cells into effector T cells.²⁴² Tfh cells facilitate B-cell differentiation and induce IL-21 production, which is critical for immunoglobulin switching.²⁴³ Several reports show changes in gene expression, and/or serum and tissue levels of several cytokines and chemokines in human and murine Gaucher disease (Table 1). Age-dependent progressive accumulation of GC and enhanced M Φ activation and immune response genes (i.e., INF γ , TNF, IL-1ra, IL-4, IL-6, CCL2, CCL3, CCL6, CCL9, CXCL1, CXCL12, CCL17, and CCL22) have been observed in lungs and livers of viable *Gba1* point-mutated mice.²⁶ These studies suggest that GC accumulation in M Φ s triggers events that contribute to the increased production of MOs and PMNs chemo-attracting proteins (e.g., MCP1/CCL2, CXCL8/IL8, KC/CXCL1) as well as IL-1 β , IFN γ , and TNF α in Gaucher disease (Table 1), which could cause the recruitment of PMNs and transformation of MOs into the effector M Φ s and DCs to initiate inflammatory reactions in visceral tissues of Gaucher disease.

X. NITRIC OXIDE (NO) AND REACTIVE OXYGEN SPECIES (ROS)

NO production from many cell types is an important effector for a variety of cytokines and chemokines.²⁴⁴ NO is produced from L-arginine by the actions of NO synthases (NOS), a family of enzymes encoded by at least three distinct genes: NOS1, NOS2, and NOS3.^{245,246}

NOS1 is found mainly in neuronal²⁴⁷ and skeletal muscle cells.²⁴⁸ NOS3 is found mainly in endothelial cells.²⁴⁹ NOS2, which is also called inducible NOS (iNOS), is expressed by variety of immunological cells upon activation by IFN- γ , TNF- α , and specific chemokines.^{250–253} The increased levels of these cytokines and chemokines in Gaucher disease (Table 1) and *Gba1* mutant mice may underlay an increased expression of the *NOS2* gene,²⁶ and NO and ROS proteins in the brain of *Gba1* knockout mice.²⁵⁴ Such a mechanism could be highly relevant to the modulation of inflammatory and perfusion alterations observed in Gaucher disease. This concept is supported by the association of NO and the generation of ROS, including superoxide anions, hydroxyl radicals, lipid hydroperoxides, and hydrogen peroxide, which promote endothelial cell dysfunction directly or indirectly by promoting formation of lipid inflammatory mediators.²⁵⁵ The enhancement of inflammatory and oxidative responses by long chain fatty acids²⁵⁶ might implicate GC in the induction of IFN- γ , TNF- α , and IL-1 β leading to enhanced iNOS expression. Clearly, such a mechanism requires direct experimental validation.

XI. PATHOGENESIS AND PROPAGATION OF GAUCHER DISEASE—A MODEL

The delineation of the numerous inflammatory and APC cell types involved in Gaucher disease pathophysiologic propagation implies a more complex disease model than that focused primarily on the M Φ s. A possible pathway for this expanded propagation pathway can be proposed. The initial M Φ s activation resulting from excess GC triggers a vicious cycle for the release of MOs and PMNs, attracting cytokines as well as C-C and C-X-C chemokines (Table 1). For example, MCP-1 recruits circulating MOs, whereas CXCL8/IL8, CXCL1/KC, and TNF- α are chemoattractants for PMNs migration into the different visceral organs. Once MOs enter visceral organs, they mature into a variety of tissue-specific M Φ s and DCs subsets (Table 2). These cells with GCase defects lead to increasing numbers of GC-containing cells with the resultant release of additional IFN- γ , IL-4, IL-6, and TGF- β cytokines, as well as the promotion of continued development of Th1- and Th2-cell-mediated inflammation. IL-6 induces T-follicular cells (Tfh), leading to activation of B cells in germinal centers and hypergammaglobulinemia. Moreover, IL-6 and TGF- β induce Th17 cell production with subsequent IL-17 production, leading to myeloid cell release of C-X-C chemokines i.e., CXCL8/IL8, with recruitment of circulating PMNs. IL-1 β , IFN- γ , and TNF- α , which are also secreted by Gaucher cell M Φ s lead to the induction of iNOS/NO2 expression and the release of NO. Together, TNF- α and KC/CXCL1 leads to additional PMNs recruitment into the visceral organs (Figure 1). The detailed mechanisms of such a pathophysiology remain to be delineated. The diversity of these cell subsets in various tissues implies a similar diversity of their functions in different tissues. The translation of such diversity into the individual and tissue-specific reaction of or to GCase defects remains to be elucidated. Clearly, the mechanistic basis for the initiation and propagation of the immunological cell involvement in Gaucher disease should provide approaches to alternative therapies for this and other lipid storage diseases.

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ABBREVIATIONS

APC	antigen presenting cells
CCL	CC chemokine ligand

CXCL	CXC chemokine ligand
DCs	dendritic cells
FLT3L	Fms-like tyrosine kinase 3 ligand
FMLP	formyl – methionyl–leucyl–phenylalanine
GC	glucosylceramide
GCSF	granulocyte colony stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HGF	hepatocyte growth factor
IFN-γ	interferon-gamma
IL	interleukin
LTB4	leukotriene B4
MCP-1	monocyte chemoattracting protein - 1
MCSF	macrophage colony stimulating factor
mDC	myeloid dendritic cell
MHC	major histocompatibility complex
MΦs	macrophages
MOs	monocytes
pDC	plasmacytoid dendritic cell
PMA	phorbol 12-myristate 13-acetate
PMNs	neutrophils
SDF-1	stromal cell derived factor-1
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha

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FIGURE 1. A schematic for a model of inflammatory propagation of Gaucher

MΦ activation due to excess of glucosylceramide (GC) could trigger the release of C-C chemokines, e.g., monocyte chemoattractant protein-1(MCP1) or CC chemokine ligand-2 (CCL2), which cause the recruitment of blood MOs into the different visceral organs. These cells then mature into MΦs and DCs subsets. Because of the GCase defects in these cells, excess of GC accumulates and in turn activates the release of interferon- γ (IFN- γ), interleukin-4 (IL-4), IL-6, and transforming growth factor- β (TGF- β). The cytokines IFN- γ and IL-4 cause the development of T helper-1 (Th1) and Th2 cell-mediated responses, whereas IL-6 facilitates the development of follicular T cells (Tfh). These responses lead to the formation and activation of the germinal center that triggers B-cell differentiation and immunoglobulin (IgG, IgA, and IgM) production, and hypergammaglobulinemia. IL-6 together with TGF- β impact Th17 cell development, which induces the production of IL-17 and subsequently the production of CXCL8/IL8 to recruit blood PMNs into Gaucher disease visceral organs. In addition to CXCL8/IL8, GC-engorged MΦs also secrete KC/CXCL1,

IL-1 β , IFN- γ , and TNF- α , which are critical for the recruitment of PMNs and release of their activation products (e.g., TNF- α , IL-6, IL-1 α , IL-1 β , and IL-1Ra) into the visceral organs. Also, TNF- α together with IFN- γ and IL-1 β induce iNOS followed by the production of NO to trigger immunological inflammation in Gaucher disease.

TABLE 1

C-C and C-X-C chemokines in Gaucher disease

Cytokines/chemokines	Full Name	References
IFN- γ	Interferon gamma	(26, 257)
TNF α	Tumor necrosis factor-alpha	(26, 254, 258)
IL-1 α	Interleukin-1 alpha	(254)
IL-1 β	Interleukin-1 Beta	(254, 259, 260)
IL-1Ra	IL-1 receptor antagonist	(26, 259, 261)
sIL-2R	IL-1a soluble IL-2 receptor	(259)
IL-4	Interleukin-4	(26)
IL-6	Interleukin-6	(26, 254, 257, 259, 262)
IL-10	Interleukin-10	(167, 257, 262)
IL-18	Interleukin-18	(263)
TGF- β 1	Transforming growth factor-beta1	(263)
HGF	Hepatocyte growth factor	(167)
M-CSF	Macrophage colony-stimulating factor	(46)
G-CSF	Granulocyte colony stimulating factor	(257)
MCP-1/CCL2	Monocyte chemotactic protein-1 or Chemokine, (C-C motif) ligand 2	(26, 257, 261)
MIP-1 α /CCL3	Macrophage-inflammatory protein-1alfa or Chemokine (C-C motif) ligand 3	(26, 261, 264)
MIP-1 β /CCL4	Macrophage-inflammatory protein-1beta or Chemokine (C-C motif) ligand 4	(261, 264)
CCL6	Chemokine (C-C motif) ligand 6	(26)
CCL9	Chemokine (C-C motif) ligand 9	(26)
CCL17	Chemokine (C-C motif) ligand 17	(26)
PARC/CCL18	Pulmonary and Activation Regulated Chemokine or Chemokine (C-C motif) ligand 18	(167, 261, 265)
CCL22	Chemokine (C-C motif) ligand 22	(26)
CXCL1	Chemokine (C-X-C motif) ligand 1	(26)
IL-8/CXCL8	Interleukin-8 or Chemokine (C-X-C motif) ligand 8	(46, 257, 261)
CXCL12	Chemokine (C-X-C motif) ligand 12	(26)

TABLE 2

Specific Phenotypes of Macrophages (MΦs) in Different Tissues.

Organ	Location and types	Markers
Liver (266–268)	Sinusoids Kupffer cells	F4/80 ^{high} CD11b ^{low} CD169 ⁺ CD68 ⁺ Mac-2 ⁺
Spleen (269–273)	Red pulp MΦs	F4/80 ^{high} CD11b ^{low} CD169 ^{low} MHCII ^{low} D163 ⁺ CD68 ⁺ CD115 ⁺ CD172a ⁺
	Marginal zone MΦs	F4/80 ⁺ SIGN-R1 ⁺ MARCO ⁺
	Marginal zone Metalophilic MΦs,	F4/80 ⁺ CD169 ⁺
	Tingible body MΦs	F4/80 ⁺ CD11b ⁺ CD68 ⁺ MFG-E8 ⁺
Lung (267, 274–278)	Alveolar MΦs	F4/80 ⁺ CD11b ^{low} CD169 ⁺ CD11c ^{high} CD68 ⁺ SiglecF ⁺ MARCO ⁺ Mac-2 ⁺
	Alveolar interstitialMΦs	CD11c ⁺ F480 ⁺ CD68 ⁺ MHCII ⁺
Lymph Node (279, 280)	Subcapsular sinus MΦs	F4/80 ^{low} CD11b ⁺ CD169 ⁺ CD11 ^{low}
	Medullary MΦs	F4/80 ^{high} CD11b ⁺ CD169 ⁺ CD11c ^{low}
	Boundary between the sinus and the T cell zone	CD11c ^{high} CD169 ⁺ MΦ
	B cell follicle MΦs	MHCII ⁺ F4/80 ⁺ CD169 ⁺ CD11c ^{high} CD8 ⁺
	Germinal centertingible body MΦs	F4/80 ⁺ CD11b ⁺ CD68 ⁺ MFG-E8 ⁺
Gut (281, 282)	Lamina propria MΦs,	MHCII ⁺ F4/80 ⁺ CD11b ⁺ CD11c ⁺ CD103 ⁺ CD115 ⁺ CX3CR1 ⁺ CD172a ⁺
	Muscular layer and serosa MΦs	MHCII ^{high} F4/80 ⁺ CD11b ⁺ CD169 ⁺ CD11c ^{low} CX3CR1 ⁺ CD103 ⁺ CD115 ⁺
Bone (283–285)	Bone marrow MΦs	CD169 ⁺ F4/80 ⁺ CD11b ^{low} CD169 ⁺ CD11c ^{low} CD68 ⁺ CX3CR1 ⁺ CD115 ⁺
	Pro-osteoclasts	CD11b ⁺ F4/80
	Pre-osteoclasts	CD11b ⁺ F4/80 ^{lowlow}
	Mature osteoclasts	CD11b ⁺ F4/80 ^{medium}
Thymus (286)	Germinal center subcapsular MΦs,	MHCII ⁺ F4/80 ⁺ Mac-2 ⁺ FcγRII ⁺ FcγRIII ⁺
	Germinal center cortex MΦs	MHCII ⁺ F4/80 ⁺ Mac-2 ⁺ FcγRII ⁺ FcγRIII ⁺
	Germinal center cortico-medullaryMΦs,	MHCII ⁺ F4/80 ⁺ Mac-2 ⁺ FcγRII ^{high} FcγRIII ^{high}
	Germinal center medullar MΦs	MHCII ^{high} F4/80 ⁺ Mac-2 ⁺ FcγRII ⁺ FcγRIII ⁺
Skin (287, 288)	Dermal MΦs	F4/80 ⁺ CD11b ⁺ CD11c ^{low} mMGL ⁺ CD206 ⁺ MHCII ^{low} CD169 ⁺
Peritoneal lavage (289)	Peritoneal MΦs	CD11b ^{high} F4/80 ^{high} CD11c ⁺
Brain (290)	Microglial cells	CD11b ⁺ CD14 ⁺ CSFR1 ⁺ CX3CR1 ⁺ CD172 ⁺ CD200 ⁺ CD45 ⁺