Lysosomes, Lysosomal Storage Diseases, and Inflammation

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Abstract
Lysosomes were originally described in the early 1950s by de Duve who was also the first to recognize the importance of these organelles in human disease. We know now that lysosomes are involved in numerous biological processes, and abnormalities in lysosomal function may result in a broad range of diseases. This review will briefly discuss the role of lysosomes in inflammation and how disruption of normal lysosomal function in the lysosomal storage diseases (LSDs) leads to abnormalities in inflammation and immunity.

Keywords
lysosomal storage disorders, inflammation

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General Role of Lysosomes in Inflammation

Lysosomes and Autophagy
The primary function of lysosomes is to degrade macromolecules through a series of enzymatic reactions that are activated at acidic pH. This process is required to degrade molecules that are internalized by cells (eg, by the process of endocytosis) or endogenous molecules that are components of normal cell structures (eg, cell membranes, cytoskeleton, nucleic acids). This latter process is referred to as autophagy or autophagocytosis and is one of the key housekeeping functions of lysosomes (for a recent review, see Huber and Teis, 2016). Autophagy is required for the normal homeostasis of cells and is activated in conditions of cellular stress, such as starvation or exposure to toxic molecules. Defective autophagy is found in many human diseases, including cancers, autoimmune diseases, and LSDs.

Autophagy plays a key role in normal host defense mechanisms, and abnormalities in autophagy can lead to numerous inflammatory changes. In healthy cells, autophagy is required to eliminate invading pathogens, to control adaptive immunity through regulation of antigen presentation, and to modulate the inflammatory response. For example, engagement of Toll-like receptor 4 (TLR4) by lipopolysaccharide on gram-negative bacteria results in ubiquitination of beclin-1 and activation of the serine/threonine protein kinase, ULK1. Both pathways lead to activation of autophagy. Engagement of other TLRs also induces autophagy as does activation of NOD-like receptors on dendritic cells. This latter process is required to direct proper antigen handling and presentation. In addition, several proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin (IL-1β), induce autophagy to improve infection control. In contrast, anti-inflammatory cytokines such as IL-4 and IL-13 antagonize autophagy induction. Type I and II interferons also largely regulate host cell defense against viruses through the activation of autophagy.

Perhaps the best studied relationship between autophagy and inflammation is IL-1β release by inflammasomes.
Inflammasomes are multiprotein complexes containing proteases (mostly caspase 1) required to activate pro-IL-1β and IL-18 into active cytokines. One of the first investigations to link autophagy with inflammation used macrophages from Atg16L1 knockout mice that are defective in autophagy. These mice exhibit increased production of active IL-1β after stimulation with lipopolysaccharides (LPS). Additional studies confirmed these findings and showed that autophagy has an important anti-inflammatory effect in healthy cells and that defective autophagy activates inflammation. Although the mechanisms responsible for this anti-inflammatory effect of autophagy are not fully known, several hypotheses have been put forward. For example, it has been suggested that defective autophagy leads to the accumulation of mitochondria in cells and elevated release of inflammasome activators through the production of reactive oxidative species (ROS) and mitochondrial DNA and/or that autophagy may be required to remove aggregated inflammasome structures, thereby reducing proinflammatory responses. Aside from the important inhibitory effect of autophagy on inflammasome activation in healthy cells, autophagy also inhibits IL-1β production through non-caspase-1 mechanisms and reduces nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation as well. It further amplifies the TLR response to improve intracellular delivery of microbial ligands, leading to the production of type I interferon. Thus, autophagy has broad and important effects on host cell immune responses and inflammation, and in the absence of normal lysosomal function and autophagy, dysregulation of these pathways becomes evident.

**Lysosomes and Autoimmunity**

Further insights regarding the role of lysosomes and inflammation have come from the study of autoimmune diseases. Autoimmune diseases are a diverse group of disorders where organisms produce autoantigens that the immune system cannot distinguish from normal antigens. Recent evidence suggests that lysosomal enzyme activities may contribute to the generation of autoantigens. For example, the lysosomal enzyme α-galactosidase A (defective in the LSD, Fabry disease) normally degrades lipid antigens to prevent their accumulation and activation of CD1d-restricted natural killer T (NKT) cells. Deficiency of this enzyme in Fabry disease causes aberrant accumulation of lipid antigens and activation of immature NKT cells, resulting in autoimmunity.

The first major autoinflammatory disease in which lysosome was suggested to play a role was Crohn disease (for review see Spalinger et al.). Crohn disease is a chronic inflammatory disorder of the intestine caused by a combination of factors including defective host response, altered mucosal barriers, and exaggerated cytokine production. Genetic variants of several important autophagy genes have been associated with susceptibility and clinical severity of Crohn disease. Variants of ATG16L1, in particular, have been linked to defective bacterial defense, aberrant antigen presentation, and increased production of proinflammatory cytokines, including IL-1β and IL-18. Other important insights regarding the relationship of autophagy, lysosomes, and human disease arise from studies of chronic granulomatous diseases (CGDs). Chronic granulomatous disease is a primary immunodeficiency characterized by defective ROS production, defects in host defense, and hyperinflammatory responses leading to colitis in a significant number of patients. Defective autophagy has also been demonstrated in patients with CGD, leading to enhanced inflammasome activation and release of IL-1β, which can be treated using the IL-1 receptor antagonist, IL1RN/IL1RA. Other epidemiology studies have shown associations of autophagy genes with other autoimmune conditions as well, including systemic lupus erythematosus and multiple sclerosis. Thus, healthy lysosomes are required to maintain a normal autoimmune response, and lysosomal dysfunction may lead to a range of autoimmune-related pathologies.

**Lysosomes, Sphingolipid Metabolism, and Inflammation**

Another important, recent link between inflammation and lysosomes has come from the study of bioactive sphingolipids, and in particular ceramide and its derivative, sphingosine-1-phosphate (S1P; for review, see Gomez-Munoz et al.). Lysosomes are a major cellular compartment involved in the breakdown and metabolism of sphingolipids, and defects in lysosomal function leads to dysregulation of these lipids and activation of inflammatory pathways. Ceramides are a diverse group of sphingolipids consisting of an 18-carbon sphingoid base backbone, sphingosine, linked via an amide bond to a long-chain fatty acid. The fatty acids present in ceramides may vary in chain length and the degree of saturation, providing structural and functional diversity to this lipid class. Ceramides are important regulators of many biological processes, including apoptosis, cell adhesion, inflammation, and infection. They are degraded through the activity of a class of enzymes known as ceramidases, releasing sphingosine and free fatty acids. Sphingosine may be further hydrolyzed to S1P by the activity of sphingosine kinases. Sphingosine-1-phosphate similarly has numerous biological roles, including the induction of cell proliferation and inflammation.

Lysosomes are a key site of ceramide production through the breakdown of sphingomyelin and/or glycosphingolipids. The lysosomal enzyme, acid ceramidase, is then required to hydrolyze ceramides into sphingosine, thereby maintaining the levels of these 2 important signaling molecules. Sphingosine is converted into S1P in the cytosol, where it may then be released into the circulation. Defective lysosomal function, as in the LSDs, disrupts the normal metabolism of sphingolipids, particularly, ceramides, sphingosine, and S1P, thereby dysregulating many important signaling pathways.

One of the best examples linking abnormal sphingolipid metabolism with inflammation comes from studies of cystic fibrosis (CF). Seitz et al were the first to show that lung cells and tissues from patients and mice with CF had elevated
ceramides and that inhibition of ceramide production (through inhibition of the lysosomal enzyme acid sphingomyelinase [ASM], which degrades sphingomyelin into ceramide) reduced inflammation and infection.²⁵ Acid sphingomyelinase is activated in CF and many other diseases, producing excess amounts of ceramides. This, in turn, alters the biophysical properties of the cell membranes, inducing abnormal cell signaling. Others have shown that several proinflammatory cytokines, including TNF-α, interferons, and IL-1β, activate ASM activity, contributing to the elevated ceramides.²⁶ Other inflammatory lung conditions, including asthma and chronic obstructive lung disease, have also been linked to excess ceramides.²⁷,²⁸ Most recently, Pewzner-Jung et al showed that sphingosine, the product of acid ceramidase activity, is required to prevent bacterial infections and that patients with CF had reduced acid ceramidase activity.²⁹ Inhalation of recombinant acid ceramidase into the lungs of CF mice reduced ceramide and elevated sphingosine and protected these mice from infection with Pseudomonas aeruginosa.

Thus, lysosomes play a diverse and important role in immunity and inflammation, in part through the regulation of autophagy, control of inflammasome release of cytokines, and the regulation of sphingolipid metabolism. In general, healthy lysosomes are required to exhibit a normal host response to infection and to maintain a normal inflammatory response. Defective lysosomes lead to abnormal autophagy, activation of inflammation, and reduced infection control.

### Lysosomal Storage Diseases and Inflammation

The LSDs represent a group of more than 60 disorders due to inherited deficiencies of lysosomal enzymes or transport proteins.³⁰ All are inherited as autosomal recessive traits except for two, Fabry disease and Hunter disease (mucopolysaccharidosis [MPS] II), which are X-linked.³¹ The result of these deficiencies is the accumulation of undegraded macromolecules, initially within lysosomes but spreading over time to other cellular compartments. The pattern of macromolecule accumulation varies with the disease. In general, it initiates with a specific enzyme substrate, but as the disease progresses and the lysosomal dysfunction continues, secondary deficiencies of other enzymes occur, leading to a complex pattern of macromolecule storage. A common, initial response by the cell to the LSD abnormalities is the production of more lysosomes. However, since these newly formed lysosomes also have inherent abnormalities, they become dysfunctional as well. Eventually, the lysosomal system shuts down, leading to abnormalities in endocytosis, autophagy, inflammation, and ultimately causing cell death.

One of the best examples linking LSDs with inflammation is Gaucher disease (acid β-glucosidase [glucocerebrosidase] deficiency). The accumulating substrate, glucosylceramide, appears predominantly in macrophages as does its deacetylated product, glucosylsphingosine. The accumulation of these lipids leads to macrophage activation, inducing the release of various cytokines, including chitotriosidase, TNF-α, IL-1β, and others.³²–³⁴ This, in turn, sends out a call signal to recruit additional immune cells, including macrophages and neutrophils, to the sites of pathology. However, since these cells are themselves dysfunctional, they simply serve to amplify the pathology and disease burden in patients, rather than correct it.

In addition to macrophage activation and cytokine release, polyclonal and monoclonal gammopathies also occur in some patients with Gaucher disease.³⁵ Monoclonal gammopathy is a risk factor for certain myeloid cancers, which have been reported to occur at a higher than expected frequency in patients with Gaucher disease.³⁶ Interleukin 6 is elevated in patients with Gaucher disease as well and is associated with the expansion of myeloid cells. Also, IL-10 is elevated and may contribute to the increased occurrence of autoantibodies and B-cell lymphomas. It is unclear how accumulation of glucosylceramide and/or glucosylsphingosine stimulates these events, but an attractive hypothesis has to do with the sphingolipid pathway discussed earlier. Both accumulating lipids in Gaucher disease are precursors of ceramide and sphingosine (and ultimately S1P) and could influence these inflammatory pathways through the production of these downstream metabolites.

Also of note, Aflaki et al have recently shown that impaired autophagy in Gaucher disease macrophages leads to inflammasome activation and elevated secretion of IL-1β. These investigators further demonstrated that treatment with a molecular chaperone (NCGC758) that enhances the function of mutant glucocerebrosidase reversed these defects, confirming the relationship between lysosomal dysfunction and inflammasome activation.³⁷

Others have studied the specific role of neuroinflammation in Gaucher disease and found highly elevated levels of IL-1β, TNF-α macrophage colony-stimulating factor, and transforming growth factor β in the brains of a neuropathic Gaucher disease mouse model.³⁰ Activation of microglia in the Gaucher disease brain has also been demonstrated. Kartha et al have also shown that patients with Gaucher type 1 disease exhibit increased systemic oxidative stress in addition to inflammation.³⁸ Thus, inflammation is a major contributing factor to the multiorgan system pathology in Gaucher disease, and targeting inflammation could potentially provide therapeutic benefits in patients with Gaucher disease.

Another important LSD in which inflammation and an abnormal immune response play a major role is Fabry disease, due to the deficiency of the enzyme α-galactosidase A.¹⁶ The primary substrate accumulating in this disorder is the glycosphingolipid, globotriaosylceramide (Gb3). In Fabry disease knockout mice, age progressive increases in Gb3 led to a progressive decrease in invariant (type 1) NKT (iNKT) cells, principally in the spleen but other organs as well.³⁹ Pereira et al also reported a decrease in CD4-positive iNKT cells, as well as a reduction in IL-4 production in patients with Fabry disease.⁴⁰ Rozenfeld et al showed a low level of Cd1d and hypothesized that this could be due to increased expression of major histocompatibility complex (MHC) class II molecules in monocytes.⁴¹ Thus, it appears that glycosphingolipid storage in
patients with Fabry disease, and Gb3 specifically, leads to dysregulation of iNKT distribution and the Cd1 pathway in general.

The proinflammatory feature of Fabry disease also has been well described, with an increase in inflammatory cytokines including IL-6, IL-1β, and TNF-α among others. This elevation appears to be related to the TLR4 pathway, since the elevated cytokine release in Fabry cells was reduced using TLR4-blocking agents. The TLR4 pathway is activated in many LSDs, and TLR4 has been shown to bind glycosaminoglycans (GAGs) that accumulate in the MPS (see below), as well as glycosphingolipids such as the gangliosides GM1 and GM2. In addition, Segura et al have shown increased endothelial inflammatory profiles in serum from patients with early-stage Fabry disease. These patients had elevated levels of endothelium-released biomarkers (TNF-α, C-reactive protein, and soluble vascular cell adhesion molecule 1), indicative of the systemic endothelial dysfunction that is believed to be the cause of the thrombogenicity in Fabry disease. Biancini et al also investigated proinflammatory cytokines, oxidative stress parameters, and Gb3 levels in patients with Fabry disease receiving enzyme replacement therapy (ERT). Their data suggest that Gb3 is directly correlated with the induction of elevated IL-6, TNF-α, and oxidative stress in patients. Also, as with other LSDs, lysosomal dysfunction in Fabry disease leads to defects in autophagy, which stimulates numerous inflammatory pathways (as described earlier).

Another intriguing but less studied LSD in which inflammation appears to play an important role is Farber disease, due to the deficiency of the enzyme acid ceramidase and the resultant accumulation of the sphingolipid, ceramide. As noted earlier, ceramide is an important signaling lipid that has potent proapoptotic and proinflammatory characteristics. As with other LSDs, Farber disease presents with a wide spectrum of clinical findings, but all patients develop subcutaneous nodules that are composed of lipid-filled immune cells, principally macrophages and neutrophils. These nodules are mostly evident at cartilaginous sites but have been found in the spleen and other organs as well. Alayoubi et al constructed a mouse knock-in model of Farber disease and found the very early elevation in several proinflammatory cytokines, principally monocyte chemokine protein 1 (MCP-1). They went on to hypothesize that the elevation in MCP-1, likely due the accumulation of ceramides, is an initiating event leading to the formation of subcutaneous nodules and other pathologies occurring in patients with Farber disease and that therapies that reduce MCP-1 would be beneficial in these patients.

The first systematic studies demonstrating the importance of inflammation in the LSDs were carried out by Richard Proia at the National Institutes of Health (NIH). Working with mouse models of GM1 and GM2 gangliosidosis, Proia and colleagues found widespread microglial activation in the brains of these animals that preceded neuronal cell death. Bone marrow transplantation (BMT) reduced inflammation and neuronal cell death, indicating a direct link between inflammation and neurodegeneration. Wu and Proia also conducted a study in Sandhoff disease mice where they bred these animals to mice lacking macrophage inflammatory protein 1α (MIP-1α). Macrophage inflammatory protein 1α release is elevated in these mice, and double-mutant mice lacking this chemokine showed improved neurological status and a longer lifespan. Groh et al have investigated the role of the inflammation-related cell adhesion molecule sialoadhesin (Sn) in Ppt1/2 and Cln3/2 mice, models of the most common form of neuronal ceroid lipofuscinoses, CLN3 disease. Microglia/macrophages in the CNS of both models showed upregulation of Sn and markers for proinflammatory M1 polarization and anti-inflammatory presentation.

Based on the early work of Proia, others have further investigated the use of anti-inflammatory therapies in patients with LSD, cells, and/or animals. Although most of the clinical studies have been isolated reports, in general some benefit has been observed. For example, a recent report revealed the therapeutic potential of Resveratrol in Gaucher disease cells and patients. Resveratrol is a natural polyphenol with beneficial anti-inflammatory, antioxidant, and neuroprotective effects. Also, Miglustat, an approved therapy for some patients with Gaucher disease, has been shown to work, at least in part, by mitigating inflammation in bronchial epithelial cells. In an interesting study, Williams et al showed the synergistic benefit of Miglustat, curcumin, and the nonsteroidal anti-inflammatory ibuprofen in a mouse model of Niemann-Pick disease type C.

Stein et al also used the nonsteroidal anti-inflammatory drug, simvastatin, in a mouse model of metachromatic leukodystrophy (MLD) and showed reduced neuroinflammation and retarded demyelination of the spinal cord (but not of the brain). This MLD mouse model is analogous to the human condition and is characterized by a sustained elevation in MIP-1α leading to an upregulation of MIP-1β, MCP-1, and several ILs (1β, 6, 9, 13), ultimately resulting in demyelination. Globose cell leukodystrophy (GLD) is another example of an LSD, which is characterized by neuroinflammation. The murine model of GLD, twitcher, exhibits dysregulation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway and an abnormal inflammatory response. Rafi et al showed a reduction in inflammation and therapeutic benefit in twitcher mice by combining BMT with CNS-directed gene therapy. Christina et al have also shown a reduction in systemic and neuroinflammation in the twitcher mice by targeting the JAK/STAT pathway with AZD 1480, an inhibitor of JAK1/2, which has been successfully used in multiple sclerosis mice.

Neuroinflammation and oxidative stress are also major components of the neuropathology present in several MPS diseases, including Sanfilippo (MPS III) and Sly (MPS VII) diseases. For example, Ausseil et al showed that MIP-1α messenger RNA was increased 10-fold in the brain of MPS IIIB mice when compared to normal. In addition, serum MIP-α was elevated in these mice beginning at 6 weeks of age and increased as the disease progressed. In these neurological forms of MPS, microglia activation via inflammation and oxidative stress contributes to cell dysfunction or apoptosis. Arfi
et al also suggested that treatment with nonsteroidal anti-inflammatory drugs such as aspirin could be beneficial both neurologically and systemically by reducing inflammation when used in conjunction with substrate reducing therapies. Simonaro et al have further shown that subcutaneous pentosan polysulfate (PPS) injection (see below) can reduce systemic inflammation, hyperactivity, P-tau formation, and the formation of activated microglia in MPS IIIA mice. Thus, inflammation has been shown to be a critical pathogenic factor in many LSDs, and anti-inflammatory drugs should be considered alone or as combination therapies with ERTs and gene therapies that target the primary enzyme defect.

**Inflammation and the MPS Disorders**

Perhaps the best studied use of anti-inflammatory therapies in the LSDs is within the MPS subgroup of disorders. The MPS comprises a group of 11 LSDs due to deficiencies of enzymes that degrade GAGs. Since GAGs are major constituents of connective tissues, these disorders primarily affect the skeletal system (cartilage and bone), skin, and other connective tissue systems. ERTs are available for 4 of these disorders and under development for several others. However, because the recombinant enzymes do not reach many of the connective tissue compartments, these therapies have limited effects in these tissues.

In 2005, Simonaro and colleagues showed that GAG storage in MPS leads to cytokine elevation in MPS cells and animals. Among these cytokines, TNF-α and IL-1β were the most predominant. Although the elevation in proinflammatory cytokines could be due to the general lysosomal dysfunction and mechanisms discussed above (eg, defective autophagy), in the case of the MPS diseases, GAG storage seemed to have an exacerbating and important additional effect. These studies also showed that in addition to proinflammatory cytokines, there was a very significant elevation in inflammatory proteases, such as the metalloproteinases, leading to degradation of extracellular matrix components, as well as increased apoptosis of connective tissue cells.

A further study investigated the mechanism of inflammation in MPS and found that GAGs bind TLR4 receptors and activate the TLR4 pathway, leading to TNF-α and other cytokine release. Several different GAGs were evaluated (eg, dermatan, heparin, and chondroitin sulfate), each of which activated TLR4 to varying degrees. Of interest, in this study, ceramide release was shown to be elevated in MPS cells (chondrocytes), likely contributing to the proinflammatory and proapoptotic cartilage phenotype. In contrast, SIP levels were elevated in synovial fibroblasts, perhaps contributing to the synovial hyperplasia that is observed in patients. These changes in sphingolipid levels are likely due to the general lysosomal dysfunction discussed above.

To demonstrate the importance of the TLR4 pathway in MPS, a study was carried out where mice with MPS type VII (β-glucuronidase deficiency) were bred to mice lacking TLR4. Remarkably, even in the absence of any other therapy, these MPS mice had a substantially improved phenotype, including enhanced bone length, reduced cartilage degradation, and improved tracheal morphology. These investigators also evaluated the use of a TNF-α antagonist in rats with MPS type VI and found reduced levels of inflammatory cytokines and enhanced cartilage integrity.

The abovementioned studies highlighted the importance of inflammation in MPS and indicated that the TLR4 pathway was commonly activated in these disorders. However, while TNF-α antagonists were effective, they remain extremely expensive and, in general, are potent immunosuppressants that pose some risk to patients. This led to the evaluation of another drug called PPS. Pentosan polysulfate is a low-molecular-weight, carbohydrate polymer with mild antithrombotic and strong anti-inflammatory properties. It has been studied for over 40 years and is currently available as an oral tablet in the United States to treat interstitial cystitis (Elmiron) and as an injectable form in some European countries to treat deep vein thrombosis (SP54). Animal studies have shown it has potent anti-inflammatory effects in models of diabetes, arthritis, and others, and it is also used in veterinary medicine to treat inflammatory arthritis (Cartrophen).

In 2 studies, PPS was evaluated in MPS-type VI rats. It was found to markedly reduce inflammation, reduce chondrocyte apoptosis, improve tracheal morphology, and improve motility in these animals. Moreover, and unexpectedly, it was also found to significantly reduce GAG levels in the treated animals. Although the mechanism(s) for this latter finding is not known, it has been hypothesized that it may be due to the structural similarities between PPS and GAGs, leading to inhibition of the GAG synthetic pathway (ie, acting as a “substrate-reducing drug”). Thus, inflammation plays an important and common role in the MPS disorders, and anti-inflammatory therapies such as PPS may have very positive effects, alone or in combination with ERTs.

Recently, Polgreen et al also showed that inflammation mediated by TNF-α is responsible for pain, decreased physical activity, and short stature in MPS I, II, and VI children, despite having received BMT, ERT, or both. They also concluded that in this patient population, resistance to human growth hormone therapy might be due to TNF-α inhibition of the hormone. Donida et al have also reported elevated plasma levels of IL-6 and pro-oxidant states in MPS four A (IVA) patients undergoing ERT.67 These studies confirm the persistence of inflammation despite therapies and warrant the use of anti-inflammatory therapies as adjuncts to alleviate pain and improve quality of life.

Most recently, PPS has been evaluated in 2 small clinical studies (adult MPS type I and type II).68,69 These studies were carried out for 12 and 24 weeks, respectively, and PPS was well tolerated by all patients. Hennermann et al showed an improvement in range of motion in the joints of 3 of 4 patients with MPS-I, with significant decreases in pain score and GAG excretion. Orii et al also recorded an improvement in range of motion in patients with MPS-II and a reduction in serum inflammatory cytokines.
In conclusion, storage of macromolecules in the LSDs activates numerous inflammatory pathways, resulting in both local (eg, brain) and systemic inflammation. Inflammation in the LSDs may be directly due to substrate storage (eg, GAGs in MPS) or indirectly due to the general lysosomal dysfunction that occurs (eg, defective autophagy). Inflammation persists in LSD animal models and patients even after treatment by ERT or BMT, indicating that adjunct anti-inflammatory therapies might be beneficial in these disorders. Such therapies might also be useful in patients for which ERT or BMT is not available or as “bridging” drugs for patients identified through newborn screening programs that cannot immediately receive these therapies.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The author declares co-inventorship on a patent regarding the use of anti-TNF-α agents in lysosomal storage disorders. In addition, the author is a consultant to Plexcera Therapeutics.

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