REVIEW

Selective Neuronal Death in Neurodegenerative Diseases: The Ongoing Mystery

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A major unresolved problem in neurodegenerative disease is why and how a specific set of neurons in the brain are highly vulnerable to neuronal death. Multiple pathways and mechanisms have been proposed to play a role in Alzheimer disease (AD†), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD), yet how they contribute to neuronal vulnerability remains far from clear. In this review, various mechanisms ascribed in AD, PD, ALS, and HD will be briefly summarized. Particular focus will be placed on Rhes-mediated intercellular transport of the HD protein and its role in mitophagy, in which I will discuss some intriguing observations that I apply to model striatal vulnerability in HD. I may have unintentionally missed referring some studies in this review, and I extend my apologies to the authors in those circumstances.

INTRODUCTION

A hallmark of all neurodegenerative diseases is the early and progressive loss of selected neuronal populations and their associated functions. Classic examples include degeneration of the entorhinal cortex/hippocampal neurons, affecting memory function in AD; loss of substantia nigral neurons, affecting initiation of motor activity in PD; loss of motor neurons in ALS, affecting muscle control; and loss of striatal neurons in HD, affecting involuntary movements. Very little is known about what mechanisms contribute to selective vulnerability in these neurodegenerative disorders. How abnormal protein function or structure that are specific to each neurodegenerative disease affects neurons and results in

characteristic symptoms of the disease remains unclear. The genetic mutations involved in these disorders further deepen the mystery because, in all cases, the gene responsible for the neurodegeneration is expressed ubiquitously, yet still leads to selective neuronal loss and dysfunction. Understanding the mechanisms of selective neuronal vulnerability is crucial to identify novel targets and develop novel therapy that mitigate the onset and/or progression of the neurodegenerative disease.

NEURONAL VULNERABILITY IN ALZHEIMER DISEASE (AD)

Loss of neurons in the cortical II layer of the entorhinal cortex is considered a major feature of Alzheimer

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disease (AD) [1]. Neurons in the entorhinal cortex that makes acetylcholine neurotransmitter and innervate the hippocampus and neocortex are also eventually degenerated in AD [2]. Memory loss and dementia are primarily attributed to the loss of neurons in the cortex and the hippocampus. Why and how do these neurons die? Pathological hallmarks of AD, such as amyloid-beta (Aβ), which forms senile plaque (SP), or hyperphosphorylated tau (HP-tau), which forms neurofibrillary tangles (NFTs), have also been found in these regions [3]. This has led to the notion that the accumulation of SP and NFTs is the principal trigger for neuronal death in AD. In support of this, exogenous Aβ and pseudo HP-tau have been shown to elicit neuronal death in various cell cultures and animal models of AD [4]. However, SP and NFTs have also been found in regions of the brain that do not show degeneration, and SP does not always coincide with NFT expression [5]. Extensive efforts have revolved around elucidating the mechanisms of regulation, formation, and enzymatic cascades, which cleave amyloid precursor protein (APP) into Aβ or convert tau into HP-tau [6,7]. Different forms of Aβ—both pathogenic and non-pathogenic types—have been described [8]. Multiple phosphorylation sites by various enzymes that target HP-tau have been described [9]. Proteins such as glycogen synthase kinase 3β and brain-specific serine/threonine-protein kinase 1 that phosphorylate tau are ubiquitously expressed [10]; thus, it remains unclear whether HP-tau is involved in the selective neuronal vulnerability of the cortex and the hippocampus in AD.

Mutations in both the APP and presenilin-1 (PSEN) causes familial AD [11]. PSEN is the catalytic component of the γ-secretase enzyme that generates Aβs by cleaving the APP into Aβs of varying lengths. There are more than 150 PSEN mutations, which comprise both loss-of-function and gain-of-toxic function mechanisms in regulating pathogenic and aggregate-prone forms of Aβ (Aβ1-42) have been reported in AD, and these studies have invigorated the amyloid hypothesis field [12,13]. Unfortunately, the mechanism of action of PSEN and its ubiquitously expressed mutants in the upregulation of Aβ and their role in selective neuronal vulnerability in AD remain mostly unknown [14]. Paradoxically, the deletion of PSEN in the cortical areas of the mouse brain, which results in a loss of Aβs, promotes neurodegeneration; this indicates that Aβs signaling may also be involved in neuronal survival [15]. Familial mutation in APP, which leads to a greater production of Aβ, has corroborated the importance of Aβ accumulation in AD pathogenesis [16]. Intriguingly, studies have indicated that Aβ itself can regulate tau phosphorylation, linking amyloid and tau in AD pathogenesis [17]. However, loss of APP did not affect tau phosphorylation in a human embryonic stem cell model with Down syndrome (DS), thus challenging

the role of the amyloid-tau cascade in this model [18].

In terms of mechanisms, studies in cell and animal models have shown that Aβ and tau alter pathways involved in N-methyl-D-aspartate receptor (NMDA) receptor function, ER stress, calcium dysregulation, and excitotoxicity, in addition to promoting metabolic defects, oxidative stress, and apoptosis [19]. One or more of these pathways is likely involved in AD, but how these pathways selectively affect the cortex and hippocampus in AD is mostly unclear. It has been suggested that vulnerable neurons in AD are degenerated due to the loss of oligodendrocytes that provide myelin, a lipid-rich layer that protects nerves [20]. Aberrant microglia response, which may be due to the accumulation of Aβ and tau, has also been suggested to play a role in neuronal vulnerability in AD [21]. However, the question of how oligodendrocytes and microglia, which are ubiquitously present, promote neuronal degeneration in and around vulnerable AD regions remains unknown. Studies in mice have demonstrated that infection can play a critical role in the onset of AD-like pathology. Frequently, *Porphyromonas gingivalis*, a gum disease bacteria, can penetrate the brain and produce Aβ, tau, and neuronal damage in it [22]. Dysregulation of blood brain barrier (BBB), especially the morphological functional alterations of cells such as pericytes and endothelial cells, which are integral to BBB, is also increasingly recognized to play a role of AD pathology [23]. Additionally, multiple AD-risk mutations have been found in AD patients, including APOE, TOMM40, PVRL2 (NECTIN2), and APOC1, which can further contribute to or increase the pathogenesis of AD [24]. Collectively, it is likely that more than one pathway or signaling within the affected regions (cell-autonomous) and outside the affected regions (non-autonomous), plus the co-ordination of non-neuronal cells, contributes to the progression of AD. However, the mechanisms that are responsible for the onset of AD and why such mechanisms affect selected regions in the AD brain remain mostly unclear.

NEURONAL VULNERABILITY IN PARKINSON DISEASE (PD)

Degeneration of the substantia nigra pars reticulata (SNr), the region that produces neurotransmitters such as dopamine, is the primary cause of PD, as it results in uncontrolled tremors and loss of initiation of movements [25]. SNr neurons contain pigment called neuromelanin, which is an oxidized product of dopamine and is considered a significant contributor to neuronal death in PD [26]. Neuromelanin can act as a source of radical ion generation, and it can capture iron and absorb pesticides such as rotenone that promote age-dependent increases in oxidative stress, resulting in the selective degeneration

of SNr neurons [27]. A recent study of transgenic mice, which are engineered to produce melanin, demonstrated that high expression of melanin degenerates SNr neurons and produces PD-like symptoms [28]. Neuromelanin can also affect the ubiquitin-proteasome system in SNr, thereby affecting protein turnover [29]. High expression of Cu,Zn superoxide dismutase in SNr indicates high levels of oxygen-free radicals endogenously produced in the SNr region [30]. Intriguingly, SNr that expresses calbindin-D28K is resistant to cell death in PD [31]. A human postmortem study, however, suggested that a differential vulnerability in PD cannot be explained by melanin or calbindin-D28k content alone, as the study found that more vulnerable neurons contain less melanin and lack calbindin-D28K expression [32]. High dopamine content due to diminished expression of the dopamine transporter in SNr might also contribute to SNr's vulnerability due to dopamine-induced oxidative stress and neuronal death [33]. However, if a high amount of dopamine is the leading cause of SNr loss, dopamine should also destroy the striatum, which it acts upon. However, the striatum does not degenerate in PD. It is possible that the location of the high dopamine concentration—cytoplasm vs. synapse—may influence the selective vulnerability of SNr. Synaptic dopamine levels combined with neuromelanin may damage SNr preferentially in PD. In general, although the SNr contains high neuromelanin and dopamine content, not every model develops PD, indicating that neuromelanin or dopamine alone is insufficient to explain SNr loss in PD.

PD also features Lewy bodies, deposits that show intense staining due to abnormal accumulation of proteins, in the SNr [34]. Each Lewy body consists of a high accumulation of protein, α-synuclein, and a 12 amino acid peptide [35]. The role of α-synuclein has been recognized as biologically important due to the discovery of missense mutations and extra copies of the α-synuclein (*SNCA*) gene in PD [36]. However, the α-synuclein and its mutants are ubiquitous proteins, and how they elicit SNr degeneration remains an enigma [37]. It has been reported that dopamine could directly affect α-synuclein aggregate propensity, contributing to the generation of more toxic oligomeric forms of α-synuclein [38,39]. α-synuclein, in turn, can alter enzymes involved in dopamine metabolism and generate toxic dopamine metabolites [40]. Alternately, α-synuclein could elicit mitochondrial dysfunction [41,42]. Interactions between α-synuclein and neuromelanin have also been reported [43]. Neuromelanin, like dopamine, can alter the α-synuclein aggregate propensity to promote toxicity [44]. However, how α-synuclein and neuromelanin orchestrate SNr degeneration remains obscure [45]. Intriguingly, α-synuclein can propagate like a prion protein and move from region to region, forming varying degrees of α-synuclein aggregates in the brain [46]. How the mechanisms of propagations occur remains a matter of intense debate, but they may involve tunneling-like cellular protrusion, exosomes, transsynaptic migration, etc. [47]. α-synuclein has also been shown to alter pathways involved in calcium homeostasis, transcriptional defects, voltage-gated channels, and mitochondrial functions [48]. The distribution of α-synuclein aggregates in both affected SNr and non-affected regions, such as the hippocampus, further raises the question of how α-synuclein aggregates selectively affect SNr [49].

Additional familial PD-causing mutations in PTEN-induced kinase 1 (PINK1) and Parkin, a ubiquitin E3-ligase, in PD have also generated enormous interest in terms of finding the mechanisms for the vulnerability [50,51]. PINK1 and Parkin have been implicated in mitochondrial turnover [52,53]. PINK1 recruits Parkin to the damaged mitochondria and removes them via mitophagy, where dysfunctional mitochondria are engulfed by autophagosomes that are degraded by fusing with lysosomes [54,55]. PD-linked mutants of PINK1 and Parkin fail to remove damaged mitochondria, thus generating mitochondrial stress [56,57]. PINK1-deficient mice show no change in SNr vulnerability; however, they do demonstrate impaired dopamine release [58,59]. These findings have led to the idea that mutant PINK1 enhances intracellular dopamine, which may promote oxidative stress followed by mitochondrial abnormalities, thus leading to dysfunction and degeneration of SNr [60,61]. This is an attractive set of data describing how the PINK1-Parkin nexus may elicit SNr damage; however, PINK1 and Parkin are ubiquitously present, including in the striatum [62]. Thus, how they promote SNr vulnerability in PD is far from clear. Other PD-causing mutants, such as leucine-rich repeat kinase 2 (LRRK2), DJ-1, and ATPase type 13A2, are ubiquitously present as well, but how they cause selective SNr loss in PD remains to be determined [63].

Much understanding of PD-like brain pathology was derived from agricultural agents such as pesticides and herbicides [64,65]. MPTP, a permeable membrane herbicide, gets converted into a toxic form, MPP+ [66]. MPP+ induces neuronal death in rodents and higher primate models that is strikingly similar to that which occurs in PD [67]. It has been postulated that MPP+ could be taken up by dopamine transporters that are abundant in SNr, leading to a blockade of mitochondrial complex I and promoting oxidative stress and toxicity [68]. However, dopamine transporters are also expressed in unaffected regions in PD [69].

Similarly, rotenone, a pesticide, also promotes SNr degeneration and PD-like symptoms and blocks mitochondrial complex I [70]. Although MPP+ and rotenone have been demonstrated to promote toxicity via blocking complex I of mitochondria, this assumption was

challenged in a study. This study showed that cultured midbrain neurons that lack complex I activity are equally affected by MPTP and rotenone, arguing that these environmental toxins affect the SNr pathway not exclusively via complex I inhibition and thus widening the mystery of SNr vulnerability in PD [71]. The fungicide benomyl can also promote PD-like symptoms via the inhibition of aldehyde dehydrogenase (ALDH), suggesting a non-mitochondrial route for SNr loss. However, it is unclear whether ventral tegmental area, which also contains ALDH, is also affected by benomyl [72].

Collectively, due to the strong link of environmental toxins (including rotenone and MPTP) and genetic components (including PINK and Parkin) to mitochondria, mitochondrial dysregulation is considered a significant trigger for SNr degeneration in PD. Such a selective trigger may occur due to the interaction of environmental and genetic factors of PD with abundant neuromelanin and dopamine in the SNr; however, the mechanistic details remain mostly unknown.

NEURONAL VULNERABILITY IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Motor neurons in the spinal cord and brain stem are the primary neuronal targets that are degenerated in ALS [73]. Circumstantial evidence has indicated that people with immune disorders are at high risk of developing ALS [74]. IgG isolated from ALS patients can induce calcium dysregulation and morphological changes in the mitochondria of motor neurons, but not in sensory or Purkinje neurons [75]. Cerebrospinal fluid from ALS patients produces degenerative changes in the neonatal rat spinal cord, indicating the presence of toxic factors circulating in the cerebrospinal fluid of ALS patients [76]. Although most cases of ALS occur sporadically, the exact reasons for its development are thus unclear, mutation of superoxide dismutase 1 (SOD1), a Cu/Zn enzyme that removes reactive oxygen radicals, has been implicated in familial ALS [77]. However, SOD1 and its mutants are widely expressed, including in unaffected brain areas, and how SOD1 induces motor neuron degeneration, which ultimately destroys neuromuscular junction in ALS, remains unknown [78]. The final onslaught of the disease may involve excitotoxicity, free radical generation, and IgG generation [79]. Neuron counts in postmortem ALS tissue and SOD1 Tg mice have shown that HP-tau, as well as choline acetyltransferase (ChAT)-, and calretinin (CR)-immunoreactive neurons, demonstrate particularly high vulnerability in the spinal cord, but parvalbumin-positive neurons are largely spared [80]. Mutant SOD1, compared to wild-type SOD1, has shown a high tendency to aggregate, which can also lead to the

demise of motor neurons [81]. Evidence from mechanistic studies has pointed to the role of mitochondria, ER stress, and calcium-mediated toxicity following either overactivation of glutamate receptors or differential expression regulated by astrocytes as the cause of motor neuron death [82]. The hippocampus also contains high levels of glutamate receptors, and SOD1 mutants have been expressed there as well; however, these regions are less vulnerable than other regions [83]. Much research has focused on the role of non-neuronal cells, such as astrocytes, which show aberrant activation of signaling in ALS as a contributing or main factor for motor neuronal vulnerability [84]. Expression of the SOD1 mutant in non-neuronal cells or selectively in astrocytes can elicit motor neuron death [85]. However, it is unclear why non-neuronal cells and astrocytes are present in unaffected areas of the brain but are not affected in ALS. Postmortem studies of ALS patients have suggested that motor neurons with large axonal diameters are vulnerable to degeneration; however, in a mouse model of ALS, a reduction in the axonal diameter did not prevent motor neuron pathology [86].

Mutations in RNA binding protein TDP-43 (A135T), which can trigger NF-KB-mediated pathogenic pathways, have also been implicated in familial ALS. Motor neurons are highly vulnerable to TDP-43 (A135T) expression compared to other neurons [87]. Hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (C9orf72), mutations in ubiquilin-2, and the calreticulin and macrophage migration inhibitory factor, also promote motor neuron loss in ALS [88]; however, the mechanisms for the selectivity remain unknown. Intriguingly, a reduced ratio of the index to ring finger length (2D:4D ratio) with high prenatal circulating testosterone is also a risk factor for ALS patients [89], but the mechanisms of how such differences can elicit selective motor neuron death are unknown. Some researchers have proposed that ALS is a multisystem disease caused by a synaptic network failure [90]. This notion further deepens the mystery of why only motor neurons are targeted in network failure models.

NEURONAL VULNERABILITY IN HUNTINGTON DISEASE (HD)

HD, also called Huntington chorea, is characterized by involuntary jerking, impaired walking, and increased muscle activity. It is caused by a CAG expansion mutation in the huntingtin (*HTT*) gene that produces glutamine (poly-Q) expanded proteins (mHTT) [91]. Despite its ubiquitous expression, mHTT promotes neuronal death in the striatum, which exhibits the most striking pathology in HD [92]. As the disease progresses, the neurons in the cerebral cortex also degenerate [93]. Within the striatum,

the medium spiny neurons (MSNs), the most abundant neurons, degenerate; however, interneurons are relatively spared [94,95]. Evidence has indicated that loss of the cortico-striatal connection, which delivers brain-derived neurotrophic factor (BDNF) to the striatum, may be the cause of MSN degeneration in the striatum [96]. It has been demonstrated that depletion of BDNF could worsen, and repletion of BDNF could rescue, HD pathology in mice [97]. BDNF, however, cannot prevent the loss of olfactory neurons in R6/2 mouse models of the disease [98]. In terms of mechanisms, it is thought that mHTT blocks BDNF delivery to the striatum [99]. Like AD, dysfunction of BBB is also linked to play a role in HD [100]. Loss of cannabinoid receptors, impairment of Na^+/K^+ ATPase, diminished mitochondrial complex II and III activity, and high dopamine concentration in basal ganglia are suggested to play a role in MSN loss [101,102]. The mouse model in which mHTT is expressed selectively in the striatum of MSN promotes motor dysfunction and abnormalities, including intranuclear inclusion bodies, motor impairment, and changes in striatal gene expression, without altering the levels of BDNF [103,104]. Studies have also indicated that expression of mHTT in both the cortex and the striatum is necessary in severe neurodegeneration, suggesting cell-cell interactions [105,106]. Thus, while it is widely known that the cortex and the striatum are the most vulnerable regions, the mechanisms by which it occurs remain unclear.

Intriguingly, selective somatic expansion of CAG in mHTT in the striatum has been suggested to play a role in neuronal vulnerability. Instability of CAG repeats can be passed from generation to generation through maternal transmission and can also occur in peripheral regions, including the blood, kidneys, and colon [107,108]. Mice that contains 72-82 CAG repeats in huntingtin show high levels of CAG repeat variations in many tissues; for instance, a high level of CAG expansion mutation occurs in striatal cells (ranging from 88-166 CAG) [109]. Similar somatic instability of CAG in huntingtin has been found in human HD patient tissue [110]. Proteins such as 7,8-dihydro-8-oxo-guanine (8-oxo-G) glycosylase (OGG1) and mismatch repair protein MutSβ are implicated in CAG expansion, but these proteins and their activities are ubiquitously present; thus, if and how they promote neuronal vulnerability in HD remains unknown [111]. Transcriptional dysregulation has been implicated in neuronal vulnerability in HD; however, this alone appears to be insufficient, as similar dysregulation of genes was observed in both MSN, which degenerates in HD, and interneurons, which do not degenerate in HD [112]. Glutamate excitotoxicity via the altered expression or overactivation of synaptic and extrasynaptic NMDA receptors in the MSN, which leads to increased calcium influx, has been reported to play a role in neuronal vulnerability in HD

[113]. Some reports have indicated that mHTT in glia is damaging to neurons and thus increases glutamate excitotoxicity [113]. Surprisingly, however, HD mouse models have been shown to be resistant to excitotoxicity, raising the question of how excitotoxicity might be the primary cause of neuronal vulnerability in HD [114]. Additionally, while receptors related to glutamate excitotoxicity are expressed abundantly in the hippocampus and cerebellum, these are not the primary sites of degeneration in HD [115].

Mitochondrial energy impairment by mHTT, such as reduced ATP production, loss of cellular respiration, and reduced PGC-1α, a regulator of mitochondrial biogenesis, has also been implicated in striatal neuron vulnerability [116]. Consistent with this, although a global loss of PGC-1α indicated striatal degeneration, MSN-specific loss of PGC-1α did not elicit neurodegeneration [117,118]. Additionally, PGC-1α is a ubiquitous protein; thus, how it selectively affects MSN in HD remains unclear [119]. A recent study indicated that the striatum is enriched in fatty acids and thus increases ROS production via astrocytes, whereas the cerebellum, which is devoid of fatty acids, fails to produce ROS and is thus resistant to damage [120]. Evidence that suggests differential fatty acid distribution is the cause of neuronal vulnerability is attractive; however, it remains to be seen whether the striatum is the only region that contains such detrimental fatty acids, and if so, why. Finally, although the striatum is the primary region in which degeneration occurs, it should be noted that the globus pallidus (GP), a part where striatum projects, has also been shown to degenerate in HD patients [121]. Whether GP loss is a primary or secondary event after striatal degeneration occurs remains unclear. Table 1 summarizes selected neurodegenerative diseases, genes and regions or neurons affected.

RHES AS A PROMOTER OF STRIATAL VULNERABILITY IN HUNTINGTON DISEASE

Our studies on HD revealed that Rhes, a striatal enriched protein, may play a crucial role in HD [122]. Rhes is a small GTPase family of proteins that consists of SUMO E3 ligase activity and attaches SUMO (small-ubiquitin-like modifiers) to mHTT, resulting in the formation of more soluble forms of mHTT and thus leads to cellular toxicity [123]. Our model, which is supported by other data, suggests that Rhes and mHTT may define the mechanisms of striatal vulnerability in HD. Consistent with this, we demonstrated that deletion of Rhes improves the HD phenotype, whereas overexpression of Rhes worsens the HD phenotype in mouse models of HD [124]. Several independent studies have implicated a toxic role for Rhes in HD [123,124]. Despite experi-

Table 1. Selected neurodegenerative diseases, genes and regions or neurons affected.

Neurodegenerative disease	Sporadic/*genetic*	Genes involved	Most vulnerable regions/neuron
Alzheimer disease	~95%/*5%*	*APP*, *PSEN*	Entorhinal cortex / hippocampus [2]
Parkinson disease	~90%/*10-15%*	*SNCA*, *PINK1*, *Parkin*	Substantia nigra [144]
Amyotrophic lateral sclerosis	~90%/*5-10%*	*SOD1*, *C9orf72*, *FUS* and others	Motor neurons [145]
Huntington disease	*100%*	*HTT*	Medium spiny neurons [122]

mental evidence linking Rhes to mHTT, the molecular mechanisms by which Rhes and mHTT promote cellular toxicity remain unclear. Our recent serendipitous finding that Rhes moves from cell-to-cell further deepened the mystery [125]. We found that Rhes induces the formation of tunneling nanotube (TNT)-like cellular protrusions, called "Rhes tunnels," through which it self-transports, as well as the cell-to-cell transport of mHTT [125]. These findings raise some critical questions that remain a future challenge. What is the physiological significance of Rhes-mediated cell-to-cell movement of mHTT, and if such intercellular transport exists *in vivo*, how does it contribute to striatal vulnerability? Recent study also implicated Rhes in mutant tau-mediated pathology [126]. Mutant Tau is also transported between cells [127].

Nevertheless, a significant number of *in vivo* studies have suggested neuron-to-neuron migration of mHTT in both HD animal models and human HD patients. mHTT aggregates have been found in healthy striatal cell transplants in the striatum of HD patients [128]. Healthy human neurons were found to contain mHTT when co-cultured with HD mouse brain slices [129]. In *Drosophila*, mHTT was found to spread from olfactory receptor neurons to various parts of the brain [130]. Similarly, human mHTT was found in the striata of normal mice that had received intraventricular placement of human HD neurons [131]. Our finding that Rhes engineer membranous tunnels, which serve as "highways" for cell-to-cell transport of Rhes and mHTT, provides a new conceptual advancement in the understanding of Rhes signaling in the striatum and its vulnerability in HD. Thus, it is essential to investigate whether Rhes tunnels could serve as a significant route for the transport of mHTT in animal models of HD. We found that Rhes induces TNT-like protrusions both with and without mHTT. Thus, it is possible that mHTT interferes with or obstructs cargo transportation via Rhes tunnels, thus producing a "traffic jam" in the striatum and, ultimately, its selective degeneration in HD. Although the exact role of Rhes tunnels remains unknown, we found that Rhes may regulate mitophagy, wherein the damaged mitochondria are removed by the autophagy process via Rhes tunnels. We discovered that Rhes can travel via Rhes tunnels from healthy cells to cells that show mitochondrial damage and interact there with damaged mitochondria via the mitophagy receptor Nix [132]. The link between Rhes and mitophagy has *in vivo* relevance for striatal vulnerability in a mitochondrial toxin model, 3-nitropropionic acid (3-NP), a known inhibitor of mitochondrial complex II (succinate dehydrogenase, SDHA) [132]. Despite the fact that 3-NP blocks SDHA in the cortex and other peripheral tissues, it degenerates striatal neurons; however, the mechanisms for this are unclear [133]. We indicate that Rhes and 3-NP interaction is critical for such selective lesions [132,133]. We propose a possibility that analogous to Rhes and 3-NP interactions, Rhes and mHTT together participate in mitochondrial damage in the striatum. Because Rhes solubilizes and transports mHTT [123] during mitochondrial stress, Rhes and mHTT migrate and interact with neighboring cells to promote excessive mitophagy that may cause striatal death in HD. These notions should be experimentally verified in further studies. We also showed that mHTT elicits mammalian target of rapamycin (mTOR) signaling, which worsens HD phenotypes [134]. Rhes binds to mTOR and increases mTORC1 activation [135], which can regulate TNT formation in astrocyte/neuron culture [136]. Therefore, Rhes and mHTT together may participate in upregulating mTOR signaling in the striatum and regulate the formation of Rhes tunnels. A growing number of studies have demonstrated that neurodegenerative disease-linked proteins use TNTs for transmission and spreading [137]. Tau fibrils are transported via TNTs in HeLa and CAD cells [138,139]. Similarly, α-synuclein has been shown to be efficiently transported via TNTs in multiple cell types [140,141]. Although Rhes cannot cell-to-cell transport wild-type Tau [142], a possibility that it can transport mutant tau via TNTs-like protrusion cannot be ruled out. How cell-to-cell transmission may participate in neuronal vulnerability in neurodegenerative disease remains to be determined.

CONCLUDING REMARKS

We understand very little about the mechanisms of selective vulnerability in neurodegenerative diseases. Therefore, there is an urgent need to identify targets

and develop therapies to halt neurodegeneration. More detailed mechanistic studies that addresses the selective neuronal vulnerability is necessary to identify disease targets and thus cure these diseases. Patient's neural cells derived from induced pluripotent stem cells or human embryonic stem cells are also considered as important sources for studying disease mechanisms and drug discovery [143]. Collectively, it remains a mystery why only selected regions of the brain are primarily degenerated in neurodegenerative diseases. It has become somewhat accepted that more than one mechanism is involved in the onset of neuronal vulnerability; however, it is tempting to predict that a "first" insult triggers a long-term "tsunami" in the disease progression. Findings demonstrating that disease-causing proteins can be transported between cells have further increased the complexity of selective neuronal vulnerability in neurodegenerative diseases. Overall, the mystery surrounding neurodegenerative diseases can be solved if we can resolve and identify the mechanisms that are visible as well as hidden molecular players.

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