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Review

Modeling Niemann Pick type C1 using human embryonic and induced pluripotent stem cells

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ABSTRACT

Data generated in Niemann Pick type C1 (NPC1) human embryonic and human induced pluripotent stem cell derived neurons complement on-going studies in animal models and provide the first example, in disease-relevant human cells, of processes that underlie preferential neuronal defects in a NPC1. Our work and that of other investigators in human neurons derived from stem cells highlight the importance of performing rigorous mechanistic studies in relevant cell types to guide drug discovery and therapeutic development, alongside of existing animal models. Through the use of human stem cell-derived models of disease, we can identify and discover or repurpose drugs that revert early events that lead to neuronal failure in NPC1. Together with the study of disease pathogenesis and efficacy of therapies in animal models, these strategies will fulfill the promise of stem cell technology in the development of new treatments for human diseases.

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1. Background and significance

Niemann Pick disease type C1 (NPC1) is a rare but devastating lysosomal storage disease that leads to severe neuronal degeneration, imposing a burden on patients, families, caretakers, and society that is disproportionate to its relative infrequency. NPC1 is caused by loss of function mutations of the cholesterol transporter NPC1, a transmembrane protein that resides on the membrane of the late endosomal/lysosomal compartment (Liscum, 2006; Sturley et al, 2004). The disease is clinically and genetically heterogeneous, with more than 350 described mutations that result in severe loss of function of NPC1 (McKay Bounford and Gissen, 2014). The resulting cellular phenotype is the significant accumulation of unesterified cholesterol and other lipids, particularly sphingolipids and gangliosides, in the lysosome. An interesting feature of the disease is that mutations of NPC1 lead to selective neuronal failure, despite the ubiquitous nature of the lipid trafficking pathway that they affect (Ordonez, 2012).

The clinical spectrum of NPC1 ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. In its most aggressive form, affected children present as toddlers and die during childhood or early adolescence. Although hepatomegaly usually precedes onset of neurological symptoms, liver involvement typically does not progress to liver failure. Spleen and bone marrow abnormalities can also occur but their contribution to morbidity and mortality are also small in comparison to central nervous system pathology and dysfunction. Neurodegeneration and neuronal failure are the primary contributors to lethality in NPC1, which has a variable clinical phenotype (Klein et al, 2014; Vanier, 2010). Patients with classic childhood onset usually appear normal for 1 or 2 years, with symptoms appearing between 2 and 4 years of age. These patients gradually develop ataxia, dystonia, dysphagia and loss of previously learned speech, reflective of the preferential susceptibility of cerebellar Purkinje neurons to mutations of NPC1. Spasticity is striking and seizures, particularly myoclonic jerks, are common. Other features include vertical supranuclear gaze palsy, dementia, and psychiatric manifestations. In the childhood-onset form, death usually occurs between age 5 to 15 years. More recently, late-onset disease has been increasingly recognized as the biochemical diagnosis of NPC1 is more widely applied in adult neurology clinics (Imrie et al, 2006). Evaluation of common NPC1 variants extracted from large exome sequencing data sets suggests that a late-onset NPC1 phenotype may have a markedly higher incidence than that described for classic NPC1 disease (Wassif et al, 2015).

Interestingly, neurodegeneration caused by mutations of NPC1 shares many clinical and pathologic features with Alzheimer's disease (AD) (Liu et al, 2010; Malnar et al, 2014). Indeed neurofibrillary tangles, a lesion associated with AD and related tauopathies, is also typical of NPC1, especially in cases with a prolonged course of disease (Mattson et al., 2012; Maulik et al, 2012). Other histopathological similarities between NPC1 and AD include axonal spheroids, β-amyloid deposition, and dystrophic neurites. Furthermore, a specific polymorphism of apolipoprotein E (apoE4), the main extracellular carrier of cholesterol in the brain, is the strongest known risk factor for the development of sporadic AD, and carries a worse prognosis in NPC1 (Fu et al, 2012; Vance et al, 2005). Added to these similarities are findings that some neuronal populations in NPC1 develop abnormalities of endosomes resembling those seen at the earliest stages of AD, and that aberrant cholesterol trafficking is associated with the potentiation of toxic AD-like processing of the amyloid precursor protein (APP) (Borbon and Erickson, 2011; Grimm et al, 2005). Therefore, NPC1 and AD may share common mechanism(s) related to onset or progression of disease in neurons, and strategies that reverse neuronal dysfunction in NPC1 could potentially be extrapolated to develop therapies for AD, a disease that affects over 5 million people in the U.S. alone with significant human and economic burdens (Brookmeyer et al, 2007).

2. Current NPC1 model systems

There are currently no FDA-approved therapies for the treatment of NPC1 and efforts to develop new therapeutic strategies to combat neurological deficits in NPC1 are urgently needed. Much of the mechanistic work to date has utilized mouse models or cultured non-neuronal cells (e.g. patient fibroblasts), and these studies predominantly focus on a direct contribution of lysosomal lipid accumulation to neuronal failure and death. Two commonly used and independently derived mutant mouse colonies have played an essential role in delineating the biochemical basis of NPC1 and have been widely used for disease modeling. One is a BALB/c mouse presenting clinical and biochemical features of NPC1 (Pentchev et al, 1984); the other is the C57BL/Ks mouse characterized as a sphingomyelinosis because of attenuated sphingomyelinase activity and excess sphingomyelin accumulation (Miyawaki et al, 1986). More recently, a knock-in mouse model expressing the most common human mutation of NPC1 (I1061T) was generated and characterized (Praggastis et al, 2015). Compared with the null NPC1 mouse, this model displays a less severe, delayed form of NPC1 disease with respect to weight loss, decreased motor coordination, cerebellar Purkinje neuron death, lipid storage, and premature death, and this model it is suitable to test the effect of proteostatic therapeutic interventions (Gelsthorpe et al, 2008). In addition, a novel mouse model carrying a single nucleotide change (D1005G-Npc1) that is comparable to commonly observed human mutations has been reported. Analysis of this mouse model revealed a more slowly developing phenotype than in mice with null mutations, which may offer advantages to model late-onset, slowly progressive forms of NPC1 that comprise a large number of human cases (Maue et al., 2012).

Although NPC1 may have a common fundamental role in lipid trafficking in mice and humans, it is unclear whether the pathological consequences of NPC1 dysfunction are the same for both species due to biochemical and physiological differences between mouse and human neurons. Specifically in NPC1 mouse models, tau and β–amyloid proteins do not readily form neurofibrillary tangles or plaques, respectively, which do form in human mutant NPC1 neurons and may

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