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Role of Lysosomal Enzymes in Parkinson's Disease: Lesson from Gaucher's Disease

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1. Introduction

The lysosome, initially discovered by Christian de Duve in 1955, is an intracellular organelle responsible of the ordered degradation of proteins, glycoproteins, proteoglycans, lipids, and other macromolecules originated from autophagy, endocytosis and phagocytosis. It is characterized by a limiting external membrane containing intraluminal vesicles. These organelles are estimated to contain 50-60 soluble acidic hydrolases (Journet et al., 2002), 55 membrane-associated proteins and 215 integral membrane proteins (Bagshaw et al., 2005). The macromolecules are decomposed by acid hydrolases in small molecules that are transported back in the cytosol by specific transporter proteins and then catabolized or re-used by anabolic processes. Lysosomal hydrolases are synthesized as N-glycosylated precursors in the endoplasmic reticulum and are transported to the lysosomes via a vectorial transport dependent on mannose 6-phosphate. Lysosomes are involved in many cellular processes like cholesterol homeostasis, autophagy, membrane repair, pathogen defense, cell signaling, apoptosis and bone/tissue remodelling; it is a fundamental organelle for cell life and not only the wastebasket of the cell. Microscopic identification of lysosomes is hard due to heterogeneity of organelles morphology dependent on their function as digestive organelles. The size and quantity of lysosomes varies in different cell types and can increase when the lysosomes accumulate non-digested material. Functional deficit of hydrolases, membrane-associated or integral membrane proteins causes lysosomal storage disorders (LSDs), a group of inherited metabolic pathologies characterized by intralysosomal deposition of undegraded macromolecules and by multisystemic phenotype (Saftig, 2006). The absence or reduced activity of a specific lysosomal hydrolase or other lysosomal proteins cause an abnormal function of the entire endosomal/lysosomal system (Bellettato & Scarpa, 2010).

More than 50 lysosomal storage disorders (LSD) are known with a total incidence of 1:7,000-1:9,000 (Fletcher, 2006). Two thirds of them involve the central nervous system (Meikle et al.,

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1999). The LSD can be classified in sphingolipidoses, mucopolysaccharidoses, mucopolipidoses, lipid storage disease, glycogen storage disease type II and lysosomal transport defects. Different LSD displayed different symptoms severity and different age onset and it depend on the organs affected and the residual enzyme activity. Generally, mutation leaving very low residual enzyme activity cause the most severe onset form of the pathologies; contrary higher residual enzyme activity delays disease onset (Kolter & Sandhoff, 1999). The disease course and severity are different in late-onset forms and can be variable even among affected siblings in the same family (Zhao & Grabowski, 2002). LSDs are often multisystemic disorders and many of these displayed a severe, progressive and untreatable neurological impairment. Almost all LSDs are related to devastating, progressive and untreatable effects on central nervous system (CNS). Neuronal loss occurs in the advanced stages of the diseases and is due to apoptosis or necrosis. The neurological symptoms are mental retardation, progressive neurodegeneration, dementia. Most LSDs show CNS involvement although the undegraded material concentration is lower in the brain than in other organs. It seems that neurons are more vulnerable than other cellular type probably for a limited cell regeneration potential or for the absence of compensatory pathways (Bellettato & Scarpa, 2010). The Neuronal Ceroid Lipofuscinoses (NCLs) are lysosomal storage diseases affecting the CNS, with progressive loss of vision, decreasing cognitive and motor skills, epileptic seizures and premature death, with dementia without visual loss prominent in the rarer adult forms (Kohan et al., 2011). GM1 type 3 Gangliosidosis is an autosomal recessive lysosomal storage disorder caused by β -galactosidase deficiency, patients were recently found to be affected by generalized dystonia associated to akinetic-rigid parkinsonism (Roze et al., 2005). The San Filippo Syndrome type B is a LSDs due to mutation in the gene encoding α -N-acetylglucosaminidase with an accumulation of heparan sulfate. Affected children shown mental retardation, dementia, behavior problems. The analysis of mutant mice showed cytoplasmic inclusion of P-tau aggregates, characteristic of tauopathies, a group of age-related dementia that include Alzheimer disease (Ohmi et al., 2009).

In some adult neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and Huntington's disease the clinical features are similar to those found in LSDs: accumulation of undegraded material, abnormal inflammatory response in the brain and changes in neurons morphology and functionality (Bellettato et al., 2010). In Parkinson's disease was found an involvement of cathepsin D, a lysosomal enzyme, in α -synuclein degradation and formation of carboxy-terminally truncated α -synuclein. Recent works suggest that impaired cathepsin D activity would result in increased α -synuclein levels that cause its aggregation (Sevlever et al., 2008). In Huntington's disease N-terminal mutant huntingtin fragments form inclusions that lead to cell death. Some protease, like cathepsin D, B and L, help to degrade mutant huntingtin but increase N-terminal fragment formation and inclusions deposition inducing neuronal disruption (Kim et al., 2006).

2. Gaucher's disease: An overview

Gaucher's disease (GD) is an inherited autosomal recessive metabolic disorder, resulting from a deficiency of the lysosomal enzyme β -glucocerebrosidase (also called acid β -glucosidase, GCase) (EC 3.2.1.45).

GD was first described as a systemic disease by Philippe Gaucher in 1882, but only in 1965 this disorder was related to the deficiency of β -glucocerebrosidase (Patrick, 1965; Brady et al.

1965). This enzyme is involved in the catabolic pathway of glycosphingolipids and is responsible for the cleavage of the β -glucosidic bond on the glucosylceramide (or glucocerebroside) (Fig. 1).

The human β -glucosidase is encoded by a gene (GBA) located on chromosome 1 (1q21) (Barneveld et al., 1983) which comprises 11 exons and 10 introns, spanning 7.6 kb of sequence. A non processed pseudogene (GBAP), which shares 96% exonic sequence homology, is located 16 kb downstream of the functional β -glucocerebrosidase gene (Horowitz et al., 1989).

The lack of GCase activity leads to accumulation of glycolipid substrates, primarily glucocerebroside and its nonacylated analog, glucosylsphingosine, in all organs, particularly in spleen, liver, lungs and bone marrow (Cox & Shofield, 1997; Beutler & Grabowski, 2001). The material stored is the product of the arrested breakdown of gangliosides, glycosphingolipids and globosides, which derived from the cellular turnover of membranes.

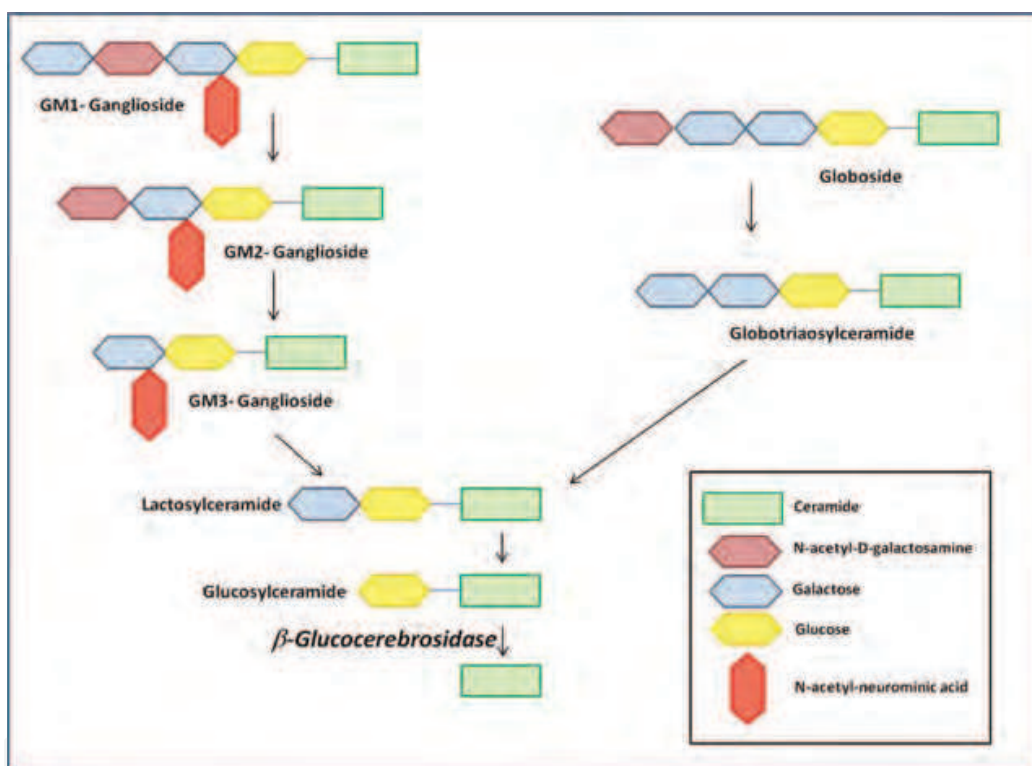


Fig. 1. Involvement β -glucocerebrosidase in the catabolic pathway of glycosphingolipids

Although in the patients the GCase is inactive in all cells, glucocerebroside accumulation occurs principally within the lysosomes of macrophages which adopt a characteristic "Gaucher's cell" morphology. Disease manifestations are related to the migration and accumulation of the Gaucher's cells, which displace healthy cells in the tissues. Furthermore the abnormal material stored in the cells of the reticuloendothelial system induces the release of inflammatory factors, including chemokines and cytokines, which leads to the cascade of pathological changes (Beutler & Grabowski, 2001; Cox, 2001; Aerts & Hollak, 1997; Moran et al., 2000; Jmoudiak & Futerman, 2005; Nilsson & Svennerhol, 1982; Pelled et al., 2005; Futerman & van Meer, 2004) (Table 1).

Gaucher's disease may occur at any age in any human population (Beutler & Grabowski, 2001; Zimran et al., 1992; Cox & Shofield, 1997; Erikson, 1986). Although the birth frequency

of Gaucher’s disease is one case per 60,000 live births in the general population (Meikle et al., 1999), it is the most frequent genetic disease in the Ashkenazi Jewish people where epidemiological data, based on estimated gene frequencies, show a prevalence of one case per 850 live births (Beutler et al., 1993).

GD has a highly variable phenotype, and even though a recent trend is to consider GD as a continuum of disease states (Goker-Alpan et al., 2003), three basic clinical forms are conventionally distinguished on the basis of the neurological involvement: the non neuronopathic form (type 1), the acutely neuronopathic form (type 2) and the subacute neurophatic form (type 3).

Products	Functions
Lysozyme	Antibacterial
Angiotensin-converting enzyme	Vasopressor
Lysosomal acid hydrolases	Digestion
Interleukin-1b, TNFa	Diverse host defence: fever, weight loss
Interleukin 6	Acute phase response, B-cell stimulation, bone resorption, trophic for mieloma cells
Interleukin 8	Granulocyte chemoattractant
Interleukin 10	Inhibits pro-inflammatory cytokines

Table 1. Macrophage secretory products icreased in Gaucher’s disease

Type 1 GD (OMIM 230800) is the most frequent form of Gaucher’s disease and account 94% of all registered cases according to Gaucher Registry. It is a chronic multisystem storage disorder which, by definition, does not involve the central nervous system. Nevertheless recent studies have shown a possible correlation between type 1 GD and some neurological manifestations (Sindransky, 2004; Cherin, 2006; Biegstraaten et al., 2008). In a number of cases these symptoms can be the consequence of secondary complications of the primary disease (e.g. compression of bone marrow or root nerve as a result of vertebral crush fractures caused by osteonecrosis), whereas in other ones they can be the product of specific GBA gene mutations, particularly in patients presenting parkinsonian syndromes (Aharon-Peretz et al., 2004; Bembi et al., 2003; Clark et al., 2005; Gan-Or et al., 2008; Machaczka et al., 1999; McKeran et al., 1985; Tayeby et al. 2003; Ziegler et al. 2007).

The type 1 GD course is slowly progressive. Generally the symptoms develop in adulthood even though various clinical manifestation may emerge in childhood. The clinical spectrum is vast and includes the complete absence of symptoms as well as the severe organ involvement with disability and occasionally fatal outcome. The patients show hepatosplenomegaly, with thrombocytopenia, anemia and leucopenia. Although in most patients these complications are not life-threatening and may go unrecognized for many years (some subjects remain asymptomatic up to the age of 70 or 80 years) (Berrebi et al., 1984), in other ones this metabolic defect can cause bruising, bleeding and high risk of infection as consequence of pancytopenia and respiratory insufficiency due to diffuse infiltration of Gaucher’s cells into the alveolar spaces, perivascular, peribronchial, and into the septal regions (Schneider et al., 1977; Lee, 1982). Asthenia and fatigability are constant and seem independent of anemia, but rather to reflect an alteration of basal metabolism and cytokine secretion (Allen et al., 1997). Moreover degenerative changes in skeleton are the leading cause of bone pain and disability in patients with type 1 disease. The infiltration of Gaucher’s cells in the bone marrow causes osteonecrosis, particularly during growth and

leads to impaired function of large joints, including hip, knee, and shoulder. Other bone symptoms include local swelling (Gaucheromas) and osteolysis as well as generalized demineralization and osteoporosis with consequent risk of fractures. Furthermore patients may show abnormal diffuse yellow-brown skin pigmentation and delays of growth, menarche and dentition. In rare cases there can be also renal involvement, pulmonary hypertension (Theise & Ursell, 1990), and cardiac abnormalities.

Type 2 (OMIM 230900) is the most severe form of Gaucher's disease which accounts for fewer than 1% cases. It manifests in early childhood; neurological deterioration progresses quickly and death generally occurs within the age of two years, in a context of psychomotor decline (Brady et al., 1993). The majority of cases of type 2 GD emerges around age of 3 months. The presenting sign is usually hepatosplenomegaly. By 6 months, neurologic complications develop. The first diagnostic symptoms are frequently supranuclear horizontal oculomotor paralysis or bilateral fixed strabismus accompanied by trismus, retroflexion of the head, progressive spasticity, hyperreflexia, positive Babinski signs and other pathologic reflexes. Other symptoms can be dysphagia and difficulty in handling secretions developed, often followed by aspiration pneumonia. Death occurs by either apnea or aspiration pneumonia.

Gaucher's disease type 3 (OMIM 231000) is particularly frequent in Norrbottnian Swedes (Erikson, 1986). It leads to subacute neurological symptoms that are less severe than those of type 2 disease. It is characterized by the presence of a later onset and a slow progressive neurological syndrome. The clinical manifestations vary. Systemic symptoms precede neurologic abnormalities and usually are similar to those seen in type 1 GD. Neurologic deterioration includes cerebellar ataxia, spastic paraparesis, psychomotor seizures, horizontal supranuclear ophthalmoplegia, myoclonic epilepsy and dementia.

Over 300 mutations of the β -glucosidase gene have been described (Beutler & Gelbart, 1996; Geabowski & Horowitz, 1997; Hruska et al., 2008). The most common are c.1226A>G (N370S), c.1448T>C (L444P), IVS2+1G>A and 84insG. The frequency and distribution of mutations vary with the population studied; in the Ashkenazi population N370S is found in 78% of patients whereas in non-Jewish populations the most frequent mutation is L444P (36%), followed by N370S (29%) (Beutler, 2006).

Although molecular analysis of the glucocerebrosidase gene in patients with Gaucher's disease has permitted broad correlations between genotype and phenotype, this does not consent a confident prediction of clinical phenotype (Cox & Sholfield, 1997; Germain, 2004). Many studies have shown the enormous clinical variation between patients who have the same genotype including monozygotic twins (Sidransky, 2004; Lachmann et al., 2004). Nevertheless the presence of N370S on one or both alleles is associated with type 1 GD and it seems to protect against neurological symptoms, except for Parkinson-like syndromes (Charrow et al., 2000; Cherin et al., 2006). On the contrary the presence of the L444P/L444P mutation is associated with the development of neurological manifestations, above all in Gaucher's disease type 3 (75% of cases) (Charrow et al., 2000). Other mutations, including 84insG, IVS2+1G>A, c.754T>A (F213I) and c.1297G>T (V394L), are generally responsible for the emergence of a neurological form, when associated with mutation L444P either alone or integrated in a complex allele.

3. Gaucher's and Parkinson's disease: Theories of a link

Parkinson's disease (PD) is the one of the common movement disorders and the second most common human neurodegenerative disease. The major diagnostic neuropathological

features of the pathology are loss of dopaminergic neurons and the appearance of Lewy bodies (LB), which are intraneuronal inclusions composed by α -synuclein and abnormal ubiquitinated proteins aggregates.

The first associations of the glucocerebrosidase enzyme with parkinsonism were discovered through careful clinical observation of people affected by GD, who in several cases developed Parkinson's disease. Although in recent years GBA mutations were found to be a major risk factor for the development of Parkinson's disease (Sidransky et al., 2009), it is not clear how these are related. However many findings suggest that GBA protein and α -synuclein are implicated in a common cellular pathway and different hypothesis have been created to explain the linkage between them.

Recent studies have shown as some mutations in the GBA gene can lead to the misfolded protein formation (Sawkar et al., 2005), contributing to parkinsonism by leading to lysosomal insufficiency, as a result of impairing autophagic pathways necessary to prevent the synucleopathies, or by crushing the ubiquitin-proteasome system.

During the life span of a protein, cellular systems continuously check on the quality of the protein and take care of its repair or removal from the cell if there is any abnormality. The advancement during the past decades in understanding the quality control system of cellular proteins has allowed the identification of unequivocal links between malfunctioning of these systems and some severe human pathologies, including major neurodegenerative disease as Parkinson's (PD) and Alzheimer's (AD).

Many newly synthesized proteins are incorrectly translated or wrongly folded as a result of errors in their sequence due to either genetic mutations or alterations during the synthesis process (Wheatley & Inglis, 1980; Vabulas & Hartl, 2005; Shubert et al., 2000; Yewdell, 2005). The role of protein catabolism in protecting cells from defective, misfolded proteins is essential to avoid the risk of long term accumulation of proteins which frequently develop abnormal intermolecular interaction, forming insoluble aggregates toxic for the cells (Squier, 2001; Kourie & Henry, 2001). So it is evident the involvement of the quality control system in maintaining cell homeostasis as well as the association between the alteration of the protein turnover and many disease states (Kundu & Thompson, 2008). The autophagy-lysosome and the ubiquitin-proteasome pathways are the two main routes of the quality control system in eukaryotic.

Autophagy-lysosomal degradation pathway is a complex system tightly regulated by series of signaling events that promote the efficient delivery of macronutrients and organelles to lysosomes for degradation by acidic hydrolases (Levine & Klionsky, 2004). It is implicated in the catabolism and recycling of long-lived proteins and organelles and it is thought to be involved in many physiological processes, including the response to starvation, cell growth control, antiaging mechanisms and innate immunity. Some years ago the autophagy-lysosome pathway was considered as a non selective form of catabolism, while now the view is changed and it is thought as a specialized system that distinguishes the substrates and chooses the route by which they reach the lysosomes. Three types of autophagy have been described: macroautophagy, microautophagy and chaperon mediated autophagy (CMA) (Cuervo, 2004). They share a common endpoint, the lysosome, but differ in substrates targeted, their regulation and the conditions in which each of them is preferentially activated.

Macroautophagy process is activated to generate essential macromolecules and energy in condition of nutritional scarcity (Mizushima, 2005) or as a mechanism to remove the altered

intracellular components (Levine & Klionsky, 2004). It can be induced also by hypoxia, neurotrophic factor deprivation, excitotoxins and accumulation of protein aggregates through PI3K and ERK-mediated pathways (Zhu et al., 2007; Boland & Nixon, 2006). Macroautophagy is described as the sequestration of complete regions of the cytosol, including not only soluble proteins, but also complete organelles, into a double membrane vesicle known as autophagosome, which is considered an immature form of autophagic vacuole (AV) (Seglen et al., 1996; Mortimore et al., 1996). The limiting double membrane is thought to arise from the endoplasmic reticulum, although the Golgi complex has also been indicated as a source (Levine & Klionsky, 2004; Mijaljica et al., 2006). Because these vesicles lack any enzyme, the trapped contents are not degraded until the autophagosome fuses with a lysosome, forming a single membrane autophagolysosome.

Macroautophagy is regulated by the action of a family of molecules, known as autophagy-related proteins (Atg), which participates in each of the different steps of this process (Klionsky et al., 2003). A series of conjugation events (protein-to-lipid and protein-to-protein) and several members of intracellular kinase families are involved (Klionsky, 2005; Ohsumi, 2001).

One hypothesis has been proposed to explain the role of dysregulated autophagy in PD pathogenesis, in patients affected to Gaucher's disease. This theory ("offensive metabolite theory") is based on the ceramide activity in the process of autophagic pathway modulation (Scarlatti et al., 2004). Ceramide is a sphingolipid mediator with an essential role in different situations correlated with autophagic system, such as cell growth, cell death, proliferation and stress response (Klionsky & Emr, 2000). Studies have shown as ceramide interferes with the inhibitory class I PI3K signaling pathway and induces the expression of an autophagy-related gene beclin 1, stimulating the autophagic process.

It's possible that the lack of β -glucocerebrosidase activity and the accumulation of glucocerebroside may interfere with the ceramide modulation system, destroying cellular pathways necessary for autophagic-lysosomal degradation and leading to the LB formation. The other types of described autophagy are microautophagy and CMA. The first one consists of direct engulfment of small volumes of cytosol (constituted by soluble proteins but also by complete organelles) by lysosomes (Ahlberg et al., 1982) through invaginations or tabulations that "pinch off" from the membrane into the lysosomal lumen where they are rapidly degraded (Marzella et al., 1981). Microautophagy participates in the continuous turnover of long-lived proteins inside many types of cells (Mortimore et al., 1988); in addition a number of studies have shown as a particular form of microautophagy can lead to preferential degradation of peroxisomes (micropexophagy) (Farre and Subramani, 2004; Mukaiyama et al., 2002; Veenhuis et al., 2000).

Chaperon-mediated autophagy is characterized by selectivity; about 30% of cytosolic proteins are degraded by this pathway. Through CMA particular cytosolic proteins are recognized by a chaperone in the cytosol, which delivers the proteins directly to the surface of the lysosome (Dice, 1990; Majeski & Dice, 2004; Massey et al., 2006). A distinctive feature of this pathway is that all substrate proteins contain in their amino acid sequence a motif, biochemically related to the pentapeptide KFERQ, required for targeting to the lysosomal compartment (Dice, 1990). A heat shock protein, hsc73 (Chiang et al., 1989), recognizes the substrates containing the motif, and brings them to the lysosome membrane, where it binds to the receptor protein, lamp2 (lysosome-associated membrane protein type 2a) (Cuervo & Dice, 1996). The substrate interacts directly with lamp2, and once unfolded, it is transported in the lysosome lumen (Salvador et al., 2000) where it is degraded.

Substrates for CMA consist of a very heterogeneous pool of cytosolic proteins, different for structure and function, but having all the same KFERQ motif. CMA acts in the degradation of many different substrates (i.e. several glycolytic enzymes, glutathione transferase, ribonuclease A) and damaged proteins: its selective role allows removal of the altered proteins without affecting neighbouring healthy ones (Kiffin et al., 2004; Cuervo et al., 1999). Many studies have shown as this autophagic pathway is activated when stress condition occurs in the cells, such as prolonged nutrient deprivation or exposure to toxic compounds (Cuervo & Dice, 1998).

Independently of the autophagic pathway, all substrates are brought to the lysosome lumen where several different lysosomal hydrolases rapidly degrade them. These enzymes are synthesized in the endoplasmatic reticulum, sorted to the trans-Golgi network by mannose-6-phosphate receptors, transported through the endosome to arrive to their lysosomal destination, where they are activated upon the exposure to the acid environment (Jadot et al., 1997). The proteolytic capacity of lysosomes comprises a mixture of endo- and exopeptidases, called cathepsins, which act in concert to degrade proteins to a mixture of amino acids and dipeptides. Expression, activation and inhibition of these cathepsins are differentially regulated, and individual cathepsins often have non-redundant functions in normal and disease states (Kroemer & Jaattela, 2005). In addition to peptidases activity, intralysosomal conditions and other lysosomal components (i.e. glycosidase, lipases, phospholipases, solphatases, nucleases and phosphatases) are designed to favor the complete degradation of the internalized products.

One route of degradation of the α -synuclein is via CMA pathway (Cuervo et al., 2004). Studies have revealed as impaired lysosomal function seems to be involved in familial forms of PD, as consequence of reduced α -synuclein degradation. So one theory is that disturbances in the lysosome (i.e. the alteration in the GCase function) contribute to reduce α -synuclein degradation and consequently promote its aggregation. This may be possible since ceramide can activate cathepsin D (aspartate protease), which in turn is responsible for the proteolytic activation of other lysosomal proteins (Heinrich et al., 1999). So the reduced activity of one protease can spark off the decremented action of other acid hydrolases causing an α -synuclein accumulation and contributing in LB formation.

The other α -synuclein degradation pathway is the ubiquitin-proteasome system (UPS). It serves as the primary route for the degradation of thousands of short-lived proteins and provides the specificity and temporal control needed for tuning the steady-state levels of many regulatory proteins (Ciechanover et al., 2000). UPS-mediated catabolism is also essential to preserve amino acid pools in acute starvation and contributes significantly to the degradation of defective proteins (Ciechanover & Brudin, 2003; Whealtley & Inglis, 1980; Vabulas & Hartl, 2005). UPS contributes also to diverse cellular processes, such as protein quality control, cell-cycle progression, signal transduction, and development (Kerscher et al., 2006).

Substrates of the ubiquitin/proteasome system (UPS) get post-translationally modified by covalent attachment of multiple ubiquitin molecules at internal lysine residues. This polyubiquitylation of substrate proteins involves three enzymes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin protein ligases (E3). E1 hydrolyses ATP and forms a thioester-linked conjugate between itself and ubiquitin; E2 receives ubiquitin from E1 and forms a similar thioester intermediate with ubiquitin; and E3 binds both E2 and the substrate, and transfers the ubiquitin to the substrate. A chain made of four to six ubiquitin moieties targets the conjugated substrate for degradation by the 26S proteasome (Richly et al., 2005; Zhang et al., 2009).

The UPS can only degrade proteins when they are in a soluble state or as a part of reversible protein complexes that can be disassembled into single protein units (Finkbeiner et al., 2006; Kopito, 2000). So any type of irreversible oligomeric structures, preaggregates, and protein aggregates cannot be handled by UPS, instead they can be degraded by the autophagic-lysosomal pathway.

A different theory ("misfolded protein theory") to explain the linkage between Gaucher's and Parkinson's disease, is that mutant misfolded glucocerebrosidase might overwhelm the UPS, causing a delay in the degradation of accumulated proteins, including α -synuclein (Dawson, 2006). Ron et al. have shown that misfolded GCase endures endoplasmic reticulum associated degradation (ERAD) (Ron and Horowitz, 2005). In this process, mutant proteins are identified as misfolded by the ER quality control system and retrotranslocated from ER to cytosol, ubiquitinated and eliminated by the ubiquitin-proteasome system. The same authors proposed that mutated GBA protein (but not WT GBA) undergoes parkin (E3-ligase)-mediated ubiquitination, creating an imbalance in protein degradation resulting in secondary toxicity. It is likely that, since GCase is not a natural substrate of parkin, the enduringly ER retention and proteasomal degradation of mutant β -glucosidase, mediated by parkin, affect its activity toward its natural substrates. Accumulation during the years of these proteins can lead to the death of cells in substantia nigra and eventually, to the development of PD.

The theories described above, cannot explain completely the correlation between the diseases. In the "offensive metabolite theory" the reducing of the released ceramide inhibits the autophagic-lysosomal functions. This can explain the development of LB and parkinsonism in Gaucher patients, but not in GBA mutations carriers.

Moreover in Gaucher patients where mutations in GBA result in no protein product (i.e. c.84dupG and IVS2+1G>A) the risk to develop PD is high. So the "misfolded protein theory" also cannot clear fully the question, even if it is probably that very truncated forms of the mutant protein still might induce endoplasmic reticulum stress and guide to crashing of UPS.

4. Genetic studies and neuropathological data

The first indication of a relationship between parkinsonism and GD was due to sporadic case reports in the literature (Neudorfer et al., 1996; Machaczka et al., 1999; Tayebi et al., 2001). In these papers it was highlighted how in some GD patients the enzyme deficiency itself could predisposed to the susceptibility to parkinsonisms.

These observations of occurrence of Parkinson's disease in some patients with non-neuropathic type 1 Gaucher disease and in their first degree relatives has led to the identification of GBA1 heterozygous mutations as a genetic risk factor for idiopathic Parkinson's disease.

In these subjects the mean age at onset of parkinsonian symptoms is lower than in patients without GD1, becoming evident at an average age of 48 years compared with 71 years in the general population (Elbaz et al., 2003).

These early observations led to several studies which revealed that patients with idiopathic PD had a higher probability of harboring GBA1 mutations compared to the general population.

The first large study was conducted by Lwin et al. (2004), using sequence analyses on brain samples from 57 subjects of different nationality, GBA alterations were detected in 12 sample (21%).

Subsequently Aharon-Peretz et al. (2004), explored the association between six GBA mutations (N370S, L444P, c.84dupG, IVS+1A>G, R496H, V394L) and PD in Ashkenazi Jews population. From the screening of 99 patients and 1,543 healthy people they identified these mutations in 31.3% of patients with PD versus 6.2% of healthy controls.

Many studies have been conducted in the years, some of these have been screened PD patients for common GBA mutations (Clarck et al., 2005; Sato et al., 2005; Tan et al., 2007; Wu et al., 2007; De Marco et al., 2008; Spitz et al., 2008; Mata et al., 2008; Gan-Or et al., 2008), others have been sequenced the entire GBA gene (Eblan et al., 2006; Ziegler et al., 2007; Clark et al., 2007; Bras & Singleton, 2009; Kalinderi et al., 2009; Neumann et al., 2009).

All of these studies evidenced a higher frequency of GBA mutations among PD patients than in matched controls, but the frequency of GBA mutations varies in relation with the study's design (population, number and type of mutations screened or whole GBA scanning).

Toft et al. (2006) searched the association between two mutations (N370S and L444P) and PD in Norwegian population. From the analyses of 311 patients and 474 controls they found these mutations in 2.3% of subjects with PD versus 1.7% of controls.

The frequency of GBA mutations ranges between 10.7% and 31.3% in PD patients from Ashkenazi Jewish and between 2.3% and 9.4% in patients from other populations.

Most of these studies were conducted on sporadic PD patients, recently Nichols et al. (2009) and Mitsui et al. (2009) specifically investigated familial PD. They demonstrated an association between GBA variants and familial PD cases as well as sporadic disease.

Most of these studies have independently reached similar results demonstrating that GBA mutations are found in patients with PD at a higher frequency than expected.

A large meta-analysis was conducted by Sidransky et al. (2009) pooling genotypic data from 16 different centers across the world. A total of 5,691 genotyped patients with Parkinson disease and 4,898 controls were evaluated; full sequencing was performed on 1859 patient and 1674 control samples. Overall, the odds ratio for carrying a GBA mutation in subjects with PD was 5.43 (95% CI 3.89-7.57), selecting mutations in GBA gene as a common risk factor for PD.

Investigators extended their studies to analyses whether GBA mutations are related with other Lewy bodies disorders. Goker-Alpan et al. (2006), analyzing the coding region of GBA gene in 75 brain's sample of autopsy cases with pathologically confirmed Lewy body disorders, found GBA mutations in 23% of LBD patients, 4% of PD patients and none within Multiple System Atrophy patients (MSA).

Afterward Mata et al. (2008), Farrer et al. (2009) and Clark et al. (2009) showed a correlation between GBA mutations and LBD, while was found no significant difference in GBA mutations incidence between MSA patients and controls (Segarane et al., 2009).

Considering the spectrum of PD clinical manifestations in GD1 patients, a wide range of symptoms have been described, varying from the more aggressive, early-onset disease, with poor response to L-dopa therapy, to the more typical PD disease (presenting with asymmetric onset of resting tremor, bradykinesia, rigidity, gait and balance disturbance, weakness, pain, cognitive decline, and depression), responsive to L-dopa (Neudorfer et al., 1996; Tayebi et al., 2003; Bembi et al., 2003; Tayebi et al., 2001; Halperin et al., 2006; Gan-Or et al., 2008; Bultron et al., 2010; Chérin et al., 2010;). The emerging evidence of the association between GBA mutations and a variety of synucleinopathies may account for the wide phenotype variability (Hruska et al., 2006; Velayati et al., 2010). Even if different studies described early-onset (< 50 years) as an element that characterizes this association, this observation might be influenced by the small number of patients involved in each study.

Trying to find an answer to this issue, Gan-Or et al. (2008) performed a study analysing a large cohort of 420 unrelated Jewish Ashkenazi PD patients, which evidenced a strong correlation between GD1 and early-onset of PD symptoms (average age at onset of 51.2 years, versus 60.7 years of the noncarriers PD population), while GBA carriers showed an average age of 57.2 years at PD onset.

They also analysed the different effects of mutation severity, observing a higher risk for PD in patients carrying severe GBA mutations as well as a decreased age of symptoms onset. Finally, when they analysed clinical PD manifestations among GBA carriers and non-carriers, they observed a reduced presence of rigidity (16.90% vs 28.57%) and an increase of weakness (16.90% vs 7.14%) in GBA carriers.

Another recent large observational study of 444 consecutive GD1 patients (Bultron et al., 2010), aiming to analyse the risk of PD occurrence, showed 11 patients (2.47%) who developed the disease at a mean age of 55.0 ± 8.8 years (range 40-65 years). Analysing GD overall severe score index (SSI) and bone disease score (Hermann score) in the overall population, they found both of them significantly higher in PD patients (SSI: 10.8 ± 0.8 vs 6.9 ± 3.7 , $p=0.02$; Herman score: 4.6 ± 0.5 vs 2.5 ± 1.5 , $p=0.002$).

Moreover, these authors estimated age and gender-adjusted risk to develop PD in three different groups of GD1 patients, finding that the range of risk was increased 11.0 to 31.3 fold in male patients and 5.7 to 13.8 fold in female patients, with an overall relative risk to develop PD in GD1 patients of 21.4 (95% CI, 10.7-38.3).

As regard the clinical response to ERT in GD1 patients with PD, all published experiences demonstrated its effectiveness on hematological and systemic involvement, while they were ineffective in correcting PD symptoms (Neudorfer et al., 1996; Tayebi et al, 2003; Bembi et al., 2003; Tayebi et al, 2001; Itokawa et al., 2006; Bultron et al., 2010). The new era of substrate reducing and chaperone therapies with small molecules that are able to cross the blood-brain barrier may open new perspectives in the treatment of central nervous system involvement in GD, including PD symptoms. A recent report of Hughes et al. (2007) that showed an improvement in the clinical conditions of a PD patient during SRT with Miglustat, introduces a new possible therapeutic approach.

5. Expression of GBA and other lysosomal enzyme in animal models of Parkinson's disease

The majority of sporadic PD cases result from interaction between genes and environment but the age remains the greatest risk factor. The first evidence of a genetic involvement in PD manifestations was the identification of three missense mutations on the α -synuclein gene, SNCA. These mutations (A30P, E46K, A53T) segregate with the disease in unrelated families and caused PD with high penetrance (Polymeropoulos et al., 1997; Kruger et al., 1998; Zarranz et al., 2004). Afterward duplication and triplication of the SNCA gene has been shown to cause PD, suggesting that high level expression of α -synuclein may also be pathogenic (Singleton et al., 2003; Ibanez et al., 2004). The degree of overexpression was found to correlate with the degree of severity of the pathology. The effects of point mutation and duplication-triplication of SNCA gene have been investigated using transgenic technology and viral infection and different mouse models were created. All PD animal models are based on the concept that parkinsonian signs are linked to dopaminergic nigral cell loss and even if they show many of the symptoms of the disease they don't display all the complexity of the neurological pathology. A lot of mouse line expressing wild-type or

mutant α -synuclein (Masliah et al., 2000; Lee et al., 2002; Richfield et al., 2002) was found to lead to the develop of granular deposits, but none of these results in the involment of dopaminergic nerve cellsof the substantia nigra. Previous data demonstrated that truncated α -synuclein (1-120) was abundantly presents in Lewy bodies extracts (Tofaris et al., 2003). There are two different animal models of Parkinson’s disease: the first one is a mouse model that express a truncated human α -synuclein (1-120) under the rat tyrosine hydroxylase promoter on a mouse α -synuclein null background (Tofaris et al., 2006). In this mouse model (TG Syn 120) were found pathological inclusions in substantia nigra and olfactory bulb, a reduction in dopamine levels in the striatum and in spontaneous locomotion and a better response to amphetamine. C-terminally truncated α -synuclein aggregates more quickly than full-lenght protein and has been found in Lewy bodies in human patients. The second one is a rat model (6OH-DA) with the lesion of the ascending nigrostriatal dopamine pathway due to 6-hydroxydopamine injection in the unilateral substantia nigra (Rozas et al., 1997; Picconi et al., 2003). These rats displayed some feautres of parkinsonian pathology. This rat model has been initially used to understand the behavioral functions of the basal ganglia, and to evaluate the brain’s ability to compensate for specific neurochemical depletions. Now this model is use has strument to understand the mechanisms of PD pathology and as an experimental basis to develop new antiparkinsonian drugs and treatment strategies, or surgical approaches (Rozas et al., 1997). To deepen the involvement of lysosomal enzyme in Parkinson’s disease, a comparative analysis of the activity of β -glucocerebrosidase (EC 3.2.1.45), α -mannosidase (EC 3.2.1.24), β -mannosidase (EC 3.2.1.25), β -hexosaminidase (EC 3.2.1.52) and β -galactosidase (EC 3.2.1.23) have been performed in different brain sections of the two animal’s model.

In particular lysosomal enzymatic activities were determined in cerebellum, cortex and brain-stem. The obtained results show a different expression in these sections of central nervous system of TG Syn 120 mouse model compared to control mice, with a decreased activity of all the enzymes in brain-stem, and an increased activity in the cerebellum. In the cortex all the enzymatic activities remain invariated.

		Beta-hexosaminidase	Alpha-mannosidase	Beta-mannosidase	Beta-galactosidase	Beta-glucosidase
brain-stem	Wistar	20.37±4.33	0.45±0.17	0.32±0.08	3.70±1.22	0.15±0.1
	6OH-DA	17.61±5.75	0.31±0.1	0.23±0.1	2.82±0.91	0.15±0.08
cerebellum	Wistar	16.43±3.42	0.51±0.23	0.36±0.13	3.88±0.83	0.1±0.04
	6OH-DA	11.27*±2.5	0.25*±0.05	0.22*±0.05	2.64*±0.81	0.08±0.02
cortico-striatal	Wistar	18.81±3.64	0.3±0.05	0.39±0.29	1.30±0.83	0.1±0.04
	6OH-DA	12.85*±0.92	0.167*±0.03	0.11*±0.03	0.48±0.38	0.05*±0.022

Table 2. Lysosomal enzyme specific activities ($\mu\text{mol min}^{-1}/\text{mg total protein} \times 1000$) in, cerebellum, cortico-striatal and brain-stem of control and 6OH-DA rats. Mean \pm SD are given. * $p<0.05$ versus control.

A more pronounced differences in lysosomal enzyme expressions were observed in 6OH-DA rats (table 2). A clear reduction of enzyme activities were found in brain-stem, cerebellum

and cortico-striatal. The chemical model show a profound involvement of the brain's areas and this is, probably, a consequence of the 6-hydroxydopamine treatment, infact the neurotoxins destroyed selectively and rapidly catecholaminergic neurons whereas the PD pathogenesis in human and in the mouse model follows a progressive course over decades. The results obtained in this rat model might explain the reduction on α -mannosidase, β -glucosidase, and β -mannosidase activities observed in the CSF of PD patients (Balducci et al., 2007).

6. CSF lysosomal enzyme activities as possible marker of synucleinopathies

Recently it became evident that accumulation of unwanted and misfolded protein play a central role in the PD pathogenesis. An involvement of the lysosomal system has been postulated. Lysosomal activity decreased over the lifespan and a lysosomal malfunction has been linked with chronic neurodegenerative disorders (Terman, 2006; Pan et al., 2008). This assumption has been confirmed by the selective inhibition of lysosomal enzyme in different cellular models that leads to protein aggregation, synaptic loss and neuronal death (Felbor et al., 2002; Bendiske & Bahr, 2003). Furthermore, in experimental system, has been noted that α -synuclein aggregation leads to inhibition of lysosomal functions, triggering a vicious cycle (Bennett et al., 2005; Cuervo et al., 2004). On the basis of these evidences was performed a comparative analysis of the activity of β -glucocerebrosidase (EC 3.2.1.45), α -mannosidase (EC 3.2.1.24), β -mannosidase (EC 3.2.1.25), β -hexosaminidase (EC 3.2.1.52) and β -galactosidase (EC 3.2.1.23) in cerebrospinal fluid (CSF) of Parkinson's disease (PD) subjects and age matched controls first (Balducci et al., 2007), and then in Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and Frontotemporal Dementia (FTD) patients as well as in age matched controls (Parnetti et al., 2009). The framework is different in the different neurodegenerative diseases, in PD patients a reduced activity of β -glucocerebrosidase, β -mannosidase and α -mannosidase was found, whereas β -galactosidase and β -hexosaminidase remain unchanged. In DLB patients, all the enzymes tested showed a decrease activity with β -glucocerebrosidase with the lower value. In FTD patients, only α -mannosidase activity was lower than controls, while the other enzymes showed unchanged activities. α -mannosidase and β -hexosaminidase are the only two enzyme that showed reduced activity in AD patients.

The data suggest a significant involvement of the lysosomal-lysosomal system in the neurodegenerative diseases examined. Moreover, the different pattern of lysosomal activity can reflect the diverse implication of the lysosomal apparatus in the distinct neurodegenerative pathologies. It has also been hypothesized that ameliorate the activity of the lysosomal system can be a possible therapeutic strategy for these disorders characterized by misfolding and aggregation of wild-type or mutant protein in the cytoplasm of neuronal cells (Lee et al., 2004).

7. Conclusion

Clinical and genetic studies suggest that mutations in the glucocerebrosidase gene are an important risk factor for the development of parkinsonism and related disorders. While Gaucher disease is an autosomal inherited disorder, patients with parkinson's disease can be Gaucher heterozygotes or homozygotes. The involvement of the lysosomal system in

parkinson's disease has also been further demonstrated by the different expression of lysosomal enzymes, such as β -glucosidase, α -mannosidase, β -mannosidase, and β -galactosidase in CSF and in the brain of animal models. The elucidation of the molecular basis of this association may contribute to understand the development of parkinsonism. Anyway it is still unclear which is the common cellular pathway that links Gaucher and Parkinson diseases.

8. References

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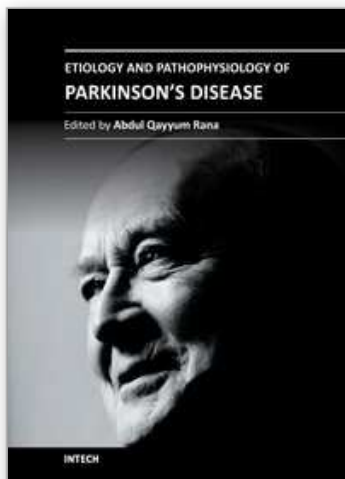
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This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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