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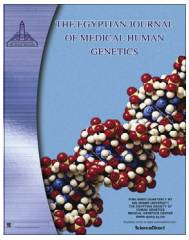

REVIEW

# Cytokines in Gaucher disease: Role in the pathogenesis of bone and pulmonary disease

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**Abstract** Gaucher disease (GD) is the most frequently encountered lysosomal storage disease caused by inborn defects of the membrane-bound lysosomal enzyme, acid β-glucosidase or glucocerebrosidase. This defective activity causes an accumulation of glucocerebroside (glucosylceramide) in the lysosomes of cells derived from the monocyte/macrophage lineage. Glucocerebroside-engorged cells, termed Gaucher cells, infiltrate various organs, leading to multisystemic abnormalities. The mechanisms by which systemic and organ-specific involvement is propagated or initiated remain unclear. Studies are increasingly recognizing the role of immune dysregulation and inflammation in the pathogenesis of Gaucher disease. Many cytokines have been reported as mediators of tissue damage in Gaucher disease. Bone and lung disease are serious causes of morbidity in non neuronopathic Gaucher disease. The progress in the understanding of the pathogenesis or relevant mechanism(s) of Gaucher disease is providing insights into additional therapeutic targets, enabling the potential for optimized patient outcomes with the use of adjunctive or supplemental agents.


**Contents**



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## 1. Introduction

Gaucher disease is an autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding acid β-glucosidase (glucocerebrosidase, GCase, *EC* 3.2.1.45) [1]. Deficient GCase enzymatic activity leads to progressive accumulation of glucocerebroside in the lysosomes of macrophages in various organs. The large macrophages storing glucocerebroside, also called 'Gaucher cells', are characterized histologically with a small excentrically placed nuclei surrounded by a bright cytoplasm with striations or crinkles [2,3].

Macrophages are a heterogeneous group of cells, whose morphology and phenotype differ depending on the tissue/organ and stimuli. They participate in tissue remodeling, host defense, and many disease processes, and can secrete both anti or proinflammatory cytokines [4].

Although an infinite number of potential phenotypes can be suggested, macrophages could be associated with two main types: classical or alternative, depending on the predominant cytokine in the environment, IFN-γ or IL-4/IL-13, respectively. Finally, the stimulus for full activation of classical or alternative macrophages is delivered by a TLR or analogous receptor [5]. Gaucher cells resemble alternative activated macrophages and are characterized by expression of chitotriosidase and CCL18 [6].

The aim of this article is to review the increasingly recognized role of immune dysregulation and inflammation in the pathogenesis of Gaucher disease, with particular emphasis on bone and lung diseases that are serious causes of disease morbidity.

## 2. Clinical spectrum and types of Gaucher disease

The symptoms associated with GD are due to the progressive accumulation of Gaucher cells in various organs. Thus, GD is a multisystemic disorder with disease manifestation at all ages dependent on the subtype of GD [1].

Three basic clinical forms of GD can be distinguished depending on the degree of neurological involvement; however, recently different forms of GD are considered rather to reflect a continuum ranging from early onset to late onset disease and from severe forms with neurological symptoms to mild forms with solely visceral manifestations [7,8].

GD-1 is the most frequent form and accounts for 94% of all registered GD cases according to the Gaucher Registry [9]. It leads to a chronic course of disease and the organs frequently affected are the spleen, liver, bone marrow and bone and, in severe cases, also the lung and kidney. Hepatosplenomegaly and hematological complications including anemia and thrombocytopenia with bleeding are common in untreated GD-1 [10]. Acute neuronopathic GD (GD-2) manifests in early childhood, neurological deterioration progresses quickly and death generally occurs within the age of 2 years. Subacute neuronopathic GD (GD-3) shows a slower neurological involvement and usually occurs in adolescence, although early onset disease has been reported [1,11,12].

## 3. Pathophysiology of Gaucher disease

The insufficient catabolism of glucosylceramide [GC] and the engorgement of macrophages by this substrate lead to visceral manifestations of Gaucher disease, but the mechanisms by which systemic and organ-specific involvement are propagated or initiated remain unclear [8,13].

GC has a ceramide backbone with a β-D-glucopyranoside bound at the 1-hydroxyl position. GC is the precursor in the synthesis of 300–400 glycosphingolipids in different mammalian cell types. These include ceramide and its degradation products that regulate cell proliferation, apoptosis, and modulation of cell signaling pathways [14]. These glycosphingolipids also have key roles in diabetes, cancer, kidney, and other common diseases [3]. Disruption of the balance between GC synthesis and degradation in Gaucher disease leads to inflammatory conditions and dysfunctions in different tissues [3,15]. A recent study points to the fundamental role for GBA (glucosidase, β, acid) gene in immune regulation, and suggests that GBA mutations in GD may cause widespread immune dysregulation through substrates accumulation [4].

Two major pathophysiological mechanisms that account for macrophage activation have been postulated. Sphingolipids have been implicated in inflammatory and apoptotic processes, and glucosylceramide might have direct activating or enhancing effects on macrophage function [16].

An alternative mechanism by which these proinflammatory and anti-inflammatory pathways could be activated is through abnormal folding of mutant proteins in the endoplasmic reticulum. Such abnormal folding initiates an unfolded protein response that can trigger apoptotic or inflammatory pathways in various tissues [17]. It has been suggested that some mutations in Gaucher disease might lead to proteins that are abnormally folded or maltrafficked [18], however there is no direct evidence of unfolded protein response in Gaucher disease [1,19].