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REVIEW

ASTROCYTES AND LYSOSOMAL STORAGE DISEASES

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Abstract—Lysosomal storage diseases (LSDs) encompass a wide range of disorders characterized by inborn errors of lysosomal function. The majority of LSDs result from genetic defects in lysosomal enzymes, although some arise from mutations in lysosomal proteins that lack known enzymatic activity. Neuropathological abnormalities are a feature of several LSDs and when severe, represent an important determinant in disease outcome. Glial dysfunction, particularly in astrocytes, is also observed in numerous LSDs and has been suggested to impact neurodegeneration. This review will discuss the potential role of astrocytes in LSDs and highlight the possibility of targeting glia as a beneficial strategy to counteract the neuropathology associated with LSDs.

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Key words: astrocytes, lysosomal storage diseases, mitochondrial dysfunction, neurodegeneration, reactive astrocytosis.

Contents

INTRODUCTION

Lysosomes are essential organelles of eukaryotic cells whose function is degradation and recycling of macromolecules that are channeled through endocytosis, phagocytosis, and autophagy (Kroemer and Jaattela, 2005). Defects in lysosomal function may curtail degradation, which can result in the accumulation of substances within the lysosome. Lysosomal storage diseases (LSDs) represent a subgroup of inborn errors of metabolism primarily resulting from a deficiency of one or more lysosomal enzymes involved in macromolecule degradation, (for review see (Schultz et al., 2011; Cox and Cachon-Gonzalez, 2012; Platt et al., 2012; Boustany, 2013), although in some LSDs, the function of mutated protein(s) has yet to be determined (Bruun et al., 1991; Rakheja et al., 2007). Since the discovery of lysosomes by Christian de Duve (De Duve, 1963, 1966), over 60 distinct LSDs have been described, with a collective incidence estimated at 1:5000 live births world-wide (Fuller et al., 2006). Roughly two thirds to three quarters of LSDs are neuropathic, which can affect multiple brain regions depending on the disease type. A few examples of LSDs that are associated with CNS pathology include, Gaucher disease, Krabbe disease, Sandhoff disease, Niemann-Pick type C (NPC), and the group of neuronal ceroid lipofuscinoses (commonly referred to as Batten Disease; (Prada and Grabowski, 2013). This review will highlight select LSDs that affect the CNS, the neuropathological events associated with these disorders, and potential roles of reactive astrocytes in disease progression. The various enzymes/proteins that are mutated in the LSDs discussed in this review are all expressed in astrocytes, since they play a critical role in lysosomal homeostasis/function. However, an intriguing finding is that not all LSDs have dramatic CNS pathology, which brings into question the functional importance of mutated genes in the brain compared to other organs, even though all

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Abbreviations: AD, Alzheimer's disease; DAMP, danger-associated molecular pattern; GBA, glucocerebrosidase; GFAP, glial fibrillary acidic protein; GLD, globoid cell leukodystrophy; INCL, infantile neuronal ceroid lipofuscinosis; JNCL, juvenile neuronal ceroid lipofuscinosis; LINCL, late infantile neuronal ceroid lipofuscinosis; LMP, lysosomal membrane permeability; LSD, lysosomal storage disease; MSD, multiple sulfatase deficiency; NCL, neuronal ceroid lipofuscinosis; NPC, Niemann-Pick type C; PD, Parkinson's disease; PPT1, palmitoyl protein thioesterase; S1P, sphingosine-1-phosphate; SCMAS, subunit C mitochondrial ATP synthase; TPPI, tripeptidyl peptidase I.

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nucleated cells contain lysosomes. Even within the CNS, neuronal loss/dysfunction in many LSDs is often restricted to specific brain regions, which remains another enigma, since typically the mutated gene is ubiquitously expressed, although it is possible that differences in expression levels may dictate susceptibility. Another variable to consider is the cell type-specific impact of the mutation in neurons, astrocytes, microglia, or other populations, such as endothelial cells and how this influences pathology via autonomous or non-autonomous pathways. Alternatively, regional changes in the expression of other molecules that normally associate with the affected protein may be differentially regulated and could conceivably influence neuronal susceptibility in LSDs.

LSDS ASSOCIATED WITH ENZYME DEFICIENCIES

Gaucher disease

Gaucher disease is caused by a deficiency in glucocerebrosidase (GBA), a lysosomal enzyme responsible for the degradation of glucocerebroside, an intermediate in glycolipid metabolism (Kampine et al., 1967; Jmoudiak and Futerman, 2005). Nearly 300 GBA mutations have been identified, including missense, nonsense, and frameshift mutations in addition to deletions, insertions, and complex alleles. Collectively, these mutations have been linked to three forms of Gaucher disease, classified as Type 1–3 (Grabowski et al., 1985). Type 1, also referred to as non-neuronopathic or adult Gaucher disease, is generally late onset and represents the most common form, with an ethnic predilection among Ashkenazi Jews (Gan-Or et al., 2008). Type 2 has the earliest onset, typically by 3 to 6 months of age, with death usually occurring by 2 years. Type 3 is a juvenile disease with an onset in early childhood. As a result of GBA deficiency, lysosomes accumulate several glycolipids, including glucocerebroside and glucosylsphingosine (Conradi et al., 1984; Farfel-Becker et al., 2014). The major cell type affected in Gaucher disease is the macrophage, where resident macrophage populations in the spleen and liver have perturbed homeostatic functions (Conradi et al., 1988). As a result, there is a marked splenomegaly, which destroys hematopoietic cells leading to anemia (Mandlebaum, 1912; Appel and Markowitz, 1971).

In terms of the CNS, the neuronopathic form of Gaucher disease has been associated with neurodegeneration in layer V of the cerebral cortex, lateral globus pallidus, various thalamic nuclei, and hippocampal CA2–CA4 regions (Conradi et al., 1984; Wong et al., 2004; Farfel-Becker et al., 2014). It is currently not well understood why these particular brain regions are selectively targeted given the ubiquitous expression of GBA; however, the collective evidence clearly indicates that it is not due to storage material accumulation (Vitner et al., 2012, 2014; Farfel-Becker et al., 2014). The neuronopathic forms of Gaucher disease are also characterized by microglial proliferation, astrocytosis, and a robust neuroinflammatory response (Vitner et al., 2012; Vitner and Futerman, 2013). A mouse model of Gaucher disease where GBA was selectively deleted in neurons and glial cells resulted in increased expression of the lysosomal enzyme cathepsin D in reactive astrocytes (Vitner et al., 2010a), which may represent a compensatory mechanism to offset GBA deficiency. However, the consequences of exaggerated cathepsin D expression in this model and the overall functional role that astrocytes play in Gaucher disease still remains to be identified. Interestingly, although the disease is known to target macrophage functions in the periphery, little information is available regarding the impact of GBA deficiency in microglia, although it has been shown that wild type microglia cannot rescue neurodegeneration associated with Gaucher disease (Enquist et al., 2007).

Krabbe disease

Krabbe disease, also known as globoid cell leukodystrophy (GLD), results from β-galactocerebrosidase deficiency, which catalyzes the hydrolysis of galactose from several sphingolipids, including galactosylceramide, lactosylceramide, and galactosylsphingosine, to generate ceramide and sphingosine (Andrews and Cancilla, 1970; Andrews et al., 1971). β-galactocerebrosidase loss leads to the accumulation of the toxic glycosphingolipid psychosine (Suzuki and Suzuki, 1985). Krabbe disease is an early onset LSD, with symptoms typically presenting around 6 months of age and mortality occurring by 2 years (Wenger et al., 1997). Krabbe disease primarily affects the CNS, resulting in extensive demyelination of cerebral white matter tracts leading to spasticity, ataxia, blindness, seizures, and severe dementia (Husain et al., 2004; Kohlschutter, 2013). The neuropathology associated with Krabbe disease has been attributed, in large part, to the abnormal accumulation of psychosine in the brain (Igisu and Suzuki, 1984a,b; Cantuti Castelvetri et al., 2013). The disease is typified by abnormal axonal transport and severe axonal loss, which is accompanied by astrogliosis (Jesionek-Kupnicka et al., 1997; Castelvetri et al., 2011). Metabolic alterations in astrocytes have been reported in a mouse model of Krabbe disease, which included increased glutamine levels and upregulation of lactate-specific monocarboxylic acid transporters (Meisingset et al., 2013). Additionally, primary astrocytes isolated from Krabbe disease mice displayed increased prostaglandin receptor (DP1 and DP2) expression (Mohri et al., 2006) and IL-6 production was elevated in reactive astrocytes in the CNS (LeVine and Brown, 1997). However, the functional significance of these alterations in astrocyte properties in Krabbe disease and how they may impact neuron survival or function remain unknown.

Microglial activation has also been reported in patients with Krabbe disease, which is consistent with a prominent neuroinflammatory response (Smith et al., 2014). This robust inflammatory response likely results from pronounced cell loss and release of danger-associated molecular patterns (DAMPs) from damaged/dying neurons that can trigger inflammatory pathways, which in turn, further exacerbate neuron damage. Indeed, psychosine has been reported to exert inflammatory and apoptotic effects in glia (Giri et al., 2002).

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