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Review

Aberrant protein *S*-nitrosylation contributes to the pathophysiology of neurodegenerative diseases

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ABSTRACT

Nitric oxide (NO) is a gasotransmitter that impacts fundamental aspects of neuronal function in large measure through *S*-nitrosylation, a redox reaction that occurs on regulatory cysteine thiol groups. For instance, *S*-nitrosylation regulates enzymatic activity of target proteins via inhibition of active site cysteine residues or via allosteric regulation of protein structure. During normal brain function, protein *S*-nitrosylation serves as an important cellular mechanism that modulates a diverse array of physiological processes, including transcriptional activity, synaptic plasticity, and neuronal survival. In contrast, emerging evidence suggests that aging and disease-linked environmental risk factors exacerbate nitrosative stress via excessive production of NO. Consequently, aberrant *S*-nitrosylation occurs and represents a common pathological feature that contributes to the onset and progression of multiple neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. In the current review, we highlight recent key findings on aberrant protein *S*-nitrosylation showing that this reaction triggers protein misfolding, mitochondrial dysfunction, transcriptional dysregulation, synaptic damage, and neuronal injury. Specifically, we discuss the pathological consequences of *S*-nitrosylated parkin, myocyte enhancer factor 2 (MEF2), dynamin-related protein 1 (Drp1), protein disulfide isomerase (PDI), X-linked inhibitor of apoptosis protein (XIAP), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) under neurodegenerative conditions. We also speculate that intervention to prevent these aberrant *S*-nitrosylation events may produce novel therapeutic agents to combat neurodegenerative diseases.

Contents

Introduction

Neurodegenerative disorders, such Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are

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associated with an insidious and progressive decline in neuronal synaptic function and eventually lead to neuronal cell death. Additional common key pathological features of neurodegenerative diseases include excessive generation of oxidative and nitrosative stress, accumulation of misfolded proteins (e.g., α-synuclein and amyloid-β [Aβ]), appearance of dysfunctional mitochondria, and increased synaptic damage. Historically, neurodegenerative diseases have been divided into two major categories: "hereditary" forms, caused by rare disease-causing genetic mutations, and much more common "sporadic" forms, possibly triggered by exposure to unknown environmental risk factors that produce excess reactive oxygen and nitrogen species (ROS/RNS). Additionally, recent studies have raised an intriguing theory that, in a large population of 'sporadic' cases, a particular genetic predisposition can augment the effect of environmental toxins via enhancement of ROS/RNS generation; this gene by environment effect (G×E) impacts the susceptibility of individuals to the disease (Cannon and Greenamyre, 2013; Elbaz et al., 2007; Ross and Smith, 2007; Ryan et al., 2013).

ROS and RNS are reactive molecules implicated both in physiological and pathological processes of brain function, depending on the severity and length of the ROS/RNS-associated stress in the brain. Among these free radical species, aberrantly increased generation of nitric oxide (•NO)-related species appears to accelerate the manifestation of key neuropathological features of disease. One well-established molecular mechanism entails the chemical reaction of an NO moiety with the sulfhydryl groups of target proteins (Hess et al., 2005; Nakamura et al., 2013). This type of posttranslational modification leads to the formation of *S*-nitrosothiols (R-SNO, where R denotes an organic group), producing *S*-nitrosylated proteins (SNO-proteins). Additionally, through reaction with superoxide anion ($O_2^{\bullet -}$), NO can form highly reactive peroxynitrite ($ONOO^-$). One way that peroxynitrite alters protein activity is via another type of posttranslational modification involving nitration of tyrosine residues (i.e., addition of a nitro group [$-NO_2$]) to form nitrotyrosine, typically contributing to cell death (Ischiropoulos et al., 1992). For instance, distinct from S-nitrosylation, α-synuclein itself can also be nitrated on critical tyrosine residues (to form nitrotyrosine), contributing to its aggregation (Giasson et al., 2000).

Protein *S*-nitrosylation represents a prominent redox reaction mediating NO signaling under both physiological and pathophysiological conditions. In this review, we mainly focus on the pathological role of aberrant protein *S*-nitrosylation that contributes to neurodegenerative conditions. We summarize recent findings on key SNO-proteins (e.g., parkin, myocyte enhancer factor 2 [MEF2], dynamin-related protein 1 [Drp1], protein disulfide isomerase [PDI], X-linked Inhibitor of apoptosis protein [XIAP], and glyceraldehyde-3-phosphate dehydrogenase [GAPDH]) that are involved in neurodegenerative disorders (Fig. 1) (Cho et al., 2009; Hara et al., 2005; Nakamura et al., 2010; Okamoto et al., 2014; Ryan et al., 2013; Uehara et al., 2006). Additionally, this review proposes the concept that aberrant formation of SNO-proteins, engendered by environmental toxin-induced nitrosative and oxidative stress, contributes to the vast majority of sporadic cases of neurodegenerative diseases. We speculate that *S*-nitrosylation contributes to the disease process onset via (i) mimicking rare genetic mutations seen in familial forms of neurodegenerative disorders, or (ii) lowering the threshold for the effects of genetic variants.

Generation of NO in the brain

Under physiological conditions, mammalian cells produce ROS/RNS at low levels, sufficient to affect diverse aspects of intracellular signaling pathways. For example, via activation of soluble guanylate cyclase or formation of SNO-proteins, NO can regulate endothelial permeability, inflammation, and relaxation/vasodilation of smooth muscle cells (Hess et al., 2005; Tousoulis et al., 2012). In neuronal tissues, NO can mediate both physiologic and pathologic pathways. For instance, low levels of NO modulate normal neuronal processes such as long-term potentiation and long-term depression, thus contributing to learning and memory formation (Haley et al., 1992; Izumi et al., 1992; Schuman and Madison, 1991; Shibuki and Okada, 1991). In addition, in response to neurotrophic growth factors, NO enhances the expression of CREB target genes to exert cellular effects (Contestabile, 2008; Riccio et al., 2006). In contrast, high and prolonged generation of NO can contribute to the pathophysiology of neurodegenerative diseases as discussed below.

In mammalian cells, NO synthases (NOSs) generate NO during the enzymatic conversion of L-arginine and molecular oxygen to L-citrulline, a process that requires several important cofactors, such as NADPH and calcium–calmodulin (Martinez-Ruiz et al., 2011). There are three members of the NOS family, including neuronal NOS (nNOS, or NOS1), which is constitutively expressed in neurons. Other relevant forms of NOS in the brain are inducible NOS (iNOS, or NOS2), which can be activated by inflammatory stimuli, and endothelial NOS (eNOS, or NOS3), which has lower expression in the brain. nNOS-mediated generation of NO

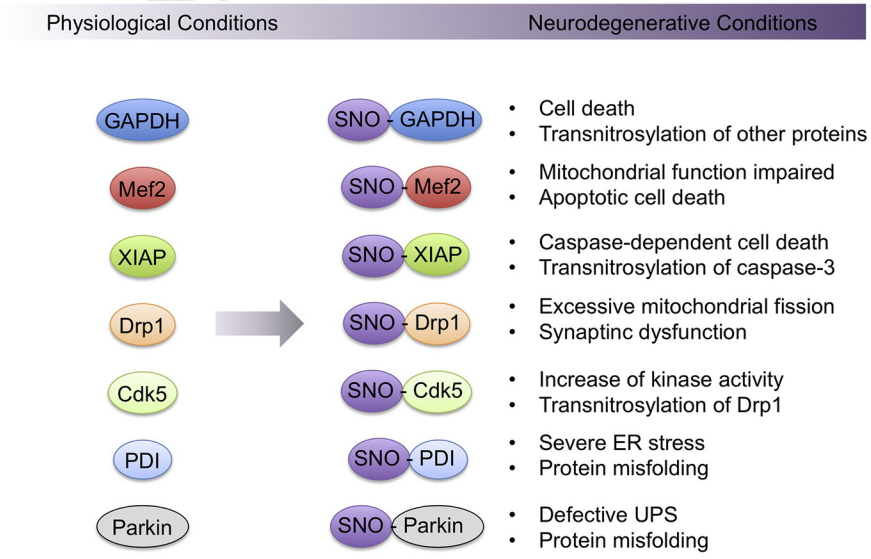

Fig. 1. Aberrantly *S*-nitrosylated proteins in neurodegenerative diseases. Summary of the proteins discussed in this review, including the effect of *S*-nitrosylation on their function in neurodegenerative disorders.

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typically entails activation of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors (NMDARs) (Fig. 2A). Specifically, both synaptic and extrasynaptic glutamate release activate NMDARs, producing Ca^{2+} influx into the neuron and leading to nNOS activation. There are two types of NMDARs, which can have opposite effects on neuronal processes: physiological activation of synaptic NMDARs (sNMDARs) leads to neuroprotective effects, while activation of extrasynaptic NMDARs (eNMDARs) manifests neurodegenerative effects (Molokanova et al., 2014; Talantova et al., 2013). $A\beta_{1-42}$ oligomers, which are thought to contribute to synaptic dysfunction in AD, trigger an increase in neuronal NO concentration predominantly via stimulation of eNMDARs (Molokanova et al., 2014; Talantova et al., 2013). Via this mechanism and others, eNMDAR activation contributes to neuronal pathophysiology by producing protein misfolding and dendritic spine loss. In addition, Aβ oligomers and toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can induce iNOS expression in astrocytes, macrophages, and microglia, thus increasing NO levels in the degenerating brain (Liberatore et al., 1999; Medeiros et al., 2007; Nakamura et al., 2013).

The balance of ROS/RNS production and various cell defense systems, such as antioxidant enzymes and molecular chaperones, influences NO levels in the brain. Mitochondrial toxins such as environmental pesticides (e.g., rotenone, paraquat, and maneb), genetic mutations, or even normal brain aging can cause deregulation of these defense systems. Neurons, as compared to astrocytes, are thought to be particularly sensitive to stress caused by excessive RNS/ROS because they have lower levels of antioxidants like glutathione. Moreover, for the maintenance of synapses and neuronal circuit activity, neurons require a high mitochondrial metabolism, which constitutively generates ROS/RNS. Once an imbalance between ROS/RNS production and cell antioxidant systems occurs, increased oxidative/nitrosative stress can precipitate the accumulation of damaged or modified molecules, which promote the dysregulation of various signaling and metabolic pathways to further enhance ROS/RNS generation.

The deletion of the *iNOS* gene in AD mouse models expressing APPSw or APPSwDI (amyloid precursor protein Swedish K760N/M671L, Dutch E693Q, and Iowa D694N mutations) aggravates amyloid pathology in the hippocampus without affecting the level of Aβ, causing mice to perform poorly in spatial memory and learning tasks compared to AD mice with intact iNOS (Colton et al., 2006; Wilcock et al., 2008). In contrast to well-known mouse models of AD, the iNOS-deficient APPSwDI mouse (APPSwDI/$iNOS^{-/-}$) also manifests aggregation and hyperphosphorylation of native mouse tau. Additionally, this APPSwDI/$iNOS^{-/-}$ model is one of the few transgenics that display neuronal loss in AD-relevant brain regions. However, another study in which iNOS was knocked out in the APP-presenilin 1 (PS1) double-transgenic mouse model of AD reported greater longevity of iNOS-deficient APP-PS1 mice, diminished formation of Aβ, and less deposition of plaques compared to APP-PS1 mice that expressed iNOS (Nathan et al., 2005). Knockout of iNOS also reduced the cognitive deficits evoked by intracerebroventricular injection of oligomerized Aβ (Medeiros et al., 2007). These contradictory results may simply stem from the use of different AD mouse models, but they also suggest that NO may have a complicated role in the pathogenesis of AD, acting as either a neuroprotective or neurodestructive factor depending on the timing, duration, and levels of its production.

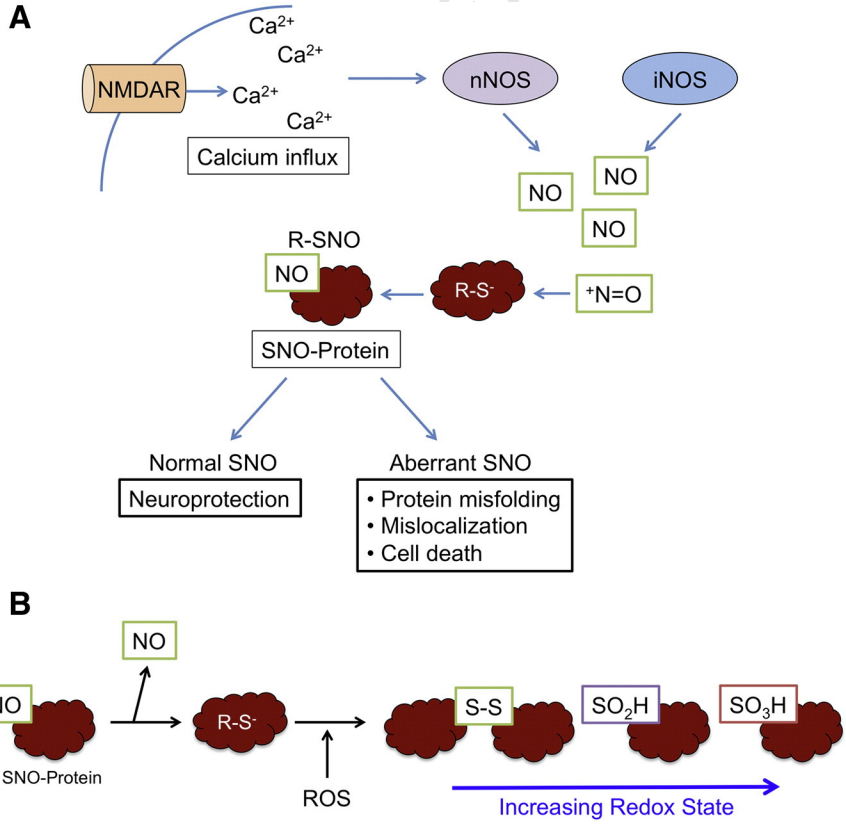

Fig. 2. NO and *S*-nitrosylation pathways. (A) After NMDAR activation, calcium influx into the neuron activates nNOS. Additionally, in several neurodegenerative disorders, macrophages generate NO from iNOS. These enzymes induce the production of NO species, which can be adducted to cysteine thiol groups to generate SNO-proteins. NO levels may be greatly increased by environmental factors, such as pesticides that are mitochondrial toxins. Physiological NO levels typically afford neuroprotection; aberrant R-SNO formation due to high levels of NO leads to protein misfolding, dysregulated protein function, mislocalization of protein, and eventually cell death. (B) Denitrosylation and further oxidation of SNO-proteins. SNO-proteins may spontaneously denitrosylate or be denitrosylated by enzymes such as thioredoxin. Once the NO moiety is removed from the protein, the same cysteine residue may react with ROS, possibly because SNO-induced conformational changes in the protein make it more reactive, forming sulfenic acid (–SOH), sulfinic acid ($–SO_2H$), and sulfonic acid ($–SO_3H$) derivatives. Alternatively, if a vicinal thiol is present near the SNO-cysteine, a disulfide bond may be formed when NO leaves the thiol. Proteins with *S*-nitrosylated cysteines may then aggregate, for example, if intermolecular disulfide bonds aberrantly form between them during denitrosylation.

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In PD models, knockdown of iNOS provides a protective effect against MPTP neurotoxicity, which mimics PD pathology and can induce the expression of iNOS in astrocytes, macrophages, and microglial cells (Liberatore et al., 1999). Moreover, in models of cerebral ischemia, nNOS knockout mice displayed smaller infarct size and fewer neurological deficits following middle cerebral artery occlusion, whereas eNOS deficient mice develop larger infarcts (Huang et al., 1994). Hence, these PD and stroke data suggest that NO derived from iNOS or nNOS mediates pathological signaling in these models.

NO/S-nitrosylation chemistry

S-Nitrosylation is a post-translational modification that can regulate a broad range of protein functions, similar to phosphorylation. It represents the covalent addition of the NO moiety to a cysteine thiol group, resulting in a SNO-protein. The chemical reaction of *S*-nitrosation is thought to involve a nitrosonium cation (NO^+) intermediate reacting with a thiolate anion (RS^-), requiring transition metal-catalyzed oxidation of free radical NO (•NO) (Lipton et al., 1993; Martinez-Ruiz et al., 2011; Nakamura et al., 2013). In recent years, the term "*S*-nitrosylation" has generally been used to reflect the biological consequences of the *S*-nitrosation chemical reaction. An additional or alternative nitrosative mechanism by which an NO group may contribute to formation of R-SNO in intact cells may involve radical recombination between •NO, which has a single electron in its outer pi molecular orbital, and a thiyl radical (RS•) (Martinez-Ruiz et al., 2011; Nakamura et al., 2013; Smith and Marletta, 2012). The *S*-nitrosothiol thus formed modulates the function of target proteins through conformational changes, alteration of protein activity, or regulation of protein–protein interactions (Hess et al., 2005; Stamler et al., 2001).

Any free thiol group is theoretically capable of being *S*-nitrosylated (and will be, if sufficient exogenous NO is added to the system), but in practice, physiologically (or even pathophysiologically) relevant levels of NO interact with only certain thiol groups (Hess et al., 2005; Seth and Stamler; Stamler et al., 2001; Stamler et al., 1997). This specificity is determined in part by neighboring protein structure: thiol groups near the regions that interact directly with NOS are more likely to be *S*-nitrosylated because of close proximity to the source of NO generation. Also, the "SNO-motif," characterized by acid/base amino acids within 6–8 Å from the target cysteine, facilitates SNO modification (Doulias et al., 2010). These acidic/basic amino acid groups facilitate deprotonation of the thiol group, which promotes *S*-nitrosylation of target thiols.

Under basal physiological conditions, low levels of NO support normal neuronal functions, including synaptic transmission, neuronal survival and energy homeostasis, via SNO-mediated regulation of specific target proteins. These SNO-proteins may be localized near NOSs, and contain SNO-sensitive thiol groups surrounded by full SNO motifs (Stamler et al., 1997). In contrast, under pathological conditions a high concentration of NO can induce *S*-nitrosylation of cysteine thiols that have only a partial SNO motif and may be located more distant to the NO source; these aberrantly *S*-nitrosylated proteins can trigger cell-destructive processes, promoting neurodegeneration in a number of disease states (Nakamura et al., 2013).

The extent of protein *S*-nitrosylation relies not only on the rate of *S*-nitrosylation but also on the rate of denitrosylation. Because often NO makes a very good 'leaving group,' some SNO-proteins are thought to spontaneously lose NO groups from their Cys thiols in a non-enzymatic manner. However, recent studies have demonstrated that at least certain sets of SNO-proteins, particularly those carrying full SNO-motifs or formed under pathophysiological conditions, are relatively stable (Benhar et al., 2009; Gu et al., 2002; Uehara et al., 2006). Denitrosylating enzymes, such as thioredoxin and *S*-nitrosoglutathione reductase, counterbalance the abundance of these stable SNO-proteins and thus can help regulate SNO signaling cascades. Moreover, as a consequence of protein–protein transnitrosylation, NO-donating proteins can be denitrosylated at the same time that the companion protein is *S*-nitrosylated. *S*-Nitrosylation often impacts protein conformation. When a protein is denitrosylated, we have found empirically that the exposed thiol often displays increased susceptibility to reaction with ROS to form sulfenic, sulfinic or sulfonic acid derivatives (Gu et al., 2002; Uehara et al., 2006). *S*-Nitrosylation of one thiol can also precipitate facile disulfide formation with a vicinal thiol and hence denitrosylation of the initial reactive thiol (Fig. 2B). In addition, when levels of NO are high, NO can essentially prevent disulfide bond formation between two vicinal cysteine thiols via *S*-nitrosylation of both thiol groups (Lipton et al., 2002; Uehara et al., 2006).

Aberrant SNO-proteins formed in neurodegenerative diseases

S-Nitrosylation of parkin

Parkin is an E3 ubiquitin ligase that has been linked to a rare form of autosomal recessive juvenile-onset parkinsonism (AR-JP) (Kitada et al., 1998). Mutations in the *parkin* gene (*PARK2*) can underlie familial AR-JP (Lucking et al., 2000) and often affect its E3 ligase activity that directs misfolded proteins to the ubiquitin–proteasome pathway for degradation (Sriram et al., 2005). Consistent with this notion, protein substrates of parkin E3 ligase abnormally accumulate during neurodegeneration (Dawson, 2006). Interestingly, parkin null mice show no significant PD-like phenotypes in the absence of an exogenous stressor; the absence of appropriate environmental triggers, compensation by other ubiquitin E3 ligases, or species-specific function of parkin may account for the lack of robust signs of parkinsonism or other neurological deficit in the absence of an inciting event (Goldberg et al., 2003; Itier et al., 2003; Perez and Palmiter, 2005; Von Coelln et al., 2004). Along these lines, our group and others have revealed that PD-linked environmental neurotoxins such as pesticides and herbicides (e.g., rotenone and paraquat), which generate excessive amounts of ROS and NO as alluded to above, compromise the neuroprotective function of parkin via formation of SNO-parkin (Chung et al., 2004; Yao et al., 2004). When *S*-nitrosylated, the E3 ligase activity of parkin is initially increased, but subsequently inhibited possibly via autoubiquitination or additional *S*-nitrosylation of additional cysteine thiol groups in parkin. Moreover, increased levels of ROS or NO can induce further oxidation of cysteine residue(s) on parkin to block its E3 ligase activity (Chung et al., 2004; Meng et al., 2011; Yao et al., 2004). NO-mediated inhibition of parkin activity decreases ubiquitin proteasomal degradation of damaged or misfolded proteins, potentially contributing to the appearance of abnormal protein aggregates, such as Lewy bodies. *S*-Nitrosylation of parkin also contributes to pathways leading to neuronal cell death (Chung et al., 2004; Lipton et al., 2005; Yao et al., 2004).

Emerging evidence suggests that parkin also plays a major role in mitophagy, the selective engulfment of mitochondria by autophagosomes with subsequent lysosomal fusion and degradation. Parkin, in conjunction with PINK1 kinase, whose gene can also be mutated in certain forms of familial PD, helps ensure mitochondrial quality control through the removal of damaged mitochondria (Youle and van der Bliek, 2012). In this scenario, PINK1 accumulates on the damaged mitochondria and subsequently recruits parkin from the cytosol to the mitochondria where PINK1 phosphorylates and activates parkin's E3 ligase activity. Activated parkin then ubiquitinates numerous mitochondrial outer membrane proteins to promote flux through the mitophagy pathway. PINK1 reportedly also phosphorylates Mitofusin2 and Miro1, which serve as receptors for parkin recruitment to the mitochondria (Wang et al., 2011). Recent studies also demonstrated that PINK1 phosphorylates mono-ubiquitin; the phosphorylated mono-ubiquitin then binds to parkin and unlocks parkin's autoinhibition, accelerating its E3 ligase activity (Kane et al., 2014; Koyano et al., 2014). Additionally, exposure of cells to mitochondrial-damaging reagents, such as carbonyl cyanide m-chlorophenyl hydrazone (CCCP) or rotenone, leads to SNO-parkin formation. The initial increase in E3 ligase activity upon

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S-nitrosylation upregulates mitophagy, whereas subsequent attenuation of parkin activity impedes mitophagy (Ozawa et al., 2013).

In addition to its E3 ligase activity, parkin acts as a p53 transcriptional repressor, thus preventing p53-associated neuronal cell death (da Costa et al., 2009). Our group recently demonstrated that *S*-nitrosylation of parkin decreases its binding affinity to the p53 promoter, resulting in enhanced p53 expression and p53-mediated cell death. This pathway appears to be active in PD, as PD mouse models and human PD patient brains manifest increased levels of both SNO-parkin and p53 expression, consistent with the notion that SNO-parkin-mediated activation of p53 provides a feed-forward mechanism for neuronal damage, contributing to the pathogenesis of PD (Sunico et al., 2013).

Collectively, the published literature suggests that *S*-nitrosylation affects parkin activity in a biphasic manner; NO initially enhances parkin E3 ligase activity followed by its inactivation. The initial and transient upregulation of parkin activity may represent a negative feedback loop to protect neurons from mild nitrosative stress. In contrast, chronic inhibition of parkin mediated by prolonged NO/RNS stress impairs not only its E3 ligase but also its transcriptional p53 repressor function, contributing to the appearance of misfolded or damaged proteins, deterioration of mitochondrial quality control, and an increase in neuronal cell death. Thus, these findings raise the interesting possibility that excessive nitrosative/oxidative stress, due to an exposure to environmental risk factors, can trigger neurodegenerative phenotypes in the common "sporadic" form of PD, via mimicking the effects of rare genetic mutations found in AR-JP and other hereditary forms of PD (Yao et al., 2004; Uehara et al., 2006; Sunico et al., 2013; Ryan et al., 2013).

S-Nitrosylation of MEF2 and other transcription factors

Myocyte enhancer factor 2 proteins (MEF2A-D) belong to the MADS (MCM1, Agamous, Deficiens, SRF) box class of transcription factors. Although MEF2 is known as a myogenic factor, one isoform, MEF2C, was originally discovered in the brain (Lipton et al., 1993). Accordingly, MEF2 regulates cell survival, apoptosis and proliferation in several organ systems, including the brain (Potthoff and Olson, 2007). MEF2 isoforms are expressed in multiple regions of the brain where they govern neurogenesis and neuronal survival via transcriptional activation of several downstream pathways (Flavell et al., 2006; Li et al., 2008; Mao et al., 1999; Okamoto et al., 2000; Okamoto et al., 2002; Okamoto et al., 2014; Ryan et al., 2013; Shalizi et al., 2006).

MEF2 contains two evolutionarily conserved cysteine residues (Cys39 and Cys41) in its DNA binding domain. We recently demonstrated that NO selectively *S*-nitrosylates Cys39 (Okamoto et al., 2014; Ryan et al., 2013). *S*-Nitrosylation of Cys39 prevents MEF2 from binding to the promoter region of downstream effector genes, thus inhibiting transcriptional activity. The decreased activity of SNO-MEF2 contributes to both impaired neurogenesis and neuronal cell damage/death (Okamoto et al., 2014; Ryan et al., 2013). Importantly, *S*-nitrosylation of the critical cysteine of MEF2 has been found to contribute to the pathophysiology of several neurodegenerative conditions, including PD, AD, and stroke. For instance, in PD models, exposure to PD-linked pesticides/mitochondrial toxins increases SNO-MEF2C levels in A9-type dopaminergic neurons derived from human induced pluripotent stem cells (hiPSCs) (Ryan et al., 2013). Human dopaminergic neurons carrying the *SNCA* gene (encoding α-syn) A53T mutation, which causes a hereditary form of PD, are more susceptible to environmental mitochondrial toxin/NO-associated cell death than isogenic control neurons. The human A53T dopaminergic neurons (designated A53T-hN) manifest aberrant formation of SNO-MEF2C at baseline and increasingly after toxin exposure, supporting the hypothesis that genetic and environmental interactions (G×E) contribute to the pathogenesis of PD. SNO-MEF2 levels are also greatly increased in experimental models of AD and cerebral ischemia (Okamoto et al., 2014). Importantly, SNO-MEF2 is also elevated in human diseased brain with these conditions (Okamoto et al., 2014).

To elucidate the link between redox-related changes in MEF2 activity and neuronal cell death, we investigated MEF2 downstream pathways in various disease models. Microarray enrichment analysis for affected transcriptional targets revealed that generation of SNO-MEF2 disrupts the MEF2-PGC1α pathway in the pesticide/mitochondrial toxin-exposed A53T-hN dopaminergic neuron model of PD (Ryan et al., 2013). Interestingly, however, additional MEF2C-regulated pathways are perturbed in other disease conditions, e.g., the antiapoptotic Bcl-xL pathway in AD and stroke animal models, thus contributing to neuronal cell death in cerebrocortical neurons (Okamoto et al., 2014). Moreover, we found that the neurogenesis pathway triggered by MEF2-induced transcription of the nuclear receptor TLX (homolog of the *Drosophila* tailless gene) is suppressed by *S*-nitrosylation of the MEF2A isoform. This nitrosylation reaction thus inhibits adult neurogenesis in AD model mice and presumably in human AD brains since SNO-MEF2A has been found there as well (Okamoto et al., 2014). Hence, redox modification of MEF2 can act as a 'molecular switch' to abrogate distinct transcriptional cascades, inhibiting either neurogenesis or neuronal survival depending on the cell types and their environment (Fig. 3). These findings support our hypothesis that aberrant *S*-nitrosylation of different MEF2 isoforms contributes at least in part to the pathology of both acute and chronic neurodegenerative diseases.

In addition to MEF2, NO is known to regulate the activity of other transcription factors by i) direct SNO modification of the transcription factor per se, or ii) *S*-nitrosylation of either interacting or upstream molecules in the same signaling pathway (Hess et al., 2005). For instance, NO can directly *S*-nitrosylate the transcription factor, NF-κB to decrease its DNA binding activity (Marshall and Stamler, 2001), whereas *S*-nitrosylation of IKKβ, JNK1, and ASK1 inhibits the activity of downstream transcription factors (Park et al., 2000, 2004; Reynaert et al., 2004). In certain cases, *S*-nitrosylation can promote transcription of the downstream targets. For instance, the transcriptional activity of HIF-1α increases upon *S*-nitrosylation at two separate cysteine residues that either stabilizes the protein or facilitates binding to its interacting partner (Cho et al., 2007; Li et al., 2007; Sumbayev et al., 2003; Yasinska and Sumbayev, 2003). As other examples, SNO modification of histone deacetylase 2 (HDAC2) aids its dissociation from chromatin, increasing acetylation of histones near downstream target genes, and subsequently promoting their transcription (Nott et al., 2008). *S*-Nitrosylation of HDM2 (mdm2 in mice), an ubiquitin E3 ligase that targets the transcription factor p53 for ubiquitin–proteasome system

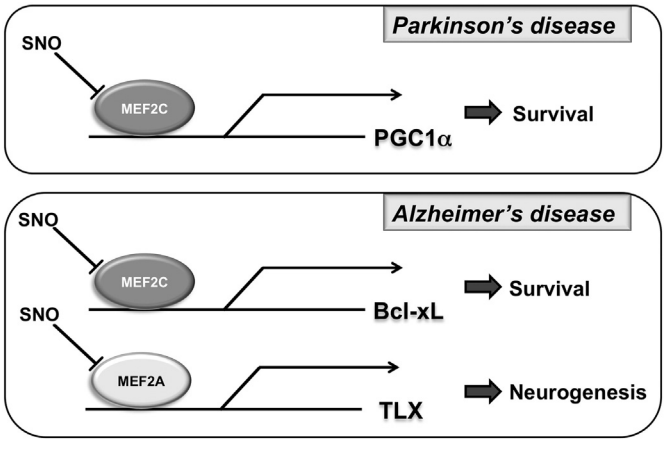

Fig. 3. Mechanism of action of SNO-MEF2 in neurodegenerative diseases. *S*-Nitrosylation/oxidation of MEF2 impairs its transcriptional activity and thus disrupts target gene expression, compromising neuronal survival and neurogenesis. Following *S*-nitrosylation of MEF2C, expression of the MEF2 target, PGC1α, is reduced in PD models, including hiPSC-derived dopaminergic neurons. In AD mouse models, *S*-nitrosylation of MEF2C led to decreased Bcl-xL expression, contributing to cerebrocortical neuron cell death. Additionally, formation of SNO-MEF2A disrupts neurogenesis in Alzheimer's models by decreasing the transcription of its target protein, TLX.

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(UPS)-dependent degradation, inhibits E3 ligase activity, thus activating p53 (Schonhoff et al., 2002). Moreover, NO dependent inactivation of Keap1 releases its binding partner Nrf2, facilitating its nuclear translocation and activating Nrf2-dependent gene transcription (Fourquet et al., 2010; Um et al., 2011). Although the effects of *S*-nitrosylation on these transcriptional regulators have been well studied, their pathophysiological relevance in neurodegenerative diseases is not yet fully understood.

S-Nitrosylation of Drp1 and Cdk5

Mitochondria are known as the powerhouses of eukaryotic cells as they generate energy through oxidative phosphorylation. Neurons in particular rely heavily on normal mitochondrial function to meet their high-energy demands. In addition to oxidative phosphorylation, mitochondrial activity depends on five important processes, namely: biogenesis, fission, fusion, transport, and mitophagy. In particular, the mitochondrial fission and fusion machineries are collectively termed mitochondrial dynamics, and are responsible for the shape, size, number, and distribution of mitochondria. In a number of neurodegenerative disorders, abnormal mitochondrial dynamics have been implicated in synaptic dysfunction and neuronal cell death (Chen and Chan, 2009).

A GTPase known as dynamin-related protein 1 (Drp1) plays a critical role in mitochondrial fission. Our group recently found that oligomeric Aβ peptide- and mutant huntingtin-induced nitrosative stress cause aberrant *S*-nitrosylation of Drp1 in models of AD and Huntington's disease (HD), respectively (Cho et al., 2009, 2010; Haun et al., 2013). The formation of SNO-Drp1 hyperactivates its GTPase activity associated with mitochondrial fission, leading to the generation of pathologically small, fragmented mitochondria that are functionally compromised. Moreover, non-nitrosylatable mutant Drp1 protected neurons from synaptic damage in AD and HD cell-based models. Additionally, our group and others have shown that Drp1 *S*-nitrosylation is significantly increased in human postmortem brains from AD and HD patients compared to control brains, suggesting that SNO-Drp1 might be a crucial factor in the pathophysiology of these diseases (Cho et al., 2009, 2010; Haun et al., 2013; Wang et al., 2009, 2012). Taken together, these findings indicate that aberrant *S*-nitrosylation of Drp1 causes mitochondrial fragmentation, thus decreasing mitochondrial function and compromising synaptic function in neurodegenerative conditions such as AD and HD.

Evidence suggests that cyclin-dependent kinase 5 (Cdk5) is an upstream regulator of mitochondrial dynamics, contributing to neuronal apoptosis (Medeiros et al., 2007). Cdk5 is a serine/threonine kinase that is highly expressed in post-mitotic neurons. Cdk5 itself is inactive, but becomes active upon binding to its regulatory subunit p35 or p39. Upon activation, Cdk5 can phosphorylate a number of important signaling proteins in neurons, including tau, MEF2 and ATM. Cdk5 has thus been implicated in various aspects of neuronal function ranging from neuronal development, differentiation, and plasticity to neurodegeneration (Ohshima et al., 1996). In neurodegenerative disorders, such as in AD, calpain-dependent truncation of p35 to p25 results in hyperactivation of Cdk5, which is capable of inducing synaptic injury and neuronal damage through hyperphosphorylation of tau, disruption of the cytoskeleton, and other pathways (Patrick et al., 1999). Concerning redox-regulated activity of Cdk5, we recently found that Cdk5 forms a complex with nNOS, facilitating *S*-nitrosylation of Cdk5 under Aβ-induced nitrosative stress conditions. *S*-Nitrosylation of Cdk5 hyper-activates its kinase activity, leading to dendritic spine loss and neuronal cell death in cell-based models of AD (Qu et al., 2011). Moreover, we found that SNO-Cdk5 levels are significantly increased in postmortem human AD brains compared to control brains. Interestingly, we recently demonstrated that SNO-Cdk5 also acts as an *S*-nitrosylase for Drp1, transnitrosylating an adducted NO group from Cdk5 to Drp1, to form SNO-Drp1. This led us to propose a unique molecular mechanism whereby nNOS-derived NO contributes to dendritic spine loss through a SNO-Cdk5-Drp1 transnitrosylation cascade (Qu et al., 2011). In conclusion, neurodegenerative disorders such as AD manifest increased levels of NO associated with aberrant formation of SNO-Cdk5 and SNO-Drp1, leading to the dysregulation of downstream pathways, synaptic dysfunction, and eventual neuronal loss.

S-Nitrosylation of PDI

S-Nitrosylation inhibits the activity of protein disulfide isomerase (PDI), a family of endoplasmic reticulum (ER) chaperone enzymes that mediates protein folding through thiol–disulfide exchange. Active in protein synthesis and maturation, this enzyme constitutes part of the cell defense system, and can be upregulated to attenuate the accumulation of misfolded proteins and decrease ER stress. *S*-Nitrosylation of PDI compromises this stress response, resulting in an increase in ubiquitinated proteins and contributing to neuronal cell death in various neurodegenerative disorders (Chen et al., 2012; Jeon et al., 2014; Obukuro et al., 2013; Uehara et al., 2006; Walker et al., 2010; Xu et al., 2014).

For example, our group initially demonstrated that SNO-PDI formation is significantly increased in the brains of patients with PD and AD, the pathology of which includes misfolded protein accumulation (Uehara et al., 2006). Rotenone, an environmental toxin linked to the development of Parkinson's-like symptoms, also contributes to the formation of SNO-PDI in cell-based models. This suggests that PDI is aberrantly *S*-nitrosylated under neurodegenerative conditions, leading to the accumulation of misfolded proteins (e.g., α-synuclein and synphilin) and severe ER stress, both of which mediate key pathological pathways leading to neuronal death (Jeon et al., 2014; Uehara et al., 2006; Walker et al., 2010; Xu et al., 2014). These pathways also trigger a mechanism called the unfolded protein response (UPR), which can lead to apoptosis if the level of aberrant proteins remains high. Consistently, PDI but not SNO-PDI can rescue cells from proteotoxicity, proteasome dysfunction, or prolonged UPR (Uehara et al., 2006).

Additionally, upon *S*-nitrosylation, PDI is unable to protect cells against the aggregation of mutant or misfolded superoxide dismutase 1 (SOD1) as seen in familial ALS. Structurally, wild-type SOD1 forms a homodimer, stabilized by a highly conserved intramolecular disulfide bond. In contrast, familial ALS-linked mutant SOD1 either forms monomers, in which the disulfide bonds are reduced, or insoluble multimers with extra disulfide bonds. Consequently, mutant SOD1 is partially mislocalized to the ER, is aggregated in intracellular inclusions, and thus contributes to cell death (Furukawa et al., 2006; Wang et al., 2006). Overexpression of PDI decreases mutant SOD1 aggregation, inclusion formation, and cell death, while knockdown of PDI increases mutant SOD1 inclusion formation, supporting the idea that PDI acts as a neuroprotective chaperone (Walker et al., 2010). *S*-Nitrosylation of PDI reverses these neuroprotective effects, leading to the accumulation of mutant SOD1 aggregation (Jeon et al., 2014). In cell culture models, mutant SOD1 increases the expression of iNOS, which triggers SNO-PDI formation and subsequent mutant SOD1 aggregation; treatment with Nω-nitro-L-arginine (L-NNA), a broad spectrum NOS inhibitor, attenuates these SNO-PDI-related cellular events (Chen et al., 2013). SNO-PDI has been found in spinal cords of animal models of ALS and stroke, as well as in lumbar spinal cord segments of human patients with sporadic ALS (Walker et al., 2010).

In summary, these findings suggest that in various neurodegenerative disorders PDI is aberrantly *S*-nitrosylated and loses its neuroprotective chaperone and isomerase activities. Thus, therapeutic agents that facilitate the specific denitrosylation of PDI could potentially decrease neuronal cell death associated with severe ER stress and protein misfolding. Moreover, because *S*-nitrosylation of PDI occurs only under degenerative conditions, SNO-PDI can also be considered as a possible biomarker for the diagnosis of several neurodegenerative diseases, including AD, PD, and ALS.

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S-Nitrosylation of caspases and XIAP

Caspases are cysteine-aspartic acid proteases responsible for the initiation and execution of apoptotic cell death. These enzymes are translated as zymogens, which must be proteolytically cleaved to be activated. Caspases require a single cysteine in their active site in order to function (Riedl and Shi, 2004). NO can *S*-nitrosylate caspases at their active-site cysteine, which inhibits their apoptotic function and promotes cell survival (Mannick et al., 1999, 2001; Tenneti et al., 1997).

X-linked inhibitor of apoptosis protein, or XIAP, directly binds to caspase-3, -7, and -9, and inhibits their activity. In addition, XIAP targets these caspases for ubiquitination and degradation, curtailing their apoptotic enzyme activity and thus contributing to neuroprotection (Holcik and Korneluk, 2001; Salvesen and Duckett, 2002; Vaux and Silke, 2005). XIAP is reportedly the most effective member of the inhibitor of apoptotic protein (IAP) family (Holcik and Korneluk, 2001; Salvesen and Duckett, 2002). Structurally, XIAP is made up of three amino-terminal BIR (baculoviral inhibitor of apoptosis repeat) domains, a UBA (ubiquitin associated) domain, and a carboxy-terminal RING finger. The BIR domains are responsible for XIAP's binding to caspases, while the RING finger represents the E3 ubiquitin ligase function (Salvesen and Duckett, 2002).

During nitrosative stress, this E3 ubiquitin ligase is *S*-nitrosylated, which abrogates its ability to inhibit caspase activity (Nakamura et al., 2010). Evidence suggests that SNO-caspase-3 (and perhaps SNO-caspase-7 and -9 as well) acts as a transnitrosylase to *S*-nitrosylate XIAP, thus transferring an NO group from caspase-3 to XIAP (Nakamura et al., 2010). This reaction represents a molecular switch within the cell, invoking the cell death pathway — after the transnitrosylation event, caspase-3 is freed from SNO-mediated inhibition to resume its pro-apoptotic function, while the newly formed SNO-XIAP is prevented from inhibiting caspases. Not surprisingly, increased SNO-XIAP has been found in brain samples from human patients with HD, PD and AD (Nakamura et al., 2010; Tsang et al., 2009). These findings support the notion that aberrantly *S*-nitrosylated XIAP contributes to the pathogenesis of several neurodegenerative diseases.

S-Nitrosylation of GAPDH

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is an enzyme that plays a role in the metabolism of glucose, transcriptional activation, and apoptosis. It is stably and constitutively expressed in most cells, and is thus considered a housekeeping gene. However, *S*-nitrosylation of GAPDH (at Cys 150 in mouse/rat or Cys152 in human) not only abolishes its catalytic activity as a glycolytic enzyme but also enables GAPDH to bind to and stabilize the ubiquitin E3 ligase, Siah1 (Hara et al., 2005; Padgett and Whorton, 1995; Sen et al., 2008). The nuclear localization signal of Siah1 facilitates entry of the GAPDH/Siah complex into the nucleus, where stabilized Siah1 contributes to degradation of nuclear substrates and initiates apoptotic signaling cascades; this sequence of events may contribute to the pathology of PD, HD, stroke, and potentially other neurologic disorders (Bae et al., 2006; Hara et al., 2006; Li et al., 2012). For instance, the GAPDH–Siah1 pathway facilitates translocation of mutant huntingtin protein (mtHtt) into the nucleus, which is in part responsible for neurotoxicity in HD (Bae et al., 2006).

In the nucleus, GAPDH binds to the acetyltransferase p300/CBP and stimulates acetylation of various target proteins (Sen et al., 2008). One of these target proteins is the tumor suppressor and transcription factor p53, acetylation of which occurs in response to cellular stress and DNA damage (Brooks and Gu, 2011). Acetylation of p53 at key sites promotes the expression of pro-apoptotic genes. Siah1 also upregulates ubiquitination of SUV39H1 (suppressor of variegation 3–9 homolog 1), the degradation of which facilitates acetylation of histone H3 and increases the transcription of CREB-target genes; these CREB-induced proteins enhance dendritic outgrowth (Sen and Snyder, 2011). Another consequence of SNO-GAPDH is its transnitrosylation of other nuclear proteins, such as SIRT1, HDAC2 and DNA-PK (Kornberg et al., 2010).

As a negative regulator of the SNO-GAPDH pathway, *S*-nitrosylated GOSPEL (*G*APDH's competitor *o*f *S*iah *P*rotein *E*nhances *L*ife) competitively binds to GAPDH instead of Siah1, preventing GAPDH nuclear translocation and subsequent neurotoxicity (Sen et al., 2009). Accordingly, SNO-GOSPEL provides a regulatory system that protects neurons from NMDAR-mediated excitotoxicity via binding to GAPDH and thus inhibiting the SNO-GAPDH-mediated apoptotic cascade (Sen et al., 2009).

The monoamine oxidase inhibitor R-(−)-deprenyl has been reported to exert neuroprotective effects in cell-based and rodent models of PD, and may slow PD progression in patients at early stages of the disease (Hara et al., 2006). At low nanomolar concentrations, this drug disrupts SNO-GAPDH–Siah1 interaction, thus blocking neurotoxicity in PD and excitotoxic models (Hara et al., 2006). Another mechanism for disrupting the SNO-GAPDH pathway involves SNO-GAPDH-mediated transnitrosylation of B23/nucleophosmin, which increases the interaction of SNO-B23 and Siah1, while decreasing SNO-GAPDH levels. Consequently, this transnitrosylation reaction attenuates the E3 ligase activity of Siah1 and abrogates the apoptotic effect of the pathway (Lee et al., 2012).

Recent studies have discovered a specific role of iNOS activity in the formation of SNO-GAPDH. In the cytosol, GAPDH is capable of forming a protein complex with iNOS, facilitating iNOS activation via the insertion of a heme group into this type of NOS. The close proximity of activated iNOS and GAPDH facilitates formation of SNO-GAPDH; however, SNO-GAPDH does not bind to iNOS and thus is unable to further enhance iNOS activation (Chakravarti et al., 2010). Hence, this pathway may represent a negative feedback loop under pathological conditions, limiting the formation of NO during nitrosative stress. In addition, a heterotrimeric complex of iNOS, S100A8 and S100A9 serves as an *S*-nitrosylase of GAPDH (Jia et al., 2014). In this model, iNOS initially *S*-nitrosylates S100A9 at Cys3, and then SNO-S100A9 displays transnitrosylase activity for GAPDH, transferring an NO group to the critical Cys residue. This selective *S*-nitrosylation of GAPDH occurs when inflammatory mediators, e.g., interferon-γ or oxidized low-density lipoprotein, trigger formation of the iNOS/S100A8/S100A9/GAPDH complex (Jia et al., 2012, 2014). In the absence of inflammation, GAPDH helps maintain translation of critical proteins by protecting the free ribosomal protein L13A from degradation. However, inflammation-induced SNO-GAPDH is unable to bind to L13A, leading to degradation of the protein via the UPS, and hence defective translational control (Jia et al., 2012). These findings provide evidence for stimulus-dependent, selective *S*-nitrosylation of GAPDH in pathologically-dysregulated protein translation. It will be important for future studies to elucidate how the iNOS/S100A8/S100A9/GAPDH complex further mediates neuroinflammation-associated neurodegeneration.

Concluding remarks

In the past decade, substantial progress has been made in our understanding of SNO signaling pathways, in particular showing that protein *S*-nitrosylation plays a key role in many aspects of biological function in health and disease (Hess et al., 2005; Nakamura et al., 2013; Seth and Stamler, 2011). In the nervous system, depending on the levels and duration of NO produced, SNO-proteins mediate both physiological and pathophysiological processes (Nakamura et al., 2013). This review has focused on recent findings concerning the neurodestructive function of specific SNO-proteins that are aberrantly formed under neurodegenerative conditions.

The possible role of environmental risk factors, such as pesticides and other mitochondrial toxins, in neurodegenerative diseases has received attention for several decades. This review raises the intriguing concept that, at least in a subset of patients with neurodegeneration,

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aberrant *S*-nitrosylation triggered by these environmental toxins may mediate their effects and contribute to disease pathogenesis. Additionally, recent evidence suggests that genetic predisposition may enhance environmental susceptibility. Along these lines, our review points to the possibility that aberrant SNO links these interactions; for instance, certain genetic backgrounds, by increasing basal NO levels, may produce increased vulnerability to environmental toxin-induced nitrosative stress, thus possibly increasing the risk of disease onset and progression (Ryan et al., 2013).

While a complete understanding of aberrant *S*-nitrosylation events in disease states is still to be achieved, emerging evidence indicates that these SNO signaling pathways contribute to the pathogenesis of a number of neurodegenerative disorders, including AD, PD, ALS, and HD. Moreover, several aberrant SNO pathways appear only in the diseased brain and not in normal aged brain, suggesting that aberrant *S*-nitrosylation may represent a unique therapeutic target for drug discovery. Hence, future research will evaluate aberrant SNO-proteins as promising molecular targets for the treatment of neurodegenerative diseases.

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