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The pathophysiology of GD – current understanding and rationale for existing and emerging therapeutic approaches

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Pathophysiologie von Morbus Gaucher – aktueller Wissensstand und Rationale für vorhandene und zukünftige Therapieansätze

Zusammenfassung. Morbus Gaucher ist eine genetische Erkrankung des Sphingolipidstoffwechsels, die durch eine Fehlfunktion des lysosomalen membranassoziierten Glykoproteins Glucozerebrosidase hervorgerufen wird. Die Folgen sind eine intrazelluläre Speicherung von Glukosylzeramid und anderen Glukolipiden. Obwohl der Gendefekt und die relevanten biochemischen Veränderungen bei GD bekannt sind, werden alle Mechanismen, die zu den Erkrankungsmanifestationen führen, bislang noch nicht vollständig verstanden. Die progressive Zunahme von Speicherzellen erklärt zwar einige der Erkrankungsmanifestationen, jedoch die gesamte Pathologie der Erkrankung scheint von komplexerer Natur mit einem Einfluß des gespeicherten Materials auf diverse intra-und ertrazelluläre Funktionen zu sein.

Im folgenden Artikel wird das Glukozerebrosidase-Gen und sein Proteinprodukt zu verschiedenen metabolischen Gesichtspunkten betrachtet und damit im Zusammenhang die aktuell verfügbaren bzw. in Entwicklung befindlichen therapeutischen Ansätze und deren Wirkungsweisen auf die pathologischen Abläufe bei GD analysiert.

Schlüsselwörter: Morbus Gaucher, Glukozerebrosidase, lysosomale Speichererkrankung, Pathophysiologie, Enzymersatztherapie, Substratreduktionstherapie, Chaperone

Summary. Gaucher disease is a genetic disorder of sphingolipid metabolism resulting from dysfunction of the lysosomal membrane-associated glycoprotein glucocerebrosidase (*GBA*) and resulting in intracellular accumulation of glucosylceramide and other glycolipids. Although the gene defect and relevant biochemical pathways have been defined, the mechanisms by which substrate accumulation causes disease manifestations are not well understood. The direct effects of a build up of substrate laden cells may account for some aspects of disease but the overall pathology is likely to be more complex with effects of stored material on a variety of intra and extra cellular functions. In this article we review the *GBA* gene and its protein product, with associated defects, lipid metabolism and storage, enzyme misfolding and endoplasmic reticulum stress, calcium homeostasis, oxidative stress and autophagy and at each point examine how therapies that are currently available, in clinical development or at earlier stages of basic research might address the pathological mechanisms.

Key words: Gaucher disease, glucocerebrosidase, lysosomal storage disorder, pathophysiology, enzyme replacement therapy, substrate reduction therapy, chaperones

Introduction

Gaucher disease (GD), the most prevalent lysosomal storage disease [1], is a genetic disorder of sphingolipid metabolism resulting from dysfunction of the lysosomal membrane-associated glycoprotein glucocerebrosidase (*GBA*, GlcCerase, acid b-glucosidase, EC 3.2.1.45). As a consequence, there is intracellular accumulation of glucosylceramide and other glycolipids derived from the breakdown of senescent blood cells and tissue debris. GD is a multisystemic disorder associated with broad heterogeneity of clinical expression. Despite elucidation of the gene defect and relevant biochemical pathways, the mechanisms by which

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substrate accumulation causes disease manifestations are incompletely understood. Several putative mechanisms have been implicated in GD (discussed below), although studies suggest that some of these events may be restricted to certain cell types. Various therapeutic options, aimed at correcting the primary or secondary disease processes, are available or under investigation; the rationale for each will be discussed in the relevant sections.

The *GBA* gene and protein product, with its associated defects

The *GBA* gene has been mapped to chromosome 1; it is 7 kb in length and comprises 11 exons. At least 200 *GBA* mutations have been identified, including missense and nonsense mutations, splice junction mutations, deletions and insertions of one or more nucleotides, and complex alleles resulting from gene conversion or recombination with a downstream pseudogene [2, 3].

The variants N370S, 84GG, IVS2 + 1G > A, and L444P account for 90% of the mutant alleles in Ashkenazi Jewish individuals with type 1 GD and for 50–60% of mutant alleles in non-Jewish individuals with type 1 GD. The frequency of the N370S allele is higher among Iberians (Portuguese: 63%; Spanish: 46%) than among other non-Jewish population groups from Western, Central, and Eastern Europe [3, 4].

The mature GBA protein is composed of 497 amino acids, with four oligosaccharide chains coupled to specific asparagine residue [5]. The three-dimensional (3D) conformation of the enzyme comprises three non-contiguous domains stabilized by the formation of three disulfide bonds [6]. Domain 1 consists of one major three stranded anti-parallel b-sheet flanked by a perpendicular N-terminal strand and loop. Domain II consists of two closely associated b-sheets that form an independent domain resembling an immunoglobulin fold. Domain III is a (b/a) 8 barrel containing the catalytic site. Analysis of the 3D structure has not shown a correlation between the spatial location of most *GBA* mutations and disease severity.

Structural predictions indicate that the glutamine residues 235 and 340 play key roles in the active site of human GBA [7]. A few mutations located near the active site result in severe disease (e.g., H311R, A341T and C342G) but most mutations are spread throughout all three domains and whilst the function of the two non-catalytic domains is unknown mutations in these domains suggest it is of some importance.

In vitro measured residual GBA activity from extracts of nucleated cells does not fully correspond with disease type or severity, and similarly genotype-phenotype correlations in GD are unreliable. However, some generalisations are possible; for example, individuals with at least one N370S allele do not develop primary central neurologic disease [8] and individuals who are homozygous for the N370S mutation tend to have milder disease than those who are compound heterozygous. However, variability in disease course among N370S homozygotes has been described [9]. To date, no explanation for the clinical variability has been provided by analysis of polymorphisms in a group of patients homozygous for the N370S allele [10].

Therapeutic approach

Gene therapy is under investigation. Although a limited trial in human subjects has been undertaken, with the use of a retroviral vector, sustained enzyme expression has not been achieved. In this instance, transduced cells would not have a proliferative advantage over uncorrected cells. Furthermore, it is unlikely that significant metabolic cross-correction would occur as only small amounts of enzyme are secreted into the circulation.

In a murine model of GD (D409V/null) intravenous administration of a recombinant AAV8 serotype vector bearing human glucosylceramidase resulted in sustained hepatic enzyme secretion, preventing glucosylceramide (GL-1) accumulation in presymptomatic mice and normalizing GL-1 levels in older mice [11]. In separate studies, nonmyeloablative doses of busulfan were administered as a pre-transplant conditioning regimen to the mouse model, in which it was shown that even WT cell engraftment in the range of 1–10% was sufficient to confer a beneficial therapeutic outcome. Additional studies are underway to optimize present protocols before gene therapy can be safely applied as a general treatment [12].

Lipid metabolism and storage

In vivo, substrate catabolism by the lysosomal GBA enzyme requires interactions with the lipid phospatidylserine and the protein saposin C [13]. Saposins are believed to interact with lipids, leading to enhanced accessibility of the lipid headgroups to the hydrolases [14]. Saposin C is therefore a cofactor for GBA in the hydrolysis of glucosyl ceramide. Individuals with deficiency of saposin C or its precursor prosaposin have normal *in vitro* GBA activity but accumulate

glucosylceramide *in vivo* and may present with a phenocopy of neuronopathic or non-neuronopathic GD [15].

Glucosylceramide (GC), the substrate of GBA, accumulates in plasma and other tissues of patients with GD as a consequence of GBA deficiency [16, 17]. Levels of 30–40 mmol/kg tissue has been found in spleen obtained from all three types of GD. Other glycosphingolipids, in particular glucosyl sphingsine (GS), have also been detected. GS is a deacylated form of GC and accumulates to lower but significant levels [18]. GC itself differs between the brain and peripheral systems, with a prevalence of stearic acid in the fatty acids in the central nervous system and palmitic acid in peripheral tissues [19]. However it is unlikely that substrate accumulation in isolation is sufficient to explain the tissue pathology since it accounts for a very small proportion of the organomegaly [20].

Gaucher cells, lipid-engorged macrophage-derived cells, are about 20–100 µm in diameter, and have small, usually eccentrically placed nuclei and cytoplasm with characteristic crinkles or striations. Detection of surface macrophage markers [21] and intense phagocytic activity [22] confirms their mononuclear phagocyte ontogeny. All macrophage-derived cells including not only Kupffer cells, and macrophages of the spleen and bone marrow but also osteoclasts, microglia, alveolar macrophages, lymph node and others have been suggested to be involved [23]. GC accumulation within the macrophage leads to a change in phenotype which has come to be known as alternative activation due to the expression of surface molecules and cytokines distinct from those found in interferon-gamma driven activation (classical activation) [21].

Cytokines found to be elevated in GD include interleukin-1b (IL-1b), interleukin-1 receptor antagonist, IL-6, tumour necrosis factor-a (TNF-α), and soluble IL-2 receptor (sIL-2R) CD14 and M-CSF [24, 25]. These factors may have a role in osteopenia (IL-1b, TNF-α, IL-6 and Il-10), activation of coagulation (IL-1b, TNF-α and IL-6) and gammopathies (IL-6 and IL-10) [26] and multiple myeloma. Thus, beyond the effects of storage bulk, there may be more subtle effects on cellular signalling and activation which account for the macrophage-driven pathology. This in turn may lead to dysregulation of other cells and systems in which storage of GC has not been identified.

Therapeutic approach

Enzyme replacement therapy (ERT) has been available since 1991; although proof of concept was initially shown using a placental-derived extract there are several recombinant enzymes currently available (e.g., imiglucerase and velaglucerase) or in advanced stages of clinical development (e.g., taliglucerase) [27–29]. Essentially, provision of exogenous enzyme compensates for the patient's intrinsic deficiency. A key to delivering the enzyme to various sites of pathology was recognition of the need to modify the native enzyme, to expose the mannose residues of its carbohydrate side-chain [30]. Uptake by cells of the reticuloendothelial system in this instance is mediated by mannose receptors, in contrast to other recombinant enzymes available for other lysosomal storage disorders that rely on mannose-6-phosphate receptors.

Although effective in controlling systemic disease, ERT has not been shown to alter ultimate prognosis in patients with neurologic disease, likely because the blood–brain–barrier (BBB) prevents the buildup of sufficient amounts of the infused enzyme [31]. ERT using recombinant enzyme is not helpful in patients with sapsoin C deficiency, as the primary defect in these patients would be a limiting factor in the intracellular hydrolysis of stored lipid.

An alternative approach to reduce substrate accumulation involves the use of substrate synthesis inhibitors. Reducing substrate burden, by partial inhibition of precursor synthesis, has been shown to restore metabolic homeostasis. In GD, this was first demonstrated with the use of the iminosugar miglustat. A more potent P-4 analogue, eliglustat is currently in trials [32]. Small molecules have the potential to cross the BBB. Unfortunately, the use of miglustat in combination with ERT in patients with type 3 GD has not been shown to improve outcome, likely because other disease mechanisms may be involved in the evolution of primary CNS complications.

Enzyme misfolding and ER stress

In addition to substrate accumulation, abnormalities of the cellular handling of the mutated enzyme itself have recently been proposed to have a role in GD pathology. Missense mutations leading to enzyme misfolding within the endoplasmic reticulum (ER) promote its premature degradation within the proteosome and are believed to induce ER stress. Variability in the rate of retention and degradation of the defective enzyme within the ER has been shown to correlate with disease severity [33]. Such a mechanism would give the presence of the abnormal enzyme a gain of function and dominant effect and may contribute to an explanation of the heterozygote manifestations of GD, such as

increased incidence of Parkinson disease, which have recently been reported. The underlying basis of this association is not known; proposed theories include enhanced protein aggregation, alterations in lipid levels, and autophagy-lysosomal dysfunction promoting the retention of undegraded proteins [34]. Unfolded protein response (UPR) activation and abnormal antioxidant response have been found in GD fibroblasts, but have not been observed in bone marrow mesenchymal stromal cells or in neurons. Thus, it is not certain that this disease mechanism is involved in the neurodegenerative process which develops in patients with type 2 and 3 GD [35–37].

Therapeutic approach

The use of pharmacologic chaperones, as a folding template for the defective enzyme, has been proposed as a means of rescuing the mutant protein and enabling its delivery to the lysosome; thereby enhancing residual hydrolytic capacity. The drug isofagamine has been shown to exhibit these properties in studies of cultured fibroblasts *in vitro*, although exploratory clinical trials have not been shown to be efficacious when given to adults with type 1 GD [38]. There is active screening for molecules that may have potential as a pharmacologic chaperone for mutant GBA [39].

Calcium homeostasis

Studies in mouse models of GD have shown that GC enhances agonist-induced calcium release from intracellular stores via the ryanodine receptor, with resultant neuronal cell death. Similar studies conducted on human brain tissue revealed that agonist-induced calcium release was significantly enhanced in brain microsomes derived from GD patients with the acute neuronopathic form (GD type 2), compared to samples from subacute (GD type 3) and the non-neuronopathic (GD type 1) patients and controls. These findings suggest that defective calcium homeostasis may be a mechanism responsible for the neuropathology seen in acute neuronopathic GD [40].

Therapeutic approach

Altering intracellular calcium levels is known to partially restore mutant enzyme homeostasis in several lysosomal storage diseases. Recently, it has been shown that increasing ER calcium levels by reducing ER calcium efflux through the ryanodine receptor, using antagonists or RNAi, or by promoting ER calcium influx by SERCA2b overexpression enhances mutant GBA homeostasis in cells derived from individuals with GD. Post-translational regulation of the calnexin folding pathway by an elevated ER calcium concentration also appeared to enhance chaperone capacity system to fold mutant misfolding-prone enzymes and increasing lysosomal GC concentration and activity [41].

Oxidative stress

Studies in GD fibroblast primary cultures revealed increased reactive oxygen species (ROS) levels and protein carbonyl content to healthy donors. The ROS rise was speculated to be due to NAD(P)H oxidase activity inhibited by treatment of cells with diphenylene iodonium chloride. The GD cells were also found to be more sensitive to H_2O_2 induced cell death, suggesting a dysregulation in the adaptive response to oxidative stress in which APE1/Ref-1 plays a central role. The up-regulation of apurinic endonuclease 1 (APE1) (a protein that repairs oxidative DNA damage) observed in GD fibroblasts has not been found in GD bone marrow mesenchymal stromal cells [35, 36].

Therapeutic approach

There have been no studies relating to the use of antioxidants in animal models in or patients with GD. In the *in vitro* studies undertaken by Deganuto et al., both ROS and APE1/Ref-1 increases noted in GD fibroblast cultures were prevented by treatment with imiglucerase (ERT).

Autophagy

Abnormalities of autophagy have been described in several lysosomal storage disorders. Analysis of brain pathology in a mouse model of neuronopathic GD has revealed the presence of abnormal autophagosomes, implicating autophagy in the neurodegenerative process [42]. However, the mouse model used in these experiments was generated by cross-breeding mice homozygous for the V394L mutation and mice null for Saposin C. In separate experiments, saposin C deficiency due to mutations involving a cysteine residue has been shown to result in increased autophagy (monitored by LC3 analysis and confirmed by electron microscopy) [43].

Therapeutic approach

There is great interest in regulating autophagy as a therapeutic option for several disorders, but no relevant

experiments have been conducted in animal models or cells obtained from patients with GD [44].

Conclusion

In GD, the accumulation of incompletely metabolized substrates accounts for the primary insult to cells, and involvement of cells derived from monocytic lineage defines the pattern of clinical disease expression. There is incomplete understanding of the various determinants of disease complications, although various mechanisms have been implicated as potential contributors to pathogenesis. At present, it is not certain which of these downstream events play a dominant role or directly relevant to development of neuronopathic disease. Various therapeutic options are being examined as means for addressing the different problems which develop in GD patients, although ERT currently represents the standard of care. Given the spectrum of disease expression and the likely multifactorial basis of disease, additional therapeutic strategies may be required to optimize treatment outcome.

Conflict of interest

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