

Review

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The inflammatory pathogenetic pathways of Fabry nephropathy

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Abstract

The high variability in clinical features and outcomes observed in monogenic diseases like Fabry disease suggests the presence of additional pathogenetic pathways beyond the lysosomal deposition of Gb3 and Lyso-Gb3. Research indicates that the deposition of Gb3 and Lyso-Gb3 can stimulate the inflammatory processes. Mononuclear immune-competent cells exposed to Gb3 deposition exhibit surface adhesion molecules and release pro-inflammatory and fibrotic cytokines such as IL β , TNF α , and TGF β , culminating in the activation of inflammatory cascades associated with oxidative stress, apoptotic mechanisms maintained by renal residents and infiltrating cells, leading to chronic inflammation and tissue fibrosis. Furthermore, in another avenue of inquiry (termed Agalopathy), the mutated galactosidase alpha gene can result in the production of an altered alpha-galactosidase A enzyme, inducing endoplasmic reticulum stress and triggering the unfolded protein response (UPR) in an effort to prevent the production of altered proteins. The UPR, in turn, instigates the release of pro-inflammatory cytokines, thereby contributing to the inflammatory milieu. Experimental findings have demonstrated that the pathogenetic mechanisms activated by Gb3 and Lyso Gb3 deposition can become independent from the initial stimulus and may exhibit limited responsiveness to therapy. Cellular pathway alterations can persist post-therapy or gene correction. Moreover, biochemical and histological lesions characteristic of Fabry disease manifest in the absence of Gb3 in the Zebrafish experimental model. This review endeavors to describe the role of these processes in Fabry nephropathy and aims to synthesize the available evidence on the pathogenesis of renal damage.

Keywords: Fabry nephropathy, inflammation, pathogenetic mechanisms



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INTRODUCTION

Renal involvement is a significant factor in Fabry disease [FD], impacting patient outcomes considerably. Prior to the availability of enzyme replacement therapy [ERT], it was the primary cause of death in Fabry patients^[1]. The clinical course of Fabry nephropathy [FN] is variable. In males with the classical phenotype, urinary concentration defects may manifest at a young age during the initial phase, often overlooked. Over time, mild proteinuria develops, followed by arterial hypertension and progressive impairment of renal function. The nephropathy follows a progressive, chronic course, with overt renal failure typically appearing in the third or fourth decade of life, potentially necessitating dialysis treatment. For eligible patients, renal transplant stands as a viable option, often yielding successful outcomes. Conversely, the renal clinical course tends to be less aggressive in females and patients with late-onset variants, where nephropathy occurs later in life. Typically, these phenotypes exhibit mild renal manifestations for a long time, with the diagnosis of Fabry disease often delayed for many years or coincidentally made during a screening program^[2].

Fabry disease is an X-linked monogenic disorder due to pathogenic variants in the GLA gene that encodes for the lysosomal enzyme α -galactosidase A. The deficient activity of α -galactosidase A causes a progressive lysosomal deposition of the glycosphingolipids: globotriaosylceramide [Gb3] and its derivative globotriaosylsphingosine [Lyso-Gb3].

Even though only one gene is involved in the pathogenesis of the disease, clinical presentation among Fabry patients is highly heterogeneous. Affected members from the same family, with the same GLA mutation, classical or late onset, can present a broad spectrum of phenotypes^[3]. Consequently, over the years, it has become more evident that the progressive deposition of Gb3 could not wholly explain the pathogenic mechanisms that are taking place in tissues and organs. Thus, it has been hypothesized that additional pathogenetic pathways could play a role in tissue damage^[4].

Many studies have been initiated to understand these processes, and the pathogenetic molecular and cellular mechanisms activated by GLA variant and lysosomal Gb3 deposition have captured significant attention from researchers. Among the altered pathways, a subtle and chronic inflammation due to Gb3/Lyso-Gb3 exposure resulting in tissue fibrosis has been extensively described^[5,6]. This review will report these studies with particular emphasis on the pathogenic development of FN.

EVIDENCE ON THE ROLE OF INFLAMMATION AND IMMUNE RESPONSE

Lysosomal deposits may act as damage-associated molecular patterns [DAMPs] or cause DAMP production by injured cells. The presence of DAMPs is sensed by pattern recognition receptors in innate immune cells, leading to pro-inflammatory activity resulting in cytokine secretion and apoptosis^[7]. The release of cytokines interacts with leukocytes, resulting in perturbation in the proportion of leukocyte subsets in peripheral blood from patients, and these cells display high surface expression of adhesion molecules^[8]. The first pieces of evidence on the presence of chronic activation of inflammation associated with Fabry disease came from studies on mononuclear cells from patients, showing a constitutive overproduction of IL1 β and TNF α ^[9,10]. When exposed to high levels of Gb3, normal dendritic cells and macrophages produce pro-inflammatory cytokines^[9]. This immune response was shown to be mediated by Toll-like receptor 4 (TLR4) ligation.

Associated with this pro-inflammatory environment, mononuclear cells from naïve Fabry patients displayed a higher apoptotic state, which is lower in patients undergoing ERT. Adding Gb3 to normal cells induces apoptosis mediated by the intrinsic pathway in which altered mitochondria play a role^[11]. Furthermore, neuronal apoptosis inhibitory protein and apoptosis-inducing factor were differentially expressed among

Fabry patients^[12].

Inflammatory pathway activation is also manifested by the presence of complement-activated components C3 and iC3b in the GLA knockout mouse model^[13] and in the serum, plasma, and brain of patients with Fabry disease^[14].

Target organs in Fabry disease, the nervous system, kidney, and heart, suffer from infiltration with immune cells that are recruited through an attempt to mitigate and heal the harmful effects of lysosomal deposits. Nervous system affection is marked by the recruitment of immune cells, as observed in the autonomic and peripheral nervous system associated with activating microglia, NK cells, macrophages, and dendritic cells in central and peripheral tissues^[15]. Immune infiltration of T cells and macrophages is also observed in cardiac and renal tissues^[6,16].

Tubular cells collected from urine samples of Fabry patients revealed impairment of mitochondrial morphology and increased oxygen consumption rate, reflecting mitochondrial dysfunction^[17]. These alterations increase autophagy, producing ROS production and proapoptotic signaling^[18]. These data suggest that mitochondrial dysfunction can contribute to inflammation pathways and renal damage.

Overall, experimental models and human investigation data are consistent with Fabry disease. The interaction between Gb3 and immunocompetent cells causes a subtle, chronic, insidious activation of innate immunity and associated processes, resulting in an overlooked inflammation. Acute inflammation is a physiological response to eliminate damage in cells or tissues. However, if the damage can not be eliminated, as in Fabry disease, inflammation becomes chronically stimulated due to continuously producing glycolipid deposits. Chronic inflammation induces a scar formation that replaces normal parenchyma with fibrotic tissue, leading to loss of organ function^[19].

GLA GENE AND ENDOPLASMIC RETICULUM STRESS: THE ROLE OF UNFOLDED PROTEIN RESPONSE

In the survey to elucidate the pathophysiology of organ affection in Fabry disease patients, the pathogenic role of endoplasmic reticulum [ER] stress and unfolded protein response [UPR] emerged as a possible hypothesis. The endoplasmic reticulum physiologically checks the correct folding of proteins before releasing them and amends or stops those with altered structures. Many Fabry disease pathogenic variants are missense, and mutated proteins are misfolded and retained in the ER instead of transported to the lysosome^[20]. High ER retention of misfolded proteins leads to ER stress, and if this stress is maintained, it leads to the activation of UPR. The UPR is a sophisticated collection of intracellular signaling pathways that have evolved to respond to protein misfolding in the ER. In addition, it has become increasingly clear that UPR signaling is essential in immunity and inflammation^[21]. There is a reciprocal regulation between ER stress and inflammation whereby ER stress can activate inflammatory pathways, and, in turn, pro-inflammatory stimuli can trigger ER stress, such that the resulting UPR activation can further amplify inflammatory responses^[22]. UPR activation in immune cells and various stromal cells leads to the induction and secretion of cytokines, such as IL-6 and TNF. Conversely, cytokines themselves can directly regulate the UPR^[23].

Apoptotic cell death mediated by UPR is carried out by the initiator caspase 12 and caspase 4. A study on mononuclear cells from Fabry patients revealed higher levels of caspase 12 but variable results of caspase 4. Further investigation showed no differences in ER stress-associated genes' expression levels, ruling out ER stress's involvement in mononuclear cells from Fabry patients' apoptotic cell death^[11].

Further studies using other cells or animal models showed different potential effects of excess misfolded GLA proteins in the ER. A GLA-knock-out HEK293 cell line model induced by transient transfection and expression of mutated GLA proteins caused ER stress and UPR activation^[24]. Different responses to ER stress and UPR may be a cell-type dependent mechanism, implying that not every cell line or tissue responds equally to an excess of misfolded proteins^[25], meaning that pathogenic mechanisms associated with UPR could be tissue-dependent.

In a fly model, expression of GLA variants resulted in ER retention, ER-associated degradation, and UPR activation, which was improved by the pharmacological chaperone migalastat^[26]. Interestingly, further research in the flies showed that UPR activation resulted in the death of dopaminergic cells and a shorter life span of the flies.

Nikolaenko *et al.* recently highlighted another point of view of ER stress, which is not directly associated with misfolded GLA due to changes in their primary sequence but with exposure to high Lyso-Gb3 levels. The evidence from a proteomic study revealed that exposure to Lyso-Gb3 affected protein folding and ubiquitination pathways. High Lyso-Gb3 levels may cause direct disruption of the chaperone system and the cytosol in the ER, increasing ubiquitination^[27].

The Role of ER stress and UPR may suggest that FD is not only a storage disease but also a gain of function component due to ER retention of mutant protein and ER stress due to an excess of accumulated glycolipids.

THE GLOMERULAR AND VASCULAR COMPARTMENT

Upon routine histochemical observation of glomeruli from Fabry kidney biopsies, Gb3 deposits are displayed as empty vacuoles in the cytoplasm of all cells, prominently in podocytes. Usually, mesangial areas are enlarged with an increase in the extracellular matrix and a proliferation of the mesangial cells. Moreover, focal segmental glomerulosclerosis can typically be present due to podocyte damage. Over time, these lesions result in diffuse global glomerular sclerosis, and clinically, the changes translate into proteinuria and progressive impairment of renal function with an overt chronic renal disease^[28].

The podocyte has been extensively investigated in FN. Sanchez-Nino demonstrated that upon exposure of human podocytes *in vitro* to increasing concentrations of Lyso-Gb3, these cells release inflammatory mediators of glomerular damage, such as Transforming Growth Factor beta [TGFβ]. TGFβ is a powerful activator of collagen and fibronectin synthesis and determines an increase in extracellular matrix production and tissue fibrosis^[29]. Later, she demonstrated that Gb3 increases the NOTCH-1 signaling, a podocyte injury mediator, with the NFκB activation. NFκB is the trigger to stimulate the release of pro-inflammatory and profibrotic cytokines^[30]. The deposition of Gb3 into the podocytes causes a progressive injury and the detachment of the cell into urine: so-called podocyturia^[31]. The podocyte has limited or no turnover. The reduction of podocytes is associated with segments of the denuded glomerular basement membrane, changes in the slit diaphragm, and subsequent areas of segmental glomerular sclerosis.

The mesangial cells proliferate, and an increase in mesangial extracellular matrix coexists. Indeed, these cells, under Gb3 deposition, release pro-inflammatory and profibrotic cytokines^[32]. Mesangial cells express the plasma membrane TLR4^[33] that, following the recognition of Gb3, start the innate immune response with the release of cytokines^[9]. Moreover, the mesangium is colonized by inflammatory circulating cells such as myofibroblasts, macrophages, and monocytes, stimulating local inflammation by releasing IL1β and TNFα^[33]. In the urine of Fabry patients, proteomic studies have found many signals of tissue inflammation.

Indeed, urinary proteomics displayed high levels of uromodulin, prostaglandins, podocalyxin, and fibroblast growth factor 23, and ERT is associated with reducing the urinary levels of these molecules^[34,35].

The glomerular capillaries can be considered highly differentiated vascular structures, and the endothelium is a target of Gb3 deposition. Gb3 exposure determines oxidative stress and overexpression of adhesion molecules, and it is associated with the oxidation of many molecules, such as DNA, lipids, and proteins, resulting in cellular dysfunction^[36]. More-over, Gb3 causes the deregulation of many endothelial pathways, such as endothelial nitric oxide synthase [eNOS], with decreased oxide bioavailability or enzyme uncoupling and increased pro-inflammatory cytokines cyclooxygenase mediated^[37]. In larger vessels, Lyso-Gb3 also induces the proliferation of smooth muscle cells that, in addition to the oxidative processes, determine a thickening of the vascular wall and indirect issues of ischemia^[38].

Finally, an imbalance between molecules inhibiting neovascularization [thrombospondin-1], fibroblast growth factor and proangiogenic elements [eNOS, angiopoietin2] was described in Fabry patients, highlighting the role of vascular structures in FN^[39].

THE INFLAMMATORY PROCESSES AND TUBULE-INTERSTITIAL RESPONSE

Tubular interstitium has a pathogenic role in Fabry nephropathy, although the related clinical signs are mild^[40]. Like every kidney cell type, tubular cells are affected by exposure to glycolipid deposits^[41]. Tubular cells are dividing cells with high metabolic expenditure and energy consumption, one of the cell types with the highest numbers of mitochondria per cell in the body^[42].

In vitro studies with tubular cell lines showed mitochondrial dysfunction^[17], increased autophagy and reactive oxygen species [ROS] production, as well as proapoptotic signaling^[18]. As the tubular system of the kidney is highly dependent on mitochondrial function to uphold the transcellular transport of solutes and active secretion of compounds into the urine, dysfunction of the central energy metabolism can result in harmful effects. Moreover, *in vitro* exposure to Gb3 and Lyso-Gb3 of the epithelial tubular cell line, HK2, resulted in transdifferentiation to myofibroblasts, displaying a profibrotic profile^[43].

The contribution of the tubular compartment to pathogenesis could also be assumed by studies with mouse models. Observations in the mouse model developed by cross-breeding the GLA-KO with Gb3 synthase transgenic mice [GLA-KO-Tg]^[44] revealed tubular glycolipid injury that affects renal function, with polyuria, polydipsia, and decreased urine osmolality, without remarkable glomerular damage^[45].

Studies on renal biopsies from human Fabry patients highlighted the tubular system. The main profibrotic cytokine, TGFβ, is produced by proximal tubular cells^[6]. This profibrotic environment induces transdifferentiation of epithelial cells into fibroblasts that were shown to be present in pericytes surrounding peritubular capillaries, mesangial cells, and the periglomerular zone. Therefore, tubular cells could be the cells in which pathological profibrotic changes are initiated. After this insult commences, it spreads to other renal areas, leading to fibrotic deposition in the glomerulus and interstitium^[30]. In a recent study, Turkmen *et al.* analyzed the subpopulations of immune infiltrating cells in renal biopsies from a small group of Fabry patients at baseline and under enzymatic replacement therapy [ERT]^[46]. This study revealed a reduction in CD8, CD16, T cells, and NK cells and an increase in CD20 B cells and CD38 plasma cells, indicating the interstitial immune infiltrating cells' active participation in the inflammation and the subsequent renal damage.

THE ROLE OF THERAPY IN MODULATING THE PATHOGENIC MECHANISMS

ERT with two molecules [agalsidase alpha and beta] has been available for Fabry disease for twenty years. Recently, oral treatment with a chaperone [migalastat] of alpha-galactosidase A has also been prescribed for patients carrying amenable mutations. Migalastat can link and stabilize the mutated enzyme and increase the lysosomal trafficking and enzyme activity. These therapies have undoubtedly changed the outcomes of Fabry patients, stopping or slowing down the progression of the disease. Notably, the scientific community agrees with two opinions: the best results were obtained in patients who start therapy early, and late treatment prescription does not have the same efficacy as early^[2,47].

Gene therapy for Fabry disease is still being carried out in a few world centers and represents an innovative solution. In Canada, five patients were treated with lentivirus-mediated gene therapy. After 3-5 years, there is persistent polyclonal engraftment with plasma and leukocyte GLA activity above baseline, with a fall in Gb3 and lysoGb3 levels^[48]. However, these procedures are expensive and not consistently successful, and some trials have been stopped.

SGLT2 inhibitors (SGLT2i), drugs blocking tubular glucose reabsorption, have demonstrated their efficacy in reducing the progression of renal damage in nephropathies and cardiovascular mortality. SGLT2i work indirectly by interfering with the glomerular-tubular balance and increasing tubular urinary flux. Most relevant studies were conducted on diabetic nephropathy in chronic renal disease, IgA nephropathy, and focal segmental glomerulosclerosis (FSGS). Recently, SGLT2i was proposed as a therapy for Fabry nephropathy, and a study is ongoing^[49].

During the last few years, several pieces of evidence have been described that can substantially explain the different results according to the therapy timing. Braun *et al.* studied human podocyte cultures with reduced alpha-galactosidase A activity^[50]. These podocytes presented Gb3 deposition, displayed dysfunction of autophagic mechanisms, and released a panel of profibrotic cytokines. Upon addition of recombinant alpha-galactosidase A, these podocytes showed complete clearance of Gb3; however, glycolipid clearance was not associated with the correction of the altered cytokine signaling pathways. The authors suggest that a point of no return can exist, after which the alpha-galactosidase A cannot wholly correct cellular dysfunction despite eliminating Gb3.

Jehn *et al.* studied the altered cellular pathways in podocytes, endothelial cells, and urinary-derived cells from patients^[51]. With proteomic analysis, GLA-deficient cells displayed dysregulated protein levels involved in lysosomal traffic, cell-cell interactions, and other activities. The rescue with inducible GLA partially restored the protein expression through a sophisticated technique with lentivirus [CRISPR/Cas9 mediated GLA]. These results proved that a deficiency of GLA activity determines severe changes in physiological pathways in all kinds of cells, and the therapy cannot completely restore physiological functions.

Recently, Braun *et al.* published a paper confirming that the therapy alleviates lysosomal dysfunction but cannot always reverse organ damage^[52]. ERT reduced Gb3 accumulation in podocytes in renal biopsies from Fabry patients, but notably, the foot-processes effacement persisted in some tracts. A CRISPR/CAS9-mediated alpha-galactosidase knockout podocyte cell line confirmed the ability of ERT to clear cellular Gb3 deposition but without resolving lysosomal dysfunction. Finally, a transcriptomic investigation identified a protein alpha-synuclein [SNCA] as a mediator of lysosomal dysfunction. Alpha-synuclein is a protein that regulates synaptic vesicle trafficking and subsequent neurotransmitter release. It has been implicated in other lysosomal diseases and is well-known for its role in Parkinson's disease. Synuclein is negatively

associated with decreased enzymatic degradation and could mediate resistance to ERT^[53].

The genetic and pharmacological [by β_2 adrenergic receptor agonist] inhibition of SNCA significantly improves lysosomal structure and dysfunction. Therefore, only with SNCA correction can ERT reach the target to amend the GLA defect.

All these experimental-based experiences share common evidence. The deposition of Gb3 is followed by dysregulation of pathogenetic pathways, resulting in severe cellular injury. The enzymatic therapy can clear the cells of Gb3 deposition but has limited effects on the dysregulated pathways. Therefore, an early start of treatment can halt or reduce the Gb3 deposition and the activation of pathological pathways such as progressive inflammation. Late therapy has a reduced effect because these dysregulated mechanisms, from a certain point onwards, become independent of Gb3 activation.

COMPREHENSIVE IDEA ABOUT GB3 DEPOSITION, INFLAMMATION, FIBROSIS, AND PROGRESSION OF RENAL DAMAGE

The pathogenesis of tissue damage in FD and, in this case, FN is very complex and still unclear. Undoubtedly, the deposition of Gb3 alone cannot explain the variability of clinical cases and the different rates of disease progression. Over the past few years, we have gathered much evidence that provides exciting and complex pathogenetic pathways.

We can suppose [Figure 1] that gene mutation can already determine changes in biological processes in the physiological activity of the endoplasmic reticulum with over-expression of the UPR. This UPR is subsequently associated with stimulating inflammation, as described in other diseases such as cancer, diabetes, and so on^[22]. In this case, we could define this as a pathology of the gene, so-called Agalopathy. We must consider the GLA-mutant Zebrafish experimental model to support this hypothesis. This model has the same functional mitochondrial alterations and structural changes of FN, but it lacks the Gb3 synthetase, so there is no Gb3 lysosomal deposition^[54].

The lysosomes are the site of a severe engulfment due to Gb3 deposition interfering with normal lysosome functions, and dysregulation of physiological processes, such as autophagy, occurs. In particular, engulfed podocytes detach from the glomerular basement membrane, and glomerular segmental sclerosis appears in light microscopy^[28].

Moreover, Gb3 deposition causes activation of inflammation through the interaction with Notch 1 and NFkB, resulting in the recruitment of leukocytes to the glomeruli, exacerbating the status. Inflammatory activation causes a chronic insult to the cells and tissues that determines a cellular de-differentiation with activation of extracellular matrix protein synthesis and release of cytokines with inflammatory (IL1 β) or profibrotic (TGF β) role. In the kidney, the mesangial cells produce an excess extracellular matrix, and metalloproteinases have reduced remotion activity. All these processes can eventually become independent from the initial Gb3 deposition, resulting in progressive renal tissue inflammation and fibrosis^[30]. Kidney fibrosis is an irreversible process resulting in progressive loss of renal function and scar tissue development.

CONCLUSIONS

In the literature, evidence demonstrates that the deposition of Gb3 is associated with alterations in immune response and subtle, non-overt processes of inflammation primarily mediated by innate immune mechanisms. All the evidence of activation of inflammatory mechanisms (Gb3 deposition, cytokines release,

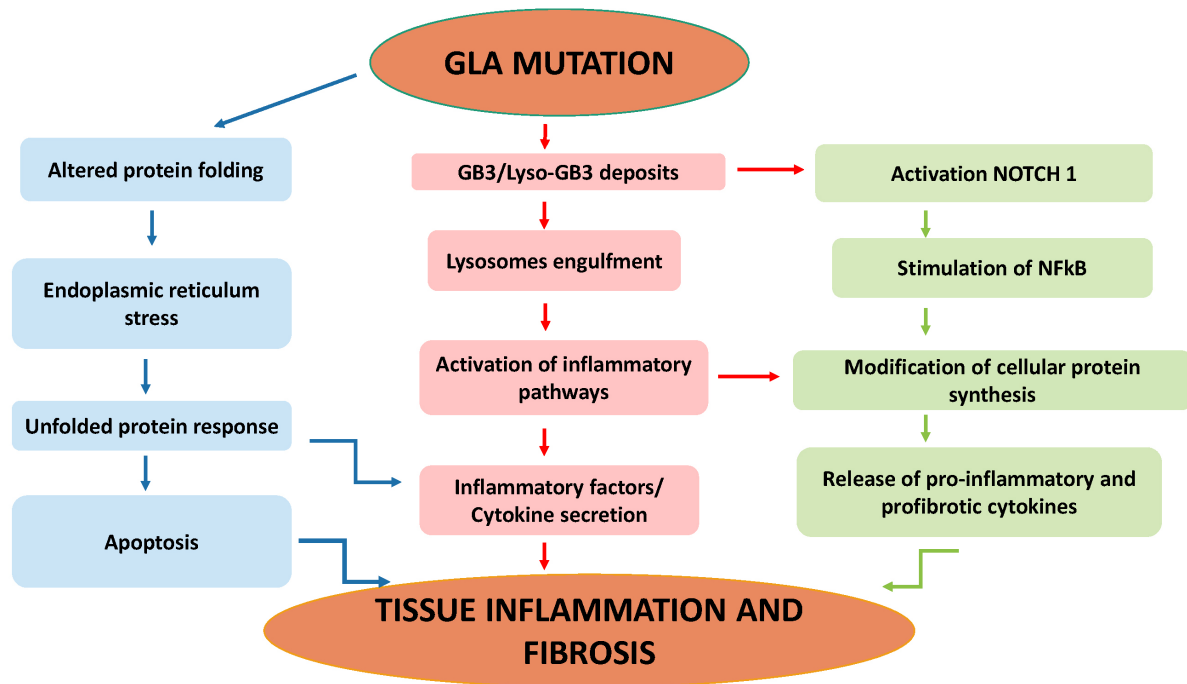


Figure 1. The molecular pathogenetic mechanisms causing renal damage in Fabry nephropathy. The GLA mutation causes the synthesis of altered proteins with stimulation of endoplasmic reticulum stress. The unfolded protein response determines the release of inflammatory cytokines and increases apoptosis (light blue boxes). The GLA mutation also causes the lysosomal deposition of Gb3/Lyso-Gb3 with derangement of lysosomal functions and release of cytokines (pink boxes). The Gb3/Lyso Gb3 deposition can stimulate the new cellular protein synthesis, activating the NOTCH1/NFkB pathway and releasing pro-inflammatory and profibrotic cytokine (green boxes). All these pathways are interconnected, and the final result is the inflammation and fibrosis of the kidney. Gb3: Globotriaosylceramide; Lyso-Gb3: globotriaosylsphingosine; NOTCH: notch receptor 1 human; NFkB: nuclear factor kappa B.

UPR, etc.) could explain the variability of the clinical picture in the same family: the individual biological response to Gb3 deposition depends on numerous and complex variables. Furthermore, it is reasonable to think that early therapy can interfere with and reduce cellular reactions to Gb3 while late treatment can limitedly prevent the progression of FN.

DECLARATIONS

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Authors' contribution

Have closely designed the review and finalized the manuscript; wrote comprehensive ideas about Gb3, inflammation, fibrosis, and the progression of renal damage, and conclusions: Feriozzi S, Rozenfeld P

Wrote introduction, the glomerular and vascular compartment, the role of therapy in modulating pathogenetic mechanisms: Feriozzi S

Wrote evidence on the role of inflammatory processes and immune response, GLA gene and endoplasmic stress: the role of unfolded protein response, the inflammatory processes and tubule-interstitial response: Rozenfeld P

Availability of data and materials

This manuscript is a review, and all data supporting the text have been officially published in the literature. All papers consulted for the text are quoted in the References.

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Consent for publication

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