Altered Pathways in Fabry Disease

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Fabry disease is a rare X-linked disease characterized by deficient expression and activity of alpha-galactosidase A (α-GalA) with consequent lysosomal accumulation of glycosphingolipid in various organs. Enzyme replacement therapy is the cornerstone of the treatment of all Fabry patients, although in the long-term it fails to completely halt the disease's progression. This suggests on one hand that the adverse outcomes cannot be justified only by the lysosomal accumulation of glycosphingolipids and on the other that additional therapies targeted at specific secondary mechanisms might contribute to halt the progression of cardiac, cerebrovascular, and renal disease that occur in Fabry patients.

Fabry disease | oxidative stress | mitochondria dysfunction | impaired autophagy

1. Introduction

The evidence that the available pharmacological treatments fail to completely resolve FD adverse outcomes, mainly at cardiac and renal level, raised the focus on secondary biochemical processes beyond the accumulation of Gb3 and derivatives that might be involved in FD pathogenesis. These may include oxidative stress (OxSt), compromised energy metabolism, impaired autophagy, and disturbed cellular trafficking [1][2][3].

2. Oxidative Stress in Fabry Disease

OxSt occurs when the physiologically generated oxidizing species overwhelm the endogenous antioxidant defenses, resulting in the disruption of the intracellular redox homeostasis [4]. OxSt plays, in fact, a key role in the onset and progression of endothelial dysfunction, atherosclerosis, inflammatory disease, and cardiovascular–renal remodeling [5][6].

In FD, the presence of OxSt was firstly assumed in terms of elevated markers of inflammation and oxidative damage. Shen et al. documented a correlation between Gb3 and increased reactive oxygen species (ROS) production in cultured vascular endothelial cells along with overexpression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin [7]. Moreover, endothelial cells incubated with plasma from FD patients revealed higher ROS generation compared to treatment with plasma from healthy subjects [7].

OxSt also causes damage at nuclear and genomic levels, which results in free radicals damaging DNA and inducing changes in gene expression. Levels of 8-hydroxy-2-dehydroguanosine (8-OHdG), one of the most abundant by-products of DNA oxidation and therefore a non-invasive biomarker of OxSt [8], were found elevated both in the serum [9] and in the myocardial tissue [10] of FD patients with cardiomyopathy, and damage at the DNA level does not seem to be fully restored by endogenous repair mechanisms in FD [11].

The tight association of OxSt with NO dysregulation was also explored in FD. It has been suggested that Gb3 buildup in the endothelium is able to dysregulate the activity of the vasoprotective endothelial nitric oxide synthase (eNOS) while increasing the expression of the inducible NOS (iNOS) [12][13]; iNOS produces larger amounts of NO compared to eNOS, which can easily react with other free radicals, producing reactive nitrogen species (RNS) such as peroxynitrite and spreading the oxidative damage to surrounding macromolecules [14]. In addition, α-GalA knockdown human endothelial cell line showed dramatically enhanced production of 3-Nytrotyrsine (3NT), a marker of nitroxidative damage of proteins, in addition to Gb3 accumulation and reduced eNOS activity [12]. Excesses of 3NT were also found in the dermal and cerebral vessels of FD patients [15] and in the plaque of apolipoprotein-E-deficient mice with α-GalA deficiency and accelerated atherosclerosis [16]. Moreover, tetrahydrobiopterin—an essential cofactor for the normal enzymatic function of NOS—was decreased in the heart and kidney of an animal model of FD and inversely correlated with Gb3 levels in animal tissue and cultured patient cells [17].

Different comparative studies showed activation of OxSt-related pathways in FD compared to healthy subjects. Biancini et al. showed that FD patients exhibit decreased levels of antioxidant defenses, such as glutathione (GSH) and GSH peroxidase (GPX); higher plasma levels of malondialdehyde (MDA), protein carbonyl groups and di-tyrosine in urine together with increased proinflammatory cytokines IL-6 and tumor necrosis factor alpha (TNF-α) [18]. In addition, urinary Gb3 levels were positively correlated with IL-6, carbonyl groups, and MDA plasma levels, suggesting a link between proinflammatory and prooxidant conditions, both likely induced by Gb3 accumulation [18]. This impaired oxidative profile of Fabry patients was further demonstrated, particularly linking the overactive OxSt with the induction of cardiovascular–renal remodeling, which is distinctive of FD [19]. In fact, an overactivation of the mechanism directly involved in ROS production in terms of increased expression of $p22^{phox}$ (subunit of the NADPH oxidase, NOX), a downregulation of heme oxygenase 1 (HO-1), endogenous antioxidant defense, and increased levels of MDA, a marker of lipid peroxidation [19]. It is of note that bilirubin, a potent antioxidant by-product of HO-1 catabolism, was found to be decreased in Fabry patients compared to controls along with reduced total antioxidant status (TAS) [20].

These data further support the hypothesis that OxSt plays an important role in the pathogenesis of the disease with reference to the vascular damage and the cardiovascular-renal remodeling that occur in FD. A better understanding of the specific molecular signaling responses to OxSt in FD could suggest new treatment strategies in order to reduce the high morbidity of these patients.

3. Mithocondrial Dysfunction in Fabry Disease

Mitochondria are known as the cellular energy powerhouse in addition to being an important source of ROS [21]. Mitochondrial ROS (mtROS) are produced as side-products of the oxidative phosphorylation process [22], and a perturbation of the mitochondrial redox homeostasis and the resulting excessive accumulation of mtROS have been linked to the development of several diseases, including cancer, pulmonary and cardiovascular disease, neurodegenerative disorders and diabetes [23].

Mitochondria disfunction has emerged as an harmful factor in the pathophysiology of LSDs, including Gaucher's disease, Niemann–Pick disease and mucopolysaccharidosis [24]; a dysfunctional mitochondria may in fact impact lysosomal function via generation of ROS as well as depriving the lysosome of ATP, which is required by the V-ATPase proton pump to maintain the acidity of the vacuoles [25]. Insights into a role of mitochondria dysfunction in FD were provided by Lücke and colleagues that documented a reduced activity of mitochondrial respiratory chain (MRC) complexes in skin fibroblasts from FD patients in terms of decreased activity of MRC complex II, IV, and V compared to controls [26]. Impaired oxidative phosphorylation and mitochondrial metabolism as indicated by decreased production of high energy phosphate molecules (e.g., ATP and creatine phosphate) were detected in the hearts of FD subjects [2][27], and downregulation of mitochondrial endonuclease G—critical for cardiac mitochondrial function [28]—was observed in Fabry cardiomyocytes [29]. At the renal level, disturbed mitochondrial structure, metabolism, and turnover were documented in renal tubular epithelial cells from male FD patients [30]. Furthermore, lyso-Gb3 accumulation in podocytes determined the upregulation of the pro-inflammatory and profibrotic Notch1 signaling pathway [31], whose overactivation affects the mitochondrial proteome and impairs mitochondrial metabolism [32]. Additional evidence on the link between OxSt and mitochondrial dysregulation in FD comes from Tseng et al. [33] that reported a downregulation of the protein expression of the superoxide dismutase 2 (SOD2), a mitochondrial antioxidant, in FD-specific human-induced pluripotent stem cells, which was associated with increased ROS generation and enhanced intracellular Gb3 buildup.

Mitochondria are uniquely characterized by their own DNA (mtDNA), a closed-circle double-stranded DNA without histones, which encodes for 37 genes, including 13 components of the mitochondrial electron transport chain [34]. Interestingly, Simoncini et al. investigated whether specific genetic polymorphism in the mitochondrial genome of a cohort of 77 Fabry patients could be accountable for specific FD phenotypes [35]. They showed that certain haploid groups were more prevalent in patients, although there was no observed correlation with gender, age of onset, or organ involvement [35].

The mitochondrial genome is also able to produce specific microRNAs (miRNAs), called mitomiRs, involved in the regulation of mitochondria protein expression and function of mitochondria-related biological processes such as energy metabolism, mitochondrial OxSt, and apoptosis [36]. Recently, a mitomiR dysregulation was unveiled in Fabry patients, shedding light on mitochondria miRNA as critical players in contributing to their aberrant mitochondrial homeostasis and pointing to mitomiRs as a novel class of biomarkers of FD [37].

4. Impaired Autophagy in Fabry Disease

Lysosomes are critically involved in the maintenance of cellular homeostasis, driving the degradation and recycling of metabolic wastes, dysfunctional organelles such as mitochondria (i.e., mitophagy [38]), or large cytosolic molecules, especially in response to environmental stress. This process takes place via the autophagy–lysosome pathway (ALP), a process that seizes cytoplasmic cargos into double-membraned vesicles called autophagosomes and direct them toward lysosomes [39]. Since autophagy plays a key role in the clearance of lysosomal substrates [40], increasing evidence suggests a key role of autophagic (dys)function in FD pathophysiology. In fact, several studies reported an autophagic dysregulation in different models of FD. Chévrier et al. firstly documented an upregulation of the autophagic marker microtubule-associated protein light-chain 3 (LC3-II) in human Fabry skin fibroblasts and in kidney biopsies along with accumulation of autophagic vacuoles in FD renal cells, assuming a disturbance of the autophagic pathway [41]. Alteration of autophagic pathways was further confirmed in α-GalA deficient podocytes that, in addition to marked upregulation of LC3-II levels, showed a decreased activity of the mammalian target of rapamycin (mTOR) kinase, a negative regulator of autophagic vesicle formation, suggesting that the overactive autophagy, beyond Gb3 accumulation, may be an additional contributor to podocyte damage and glomerular injury occurring in Fabry patients [42]. Moreover, autophagy was recently addressed as a key mechanism triggering renal tubulointerstitial fibrosis in an animal model of FD [43]. The role of autophagy disorders in FD was also assessed in the context of neurological [44] and corneal [45] complications.

In LSDs, the lysosomal trapping of sphingolipids within lysosomes and the altered lipid recycling and trafficking has a direct effect on the lipid composition and the biophysical properties of plasma and intracellular membranes [2][46]. In FD, changes in the lipid composition of membranes were assessed in patients' fibroblasts [47], in the inner mitochondrial membrane [48], and in specialized intracellular membrane domains termed lipid rafts [49]. Consequently, changes in the lipid composition may alter the stoichiometry and functionality of their protein components (e.g., ion channels [50][51]), further perturbing the signal transduction.

This disturbed intracellular environment might also affect ERT efficacy since the therapeutic effect relays on the proper intracellular uptake of the infused enzyme via the endolysosomal pathway. After the binding of the administered enzyme with a membrane receptor—such mannose-6-phosphate receptor (M6PR), megalin, or sortilin [52]—an essential component in the trafficking is the generation and maintenance of a proper low endolysosomal pH gradient, which enables dissociation between the receptors and their ligands, the recycling of receptors back to the apical membrane, and the progression of the vesicles toward lysosomes [53]. A key protein involved in the vesicular acidification is the chloride channel Cl^-/H^+ antiporter ClC-5, mainly located in the early endosomes [53]. In this regard, in renal proximal tubule cells, a loss of ClC-5 was associated with trafficking defect along with lysosomal dysfunction, OxSt, and dedifferentiation [54]. Moreover, a downregulation of ClC-5—along with cubilin and megalin, two endocytic receptors responsible for the reabsorption of the vast majority of proteins filtered in the glomeruli—was cytologically assessed in renal biopsies of two cases of FD [55]. Therefore, it is reasonable that ClC-5 downregulation and the following impaired intracellular trafficking might affect and limit the therapeutic effect of ERT towards the natural progression of the disease.

Finally, the above-described endosomal–lysosomal abnormalities have been recently associated with the likely protection from COVID-19 that Fabry patients seem to exhibit, in view of the unfavorable host cellular environment

for SARS-CoV-2 infection and propagation, that does not seem to be affected by ERT treatment [56]. However, a molecular mechanistic explanation of this naturally occurring protection is still unknown.

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