Taking out the garbage: cathepsin D and calcineurin in neurodegeneration

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Abstract
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Introduction
With the continuously rising age of our society, the prevalence of age-related pathologies such as neurodegenerative diseases is increasing drastically. Although tremendous effort is made to ad-

to address this health issue, the cellular and molecular events promoting 
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dosage of yeast CatD compensated the αSyn-driven loss of vacuolar proteolytic capacity, decreased αSyn oligomers and aggregates, prevented the acidification of the cytosol and ultimately inhibited cell death.

Interestingly, these cytotoxic effects of yeast CatD required functional calcineurin signalling. Although the existence of a CatD-calcineurin interplay remains to be validated in higher eukaryotic cells, an evolutionary conservation of a coordinated action of these proteins seems likely, since the function of each protein per se is highly conserved between yeast and humans. While disturbances in Ca²⁺ homeostasis and signalling have been connected to all major proteinopathies (Shah et al., 2017), the exact role of calcineurin in neurotoxicity is controversially discussed and both positive and negative effects of its phosphatase activity were reported in various models of neurodegenerative disorders (Kipanyula et al., 2016). In yeast and neuronal cell culture models of PD, insufficient as well as excessive calcineurin activity has been shown to be fatal, while moderate activity levels counteracted αSyn cytoxicity (Caraveo et al., 2014). Our recent findings might also indirectly indicate that calcineurin signalling is protective in the presence of high CatD activity. Genetic inactivation of calcineurin via deletion of CNB1, the gene coding for the regulatory calcineurin subunit, caused a prominent mislocalization of both yeast CatD and its sorting receptor Pep1. Comparable to the effects of αSyn expression, this resulted in decreased vacuolar CatD activity (Aufschnaiter et al., 2017). Thus, calcineurin is essential for efficient endosomal trafficking and recycling, which might contribute to the cytotoxic effects of moderate calcineurin activity observed in cellular PD models.

The Retromer as Nexus between CatD and Calcineurin in PD?

Interestingly, mislocalization of M6P receptors such as Pep1 at the lysosomal/vacuolar membrane points towards defects in its retrieval and recycling, a process requiring the so-called retromer complex. This highly conserved multimeric protein complex, originally discovered in yeast, consists of two parts: the trimeric cargo-selective complex, composed of Vps26, Vps29 and Vps35, and a sorting nexin dimer (Seaman et al., 1997; Cullen and Korswagen, 2011). The retromer represents a master regulator of endosomal sorting and governs the recycling of distinct transmembrane proteins and receptors from endosomes back to either the trans-Golgi network or the plasma membrane. Thus, deregulated retromer activity perturbs protein trafficking and impairs lysosomal function, partly due to insufficient delivery of acid hydrolases (Arighi et al., 2004). The point mutation D620N in the retromer subunit Vps35, which is responsible for cargo recognition, has been linked to familial and sporadic late-onset forms of PD (Zimprich et al., 2011). The D620N mutation as well as Vps35 deficiency have been shown to cause sorting defects of M6P receptors and in consequence insufficient lysosomal delivery of its ligand CatD (Follett et al., 2014). Still, the mechanisms underlying Vps35-associated PD phenotypes seem to be rather complex, as not only Vps35 deficiency and mutation but also high levels of Vps35 and pathogenic variants have been linked to neuronal degeneration in various cellular and animal models (for recent reviews, see (McMillan et al., 2017; Williams et al., 2017)). For instance, loss of Vps35 function has been shown to enhance Syn aggregation and toxicity in PD models ranging from yeast and fly to rodents, while in other studies, high levels of Vps35 or of the pathogenic variant D620N triggered neurodegeneration. The D620N mutation does not interfere with retromer assembly or stability, and several cargo proteins are thought to be sorted correctly, indicating that probably rather discrete effects involving specific ligands or cellular destinations are involved (Williams et al., 2017). Thus, depending on the cellular model and scenario used, slight alteration or impairment of retromer activity might have different outcomes.

While we show that calcineurin contributes to correct endosomal sorting of the yeast M6P receptor Pep1 and thus sufficient CatD activity in the vacuole (Aufschnaiter et al., 2017), the molecular underpinnings of this cytotoxic effect remain to be investigated. As the lack of calcineurin causes a sorting defect frequently observed in mutants defective in endosomal recycling due to mutations in retromer subunits, it might well be that calcineurin is directly or indirectly involved in the fine-tuning of retromer activity and/or assembly. High levels of αSyn might interfere with this regulatory circuit, thus impairing efficient endosomal protein sorting and, in consequence, reducing lysosomal proteolytic capacity. Furthermore, the localization of proton transporters at the plasma membrane and the limiting vacuolar membrane might be affected by these changes in endosomal sorting and recycling, leading to the observed acidification of the cytosol. As an acidic environment has been shown to increase the aggregation propensity of αSyn, this drop in cytosolic pH might subsequently enhance αSyn aggregation and might thereby reinforce its detrimental effects. High-level expression of yeast CatD reinstalled proper vacuolar proteolytic capacity and counteracted αSyn toxicity in wild type cells, while mutants lacking functional calcineurin were unable to deliver and/or activate CatD properly. Thus, at least basal calcineurin activity is required for efficient M6P receptor-mediated sorting of yeast CatD to the vacuole (Aufschnaiter et al., 2017). As mentioned above, moderate activation of calcineurin has been shown to be neuroprotective, while deficiency as well as hyperactivation were neurotoxic in various models, including yeast, C. elegans, neuronal cell culture, mice and post-mortem samples of PD patients (Kipanyula et al., 2016). Whether these pleiotropic effects of calcineurin on neuronal (dys)function involve a regulation of retromer activity, alternative endosomal sorting mechanisms or cellular processes such as cytoskeleton dynamics necessary for proper transport of endosomes remains to be investigated. Further research will be needed to investigate a potential connection between calcineurin, CatD trafficking and the retromer complex in PD and other proteinopathies.

While our results indicate that CatD-mediated cytoprotection against αSyn toxicity does not require the autophagic machinery (Aufschnaiter et al., 2017), the autophagy-lysosome system has a crucial role in the pathophysiology of PD (Beilina and Cookson, 2016). Many PD-associated gene products, including αSyn, LRRK2, Vps35, glucocerebrosidase, PINK1, Parkin, Bbox7 and ATP13A2 have a physiological role in distinct subtypes of autophagy or differentially influence this degradative pathway. Furthermore, at least some of these proteins also affect CatD function.

Mutation or depletion of ATP13A2, a lysosomal ATPase connected to distinct forms of PD, has been shown to cause severe lysosomal alterations in dopaminergic neuronal cell lines and PD patient samples, ranging from diminished lysosomal acidification and impairment of autophagy to reduced proteolytic capacity resulting from abnormal CatD processing (Dehay et al., 2012). High levels of pathogenic variants of the leucine-rich repeat kinase 2 (LRRK2) drive the formation of enlarged and non-functional lysosomes with reduced proteolytic activity and decreased pH. Interestingly, these LRRK2-induced changes were associated with an upregulation of ATP13A2 (Henry et al., 2015). As mutations in LRRK2 are frequently accompanied by additional variations in PD-associated
gene products with lysosomal function such as ATP13A2, one might speculate that increased lysosomal burden due to these additional genetic alterations might cause penetrance of LRRK2 mutations in PD (Lubbe et al., 2016). Comparable to the effects of high levels of aSyn, LRRK2 has been shown to influence the retromer complex, and overexpression of Vps35 protected against the toxic consequences of pathogenic LRRK2 variants (MacLeod et al., 2013).

CatD, Calcineurin and the Retromer: a Common Theme in Proteinopathies

CatD, the retromer complex and calcineurin have also been implicated in the pathophysiology of AD, though no connection between this Ca2+-activated phosphatase and endosomal sorting has been established so far. However, in cell culture and mouse models, calcineurin has been shown to be involved in vesicle endocytosis as well as in the regulation of autophagy via lysosomal Ca2+ signalling (Wu et al., 2014; Medina et al., 2015), and disturbances of these processes are tightly linked to AD pathogenesis. AD is associated with abnormal processing of the amloid precursor protein, leading to amyloid beta deposition as well as the hyperphosphorylation and intracellular accumulation of the microtubule-associated protein tau. Evidence for a role of CatD in AD came from studies that identified CatD immunoreactivity in neuritic plaques, histological hallmarks of AD (Bernstein et al., 1989; Cataldo et al., 1990, 1995). CatD is suggested to provide neuroprotection by preventing excessive tau accumulation and in line, CatD deficiency causes lysosomal expansion and an enrichment of C-terminally truncated tau variants that promote neurotoxicity (Khurana et al., 2010). Furthermore, a dysfunction of the retromer complex has been reported to cause increased pathogenic processing of the amyloid precursor protein, microglial abnormalities and a reduction of CatD levels, which in turn reinforces toxicity mediated by C-terminally truncated tau (Small and Petsko, 2015). The hyperphosphorylation of tau, a common feature of AD and, to some extent, also of HD pathology, might be directly influenced by calcineurin. This phosphatase has been shown to directly bind to and dephosphorylate tau, thereby regulating microtubule system dynamics (Hoffman et al., 2017). In this line, a reduction of calcineurin activity was reported in post-mortem samples of AD patients. However, as described for PD above, controversial studies exist, describing an upregulation of calcineurin, impact their pathophysiologies.

Outlook

Taken together, impairment of lysosomal function represents a key event in neurodegenerative diseases. Even though the malfunction of a diverse set of proteins triggers the pathogenesis of these disorders, many of them directly or indirectly reduce the proteolytic activity of CatD and/or impair lysosomal function (Figure 1). A sophisticated machinery that ensures proper targeting and activation of CatD, including the retromer complex, is required for efficient breakdown of proteins delivered to the lysosomes via autophagy and endosomes and thus represents a common target of different proteinopathies. While we demonstrate that calcineurin activity essentially contributes to this process in a yeast model for PD, it remains to be evaluated whether this regulatory axis is conserved in higher eukaryotes and if it impacts neurodegenerative diseases beyond PD.

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References

Aufschnaiter A, Habernig L, Kohler V, Diesl J, Carmona-Gutierrez D, Eisenberg T, Keller W, Büttner S (2017) The coordinated action of calcineurin and cathepsin D protects against a-synuclein toxicity. Front Mol Neurosci 10:207.

Arighi CN, Hartnell LM, Aguilar RC, Haft CR, Bonifacino JS (2004) Role of the mammalian retromer in sorting of the cation-independent mannose 6-phosphate receptor. J Cell Biol 165:123-133.

Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, Trojanowski JQ, Iwatsubo T (1998) Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson’s disease and dementia with Lewy bodies. Am J Pathol 152:879-884.

Belina A, Cookson MR (2016) Genes associated with Parkinson’s disease: regulation of autophagy and beyond. J Neurochem 139 Suppl 1:91-107.

Benes P, Vetrivka V, Fursek M (2008) Cathepsin D—many functions of one aspartic protease. Crit Rev Oncol Hematol 68:12-28.

Bernstein HG, Bruszis S, Schmidt D, Wiederanders B, Dorn A (1989) Immunodetection of cathepsin D in neuritic plaques found in brains of patients with dementia of Alzheimer type. J Hirnforsch 30:613-618.

Caraveo G, Auluck PK, Whitesell L, Chung CY, Baru V, Moharorov EV, Yan X, Ben-Johny M, Soste M, Picotti P, Kim H, Caldwell KA, Caldwell GA, Sulzer D, Yue DT, Lindquist S (2014) Calcineurin determines toxic versus beneficial responses to alpha-synuclein. Proc Natl Acad Sci U S A 111:E3544-3552.

Cataldo AM, Thayer CY, Bird ED, Wheelock TR, Nixon RA (1990) Lysosomal protease antigens are prominently localized within senile plaques of Alzheimer’s disease: evidence for a neuronal origin. Brain Res 513:181-192.

Cataldo AM, Barnett JL, Berman SA, Li J, Quarless S, Bursztajn S, Lippa C, Nixon RA (1995) Gene expression and cellular content of cathepsin D in Alzheimer’s disease brain; evidence for early up-regulation of the endosomal-lysosomal system. Neuron 14:671-680.

Cullen PJ, Korswagen HC (2011) Sorting nexins provide diversity for retromer-dependent trafficking events. Nat Cell Biol 14:29-37.

Dehay B, Ramirez A, Martinez-Vicente M, Perier C, Canron MH, Doudnikoff E, Vital A, Vila M, Klein C, Bezard E (2012) Loss of P-type ATPase ATP13A2/PARK9 function induces general lysosomal deficiency and leads to Parkinson disease neurodegeneration. Proc Natl Acad Sci U S A 109:9611-9616.

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kortun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, Teasdale RD (2014) The Vps35 D620N mutation linked to Parkinson’s disease disrupts the cargo sorting function of retromer. Traffic 15:230-244.

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In healthy cells (left panel), a sophisticated and evolutionary conserved machinery governs the targeting and processing of CatD into lysosomes. CatD is an aspartyl protease important for the degradation of cargo delivered to lysosomes and thus contributes to cellular protein homeostasis. The retromer complex functions as a master regulator of endosomal sorting and facilitates correct trafficking and recycling of the mannose-6-phosphat (M6P) receptor, the major sorting receptor for CatD. We could show that at least basal levels of the Ca2+/calmodulin-dependent phosphatase calcineurin are required for efficient sorting of M6P and CatD in yeast, leading to speculations that calcineurin might contribute to the regulation of the retromer (Aufschnaiter et al., 2017). Blue arrows indicate pathways only identified in yeast so far; black arrows represent pathways established in yeast and higher eukaryotes; arrows with question marks reflect potential but unverified pathways. In neurodegenerative diseases (right panel), multiple proteins and pathogenic variants associated with these disorders (here illustrated for Parkinson’s disease and Alzheimer’s disease related gene products) have been shown to impair sorting processes of CatD via the M6P receptor and the retromer, ultimately resulting in reduced protease activity. This reduction in lysosomal degradative capacity is accompanied by morphological alterations, resulting in a reduced number of lysosomes and lysosomal enlargement. Dysregulation of calcineurin signalling is frequently observed in different neurodegenerative diseases and we reported an essential role of calcineurin in CatD-mediated cytoprotection against αSyn toxicity. In aggregate, a complex interplay of calcineurin, CatD and the retromer might essentially contribute to lysosomal function and thus neuronal health. Bar-headed lines represent pathways that are inhibited in the course of Parkinson’s disease (red) or Alzheimer’s disease (orange). Bar-headed lines with question marks reflect potential but unverified interferences.

**Figure 1 Interplay of cathepsin D (CatD), calcineurin and the retromer in health and neurodegenerative diseases.**

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