The Many Facets of Fabry Disease in the Kidney-Heart Axis

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ABSTRACT

Lysosomes are ubiquitous throughout all cell-types of the body and an inherited or acquired metabolic defect can potentially be causative of a disease phenotype as occurs in several lysosomal storage diseases (LSD). Fabry disease (FD) is one of the most prevalent LSD and is characterised by a deficient activity of the lysosomal enzyme alpha-galactosidase A (GLA) which is unable to exert its catabolic and clearance functions, thus leading to the accumulation of a specific type of ceramides— globotriaosylceramides (Gb3) in lysosomes. Many complications arise from FD, affecting manly the cardio-renal axis, the nervous system and skin. Since, this condition affects multi-tissues and organ-systems there is an unmet need to investigate how the molecular landscape is modulated after a single trigger caused by a mutation in GLA.

INTRODUCTION

Collectively, lysosomal storage diseases (LSD) are estimated to occurinone per five thousand live births and represent a group of 50 monogenetic disorders [1], affecting the normal function within vesicular structures of cells, in particular lysosomes, with relevant local and systemic metabolic consequences throughout body.
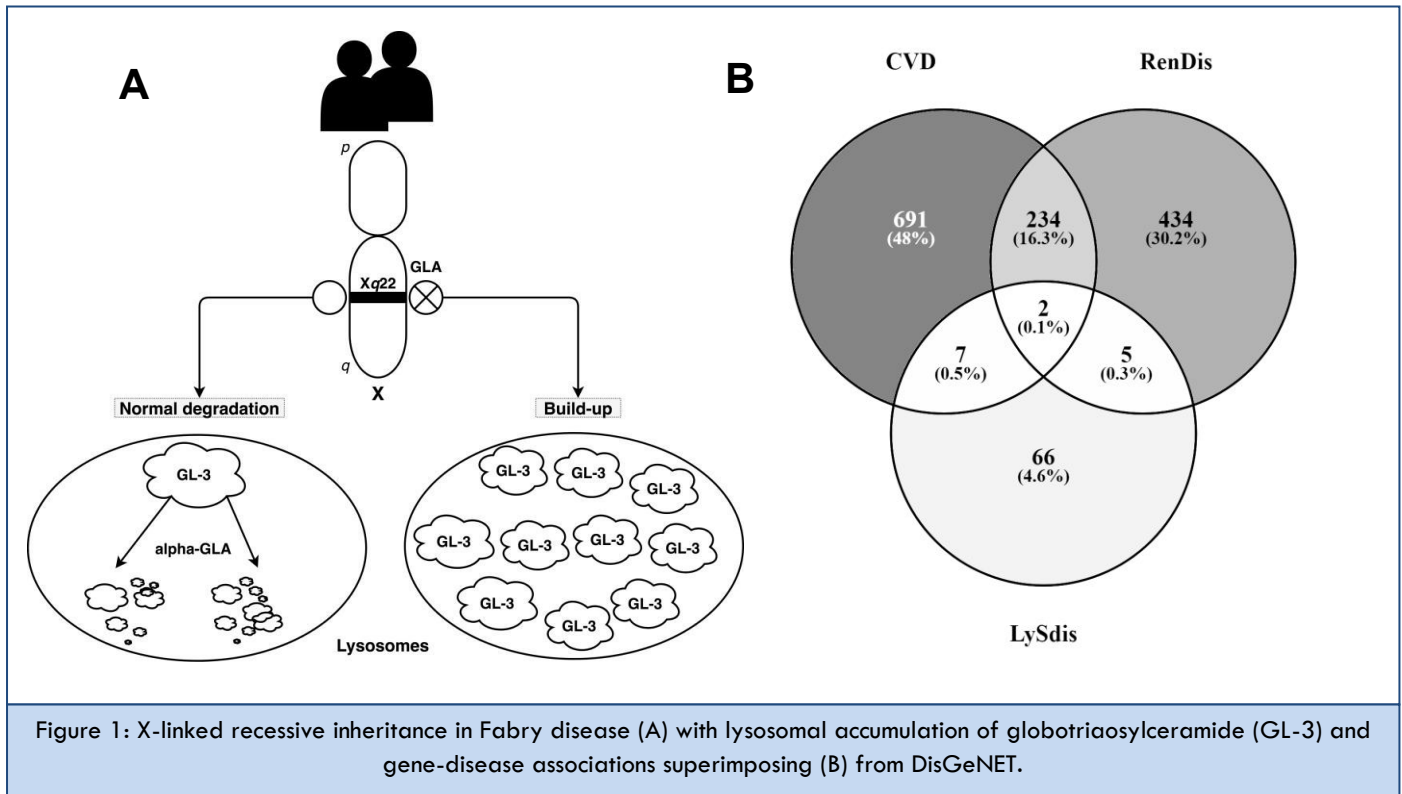
Fabry disease (FD) (Figure 1A) is a recessive inherited disorder with a prevalence of one per forty thousand male live births and is caused by a single mutation of the lysosomal enzyme alpha-galactosidase A (GLA) in the X-chromosome [2]. This condition is manifested by impairment of the GLA activity resulting inintra-lysosomal accumulation of globotriaosylceramide (Gb3) and other glycolipid derivatives across many cell-types throughout the body. This phenomenon triggers a cascade of events, from disruption at the cellular-level of basic metabolic processes to activation of the immune-system followed by inflammatory response that ultimately leads to increased susceptibility of renal, cardiac, cerebrovascular, and skin complications [2,3].

The lysosomal accumulation of these ceramides in the vascular endothelium is known to cause low blood perfusion and is accepted as the main overlapping clinical parameter found in many FD manifestations affecting the renal-heart axis, nervous system, and skin [4,5]. Additionally, many FD patients exhibits vascular trauma and recurrent thrombotic episodes mostly due to lower plasma levels of thrombomodulin and elevated levels of plasminogen activator inhibitor [4]. Moreover, FD patients are at high-risk of stroke due to compromised endothelium-dependent vasodilation prompted by concurrently altered levels of nitric oxide and impaired activity of endothelial nitric oxide synthase [5]. Therefore, renal-heart failure and stroke remain the main cause of death among FD patients [6,7]. The life-span of FD patients can be extended by renal replacement therapy (e.g. dialysis, kidney transplantation) and by

The Many Facets of Fabry Disease in the Kidney-Heart Axis. Journal of Nephrology & Kidney Diseases. 2018; 1(2):120.

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enzyme replacement therapy through the clinical routine use of agalsidase-alpha and agalsidase-beta that mimic GLA activity, and the first is being consistently reported as an improver of the renal-cardiac function and cerebrovascular-flow [3,8].

Gene-disease associations (GDA) databases such as DisGeNET [9] (Figure 1B) use supportive evidence from the literature and other disease databases to prioritise GDA. For instance, the best scored genes associated with FD are the following: GLA,

NAT8, NOS3, IL6, CRP, VDR, NAIP, NOS2, ICAM1 and SELE. Regarding superimposed genes associated with cardiovascular conditions, this list is: AGT, involved in cholesterol transport (APOA1, APOA4, APOH), platelet activation (FGA, RNASE1) degranulation (SERPINA3, ALB, TF), HBA1 and RNASE2.Likewise, overlapping genes in FD concerning renal conditions are: IL1A, VCAM1, PON1, IL1B, TNF, AGT, NOS3, NAT8, MGP, and G6PD.

Figure 1: X-linked recessive inheritance in Fabry disease (A) with lysosomal accumulation of globotriaosylceramide (GL-3) and gene-disease associations superimposing (B) from DisGeNET.

CVD: Cardiovascular Diseases; RenDis: Renal Diseases; LySdis: Lysosomal Storage Diseases

Previously we reported a systematic and systems biology-derived approach in renal disease associated with FD [10], and found that perturbed biological processes are associated with activation of the acute inflammatory response, regulation of wound healing, extracellular matrix (ECM) remodelling, regulation of peptidase activity and cellular response to reactive oxygen species (ROS). Furthermore, the involvement of platelet activation (C1QTNF1, COL1A2, COL3A1, FGA, GP6, HSPB1, RNASE1, YWHAZ), initiated by binding of collagen (COL1A2, and COL3A1) to the platelet glycoprotein VI (GP6), leads to signal transduction through the involvement of FcR gamma-chain, the Src kinases and the linker for activation of T-cell family member 1 (LAT) adapter protein, and consequently

to the activation of phospholipase C gamma 2 (PLCG2) [11]. Ultimately, the process leads to the activation of the ligand-binding function of integrin beta-3 to bind fibrinogen alpha chain (FGA). Subsequently platelet adhesion and aggregation are mediated, resulting in overall platelet spreading, granule secretion (degranulation), stabilisation of platelet adhesion and aggregation, and finally clot retraction.

Moreover, we also described plateletgranule secretion with subsequent exocytosis of histamine and serotonin with further thrombus establishment at sites of vascular injury, a process relevant in the pathogenesis of many ischemic cardio- and cerebrovascular conditions [12,13]. Additionally, release of prostaglandin contributes to inflammation resolution and

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promotes wound-healing important to restore tissue integrity and the earliest is known to be involved in smooth muscle contraction/relaxation and as well a potent inhibitor of platelet aggregation [14].

Additionally, the earlier event of disruption in the trade-off between production and degradation of extracellular matrix (ECM)throughout a long-term tissue injury can result in the deposition of ECM and consequently lead to pathological fibrosis [15] as observed in diabetic nephropathy and FD [16,17]. In a similar way, activation of many peptidases was also described and therefore exert direct proteolytic activity against ECM molecular entities or alternatively by activation of other proteases. For instance, proteolytic-antiproteolytic imbalance due to increased levels of collagens (COL11A1, COL1A2, COL3A1, COL4A2, and COL4A6) and augmented expression of cathepsins (CTSB) a main driver of proteolysis due to activation of a cascade of proteases which contrasts with over expression of several protease inhibitors (PI3, SERPINA3, SPINK1, SPINT1, ITIH4, and CSTB) [10]. Concomitantly, the association between altered states of ECM and overall FD severity could be indicative that ECM-turnover may play a role in FD pathogenesis [18,19].

Other known hallmarks in many cardiovascular diseases, such as enduring oxidative stress, was also reported in FD, for instance the activation of reactive oxygen species (ROS) response molecular elements. This is reinforced by the fact that Gb3 promotes oxidative stress and leads to an augmented expression in endothelial cells of many adhesion proteins [20].

In contrast, other studies report that, based on the molecular aspects of FD, many patients are more likely to resemble abnormalities related with renal insufficiency than to the underlying primary disease itself [21].

CONCLUSION

A growing body of evidence in FD investigations supports the general hypothesis that an augmented profile of endothelial inflammation is earlier established in tandem with a hold-up of several phases of wound-healing, which leads to a long-lasting inflammatory phase. The pathogenicity of FD has long been solely credited to the long-term and continuous deposition of Gb3 in the vascular endothelium. Nevertheless, this initial metabolic defect is also known to trigger a cascade of molecular events that leads to earlier fibrosis, endothelial dysfunction and, with the advance of the disease, may promote recurrent thrombotic events during a patient's life.

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