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Protein *S*-nitrosylation: role for nitric oxide signaling in neuronal death

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Abstract

One of the signaling mechanisms mediated by nitric oxide (NO) is through *S*-nitrosylation, the reversible redox-based modification of cysteine residues, on target proteins that regulate a myriad of physiological and pathophysiological processes. In particular, an increasing number of studies have identified important roles for *S*-nitrosylation in regulating cell death. These roles include double-edged effects dependent on the levels, spatiotemporal distribution, and origins of NO in the brain: in general *S*-nitrosylation resulting from the basal low level of NO in cells exerts anti-cell death effects, whereas *S*-nitrosylation elicited by induced NO upon stressed conditions is implicated in either pro-cell death effects or serves as a negative feedback mechanism and inhibits cell death. Furthermore, in addition to these cascades, mainly associated with apoptosis, massive levels of NO can lead to necrotic cell death. This review focuses on the proteins that are regulated by *S*-nitrosylation during cell death, in particular neuronal cell death and apoptosis. These mechanisms are involved in the pathogenesis of several diseases including degenerative diseases of the central nervous system (CNS).

Keywords

Nitric oxide; *S*-nitrosylation; Apoptosis; Caspases; XIAP; GAPDH

1. Introduction

Apoptosis is a mode of cell death that regulates tissue homeostasis during normal development and maintains adult organism under various conditions, including adaptive responses to cellular stress. Dysregulation of apoptosis can lead to various pathological conditions [1, 2, 3, 4, 5]: insufficient apoptosis can lead to the development of cancer and autoimmune diseases, whereas excessive or inappropriate apoptosis leads to tissue damages, including stroke, myocardial infarction, ischemia, and neurodegenerative diseases.

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Nitric oxide (NO) is an important signaling molecule that acts in many tissues to regulate a diverse range of physiological processes, which include vasodilation, neuronal function, inflammation and immune function [6, 7, 8]. The major enzymes that generate endogenous NO in mammalian cells are three types of nitric oxide synthases (NOS) [(the l-arginine-dependent neuronal nitric oxide synthase (nNOS, NOS1), inducible NOS (iNOS, NOS2), and endothelial NOS (eNOS, NOS3)] [9]. Excessive generation of NO and NO-derived reactive nitrogen species, mainly peroxynitrite ($ONOO^-$), NO_2 and N_2O_3, has been implicated neuronal cell death and apoptosis [10, 11, 12, 13, 14, 15, 16]. Reactive nitrogen species can elicit reversible *S*-nitrosylation of thiol groups [17, 18] and irreversible protein tyrosine nitration [19, 20] in target proteins. These roles include double-edged effects dependent on the levels, spatiotemporal distribution, and origins of NO in the brain.

Tyrosine nitration is a reaction of amino acid tyrosine of target proteins with peroxynitrite ($ONOO^-$), which leads to a covalent addition of a nitro group ($-NO_2$) to one of the two equivalent ortho-carbons of the aromatic ring of tyrosine residues. Tyrosine nitration affects protein function and structure, which includes a change in the rate of proteolytic degradation and a loss of protein activity [19, 20, 21, 22, 23, 24, 25]. Elevated levels of protein tyrosine nitration underlie various age-related neurodegenerative diseases and can be used as a marker of these conditions [22, 23, 24, 25].

One of the key cellular roles of NO is reversible protein modification, such as *S*-nitrosylation, a covalent addition of an NO group to a cysteine thiol/sulfhydryl (RSH or, more properly, thiolate anion, RS-), resulting in formation of an *S*-nitrosothiol derivative (RSNO) [17, 18, 26]. In analogy to phosphorylation by kinases, *S*-nitrosylation by NOSs influences protein activity, protein-protein interactions, and protein location, thus serving as the prototypical redox-based signal [27]. *S*-Nitrosylation is readily reversible with high spatial and temporal specificity. In addition, there are two major physiologically relevant denitrosylases to remove NO group from *S*-nitrosylated Cys thiol side chains [glutathione/S-nitrosoglutathione reductase (GSH/GSNOR) and the thioredoxin/thioredoxin reductase (Trx/TrxR)] [28, 29]. The level of *S*-nitrosylation of any cellular protein depends on the balance between nitrosylation and denitrosylation [28]. *S*-Nitrosylation upon excessive generation of NO and NO-derived reactive nitrogen species (“nitrosative stress”) affects cellular homeostasis and pathological conditions [4, 6, 30, 31, 32, 33, 34]. Thus, regulatory mechanisms of nitrosylation/denitrosylation are crucial in *S*-nitrosylation-mediated cellular physiology and pathophysiology. The present review focuses on different targets and functional consequences of *S*-nitrosylation during cell death and apoptosis.

2. Anti-cell death mechanism associated with NO and protein *S*-nitrosylation: caspase inactivation and anti-apoptotic effects

Apoptosis, characterized by cell shrinkage, membrane blebbing, and DNA fragmentation, is a highly regulated process leading to cell death [35]. The principal regulators of this process in the initiation and execution are the caspase family proteins, cysteine proteases. Caspases are expressed as inactive zymogens in resting cells, and upon exposure to a proapoptotic signal, the zymogen forms of caspases become proteolytically cleaved and activated. Initiator caspases (such as caspase-8, -9, and -10) can cleave other caspases, while executioner caspases (including caspase-3, -6, and -7) cleave substrates, which affect the death cascade [36]. Most caspases contain a single cysteine at the catalytic site, which is susceptible to redox modification and can be effectively modified by *S*-nitrosylation in the presence of NO with the subsequent inhibition of enzyme activity (Fig. 1) [10, 37, 38, 39].

NO reportedly inhibits the enzymatic activity of caspase-3 and -8 via *S*-nitrosylation of active-site cysteine residues and suppresses apoptosis of hepatocytes *in vitro* and *in vivo*

[40, 41, 42]. Furthermore, other studies showed that NO prevents cells from apoptotic cell death by basal *S*-nitrosylation of caspases [43, 44, 45]. *S*-Nitrosylation has also been shown to reduce the activity of caspases in neurons [46, 47, 48, 49, 50]. Furthermore, cortical neurons treated with several NO donors, including *S*-nitrosothiols, exhibited a significant reduction in staurosporin-induced caspase-3 and caspase-9 activation, probably owing to the NO-mediated *S*-nitrosylation of the cysteine residue at the catalytic site of these caspases [51]. These studies indicate that endogenous NO generated by NOS exerts an antiapoptotic function by *S*-nitrosylated inhibition of caspase activity (Fig. 1).

3. Pro-cell death mechanisms associated with NO and protein *S*-nitrosylation

3.1 Caspase activation by denitrosylation and XIAP *S*-nitrosylation

In several elegant studies Mannick et al [52, 53] documented that that *S*-nitrosylation-denitrosylation of caspase-3 were mechanisms by which this ligand was controlling the general process of apoptosis: in human B lymphocytes caspase-3 is constitutively *S*-nitrosylated under basal conditions and keeps the zymogen in an inactive state, which protects cells from apoptosis, whereas activation of the pro-apoptotic FAS receptor promotes denitrosylation of the catalytic cysteine as well as proteolytic cleavage of caspase-3 and induces apoptosis (Fig. 2) [52, 53]. Further study has clarified that cytosolic caspase-3 is largely present in its reduced and unnitrosylated state, whereas mitochondria-associated pool of caspase-3 that is constitutively *S*-nitrosylated in resting cells, which is the target of denitrosylation upon FAS stimulation [45]. Under pro-apoptotic conditions Trx/Trxr proteins denitrosylate SNO-caspase-3, which results in activation of caspase-3 [53, 54]. More studies are needed to show that similar mechanisms operate in neuronal cells.

Caspase activation during NO stimulation also occurs as a result of down-regulation of X-linked inhibitor of apoptosis protein (XIAP) [55]. XIAP interacts with active caspases-3/-7/-9 in the cytosol and is thought to be the most potent endogenous caspase inhibitor. Under normal conditions, XIAP efficiently bind and inhibit the catalytic activity of apoptotic caspases [56]. Additionally, XIAP serves as an E3 ligase that ubiquitinates caspases and thus targets caspases for proteasomal degradation [57, 58, 59, 60, 61]. Under nitrosative stress conditions, NO suppresses the E3 ligase activity of XIAP by *S*-nitrosylation of the RING figure domain of the protein (cysteine 450), thus stabilizing caspases and sensitizing the neurons to apoptotic stimuli (Fig. 2) [62]. Constitutively *S*-nitrosylated caspases (e.g., caspase-3) as described above [53] can be a source to transfer of NO to XIAP via transnitrosylation and contribute to an additional mechanism to produce SNO-XIAP, inhibit its E3 ubiquitin ligase activity, leading to neuronal death [62]. In addition, XIAP is also *S*-nitrosylated in the BIR domain (baculoviral IAP repeat) by high concentrations of NO, leading to XIAP unable to bind and activate caspase-3 [50].

3.2 GAPDH nuclear translocation by *S*-nitrosylation

We reported that a small pool of GAPDH is translocated from cytosol to the nucleus upon exposure to stressors and participates in cellular dysfunction, death, and apoptosis [63], with other groups also replicating this observation [64, 65, 66, 67, 68, 69, 70, 71, 72]. This indicates that GAPDH may act as a relay molecule between distinct cellular compartments, such as the cytosol and nucleus, upon stressed conditions. The signaling is mediated by *S*-nitrosylated GAPDH at the catalytic site cysteine-150, allowing GAPDH to interact with the Siah (an E3 ubiquitin ligase, which possesses a nucleus localization signal), which leads to nuclear translocation of the GAPDH-Siah protein complex [73]. Inside the nucleus, GAPDH stabilizes Siah, which together with *S*-nitrosylated GAPDH is likely to facilitate ubiquitination and degradation of the nuclear co-repressor N-CoR [73, 74]. Further studies

have also shown that nuclear translocated GAPDH is acetylated at lysine-160 by the histone acetyltransferase p300/CBP via direct protein interaction, which in turn stimulates the catalytic activity of p300/CBP. This nuclear event leads to the acetylation of downstream targets, including the tumor suppressor p53 [75]. By both of these mechanisms, the nuclear GAPDH-Siah complex may regulate gene expression associated with cellular dysfunction and death (Fig. 2).

We have recently reported a novel protein, GOSPEL (GAPDH's competitor Of Siah Protein Enhances Life) through the yeast two-hybrid screening of GAPDH's interactors, which can antagonize cell death induced by *S*-nitrosylated GAPDH in neurons [76]. GOSPEL, a cytosolic protein, is highly expressed in organs with high expression levels of GAPDH, such as skeletal muscle, lung, heart, and brain. Under basal conditions GOSPEL physiologically binds GAPDH, retaining GAPDH in the cytosol [76]. GOSPEL is also *S*-nitrosylated at cysteine-47, and *S*-nitrosylated GOSPEL competes with Siah for binding to GAPDH and retaining GAPDH within the cytoplasm. Thus, the competitive binding between GOSPEL and Siah for GAPDH is likely to block cell death and maintain cellular homeostasis when cells are initially exposed to stressors and cellular NO levels are elevated but not massive yet (Fig. 3). However, once the level of nitrosative stress and cellular NO exceed a threshold, the GAPDH-Siah binding driven by *S*-nitrosylation of GAPDH predominates over GAPDH-GOSPEL interaction and leads to cellular dysfunction and death [76]. Therefore, it is likely that the protein GOSPEL can act as a regulator of this pro-cell death pathway by preventing the initial formation of the GAPDH-Siah1 complex.

The involvement of *S*-nitrosylation in GAPDH-mediated cell death is further supported by the study with thyroid carcinoma cells in which *S*-nitrosylation and nuclear translocation of GAPDH is observed after the exposure to TNF-related apoptosis-inducing ligand (TRAIL) [77].

4. Contribution of NO and protein *S*-nitrosylation in the brain diseases

Increasing evidence suggests roles for nNOS-derived NO and protein *S*-nitrosylation in brain disorders[1, 4, 5, 26, 31, 33, 34]. In addition, a massive induction of iNOS, excessive amount of NO, and *S*-nitrosylation of protein targets, such as parkin [78], are elicited in microglia and astrocytes in inflammation, especially in association with neuronal loss in brain disorders, including Alzheimer's and Parkinson's diseases involves inflammation [79].

Recent studies have shown dysregulated *S*-nitrosylation of many proteins involved in neuronal death and neurodegenerative disorders, including Parkin, protein disulfide isomerase (PDI), peroxiredoxin 2 (Prx2), XIAP, Dynamin-related protein 1 (Drp1), Heat Shock Protein 90 (HSP90), matrix metalloproteinase-9 (MMP-9), phosphatase and tensin homolog (PTEN), and GAPDH (Table 1) [50, 62, 78, 80, 81, 82, 83, 84, 85, 86, 87, 88]. Moreover, alterations in the activity of denitrosylases that remove NO groups may also contribute to diseases. A subset of patients with familial amyotrophic lateral sclerosis (ALS) that have mutations in superoxide dismutase 1 (SOD1) are reported to result in elevated denitrosylating activity of SOD1, leading to the depletion of cellular SNOs, including nuclear SNO-GAPDH, which might be linked to disease pathogenesis [89].

Parkin, an ubiquitin E3 ligase whose mutation is known to cause an autosomal recessive juvenile Parkinson's disease (PD) [90], has been identified as a target of *S*-nitrosylation (in Zn-binding cysteine residues in the RING domain of parkin) [81]. *S*-Nitrosylation of parkin increases its E3 ligase activity [81], promotes its auto-ubiquitination, inhibits its enzymatic activity, and compromises its neuroprotective function [78, 81]. Recently parkin was shown to colocalize with classic senile plaques, amyloid-laden vessels, and astrocytes associated with both lesions, in brains from patients with Alzheimer's disease (AD) [91].

PDI is an endoplasmic reticulum (ER)-associated chaperone protein that prevents neurotoxicity caused by ER stress and protein misfolding [92]. PDI is *S*-nitrosylated at active site cysteine residues, resulting in the inhibition of its disulfide isomerase activity and accumulation of misfolded protein in the ER [92]. Increased *S*-nitrosylation of PDI has been found in the brain from patients with PD and AD [92] and the spinal cord from patients with sporadic amyotrophic lateral sclerosis [88]. Cumulative *S*-nitrosylation of parkin and PDI might underlie the accumulation of misfolded and ubiquitylated proteins that ultimately leads to cell death.

XIAP, a well-known anti-apoptotic protein, is reportedly overexpressed in patients with PD and AD [50, 62, 93]. The increased level of XIAP *S*-nitrosylation is reported in PD patients [50, 62]. As described in subsection 3.1, *S*-nitrosylation of XIAP is involved in regulating neuronal death [50, 62].

Prx2, a 2-Cys peroxiredoxin, a member of a family of abundant antioxidants is known to protect against oxidative stress in neurons [94]. The levels of Prx2 are increased in the frontal cortex of patients with AD and PD [95, 96]. Prx2 is *S*-nitrosylated at cysteine residues, which impairs its protective function against oxidative stress. The increased level of Prx2 *S*-nitrosylation is reported in PD patients [84].

The mitochondrion undergoes consistent fusion and fission to maintain its proper function, and dysregulation of mitochondrial fusion or fission has also been implicated in neurodegeneration [97, 98, 99]. Drp1, one of the important proteins that regulate mitochondrial fission, was shown to be *S*-nitrosylated at cysteine 644, which promotes its multimerization and thus mitochondrial fission, which causes neuronal damage [85]. *S*-Nitrosylated Drp1 was enhanced in brains from patients with AD [85]. Furthermore, exposure of nNOS-expressing cells to β-amyloid peptide results in the *S*-nitrosylation of Drp1 [85].

HSP90, a chaperone protein and co-activator of eNOS, is another *S*-nitrosylated protein. *S*-Nitrosylation of HSP90 abolishes its ATPase activity, which is required for its function as molecular chaperone [83]. The brain from patients with AD exhibits increased levels of HSP90 where it is thought to maintain tau and Aβ in a soluble conformation, thereby averting their aggregation [100, 101].

MMP-9, a protein involved in remodeling of extracellular matrix, is induced [102, 103] and *S*-nitrosylated during cerebral ischemia (stroke) [80]. *S*-Nitrosylation results in pathological activation of MMP-9, contributing to neuronal injury and death during stroke [80]. However, a study by McCarthy and co-workers [104] demonstrated that NO is incapable of directly activating pro-MMP-9 and that *S*-nitrosylation of MMP-9 propeptide by NO donors is unrelated to their ability to regulate MMP-9 activity.

PTEN governs the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway which may be a pro-survival pathway in neurons [105]. It has been reported that PTEN protein levels are reduced in AD brains accompanied by elevated Akt phosphorylation [106, 107, 108]. It was recently shown that *S*-nitrosylation of PTEN was markedly elevated in the brains in the early stages of AD [87]. Excess NO leads to S-nitrosylation and ubiquitination of PTEN, resulting in loss of its enzymatic activity and degradation [87].

A pathological role for nuclear GAPDH has been suggested in several neurodegenerative disorders. Nuclear accumulation of GAPDH has been found in fibroblasts and in postmortem brains from patients with polyglutamine diseases (such as Huntington's disease or dentatorubral-pallidoluysian atrophy) [68, 109], PD [66], and AD [70, 110]. Several studies have demonstrated that GAPDH is subject to many different types of oxidative

modification in AD brain, which drastically affect its structure and function, including *S*-glutathionylation and nitration [111, 112] and is comprehensively reviewed by Butterfield et al [86]. Moreover, promising pharmacological evidence provided by Deprenyl and TCH346 that may inhibit GAPDH-Siah binding and nuclear translocation of the GAPDH-Siah protein complex [113], further supports a role for nuclear GAPDH in cell dysfunction and death, especially in association with neurodegenerative disorders.

6. Concluding remarks

NO signaling, through *S*-nitrosylation and denitrosylation, can regulate cellular homeostasis in order to maintain the balance between induction and prevention of cell death/apoptosis, in a context-dependent manner. In general *S*-nitrosylation resulting from basal low level NO in cells exerts anti-cell death effects, whereas *S*-nitrosylation elicited by induced NO upon stressors leads to pro-cell death effects. It is increasingly evident that dysregulated *S*-nitrosylation/denitrosylation could contribute to pathophysiologies characteristic of a wide range of disorders, in particular degenerative diseases of the CNS. Therefore, understanding of their regulatory mechanisms and identifying potential targets may aid therapeutic intervention in a wide range of brain diseases.

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Research Highlights

- The present review focuses on different targets and functional consequences associated with nitric oxide and protein *S*-nitrosylation during neuronal cell death.
- Double-edged effects of *S*-nitrosylation depends on the levels, spatiotemporal distribution, and origins of NO in the brain
- These mechanisms are involved in the pathogenesis of several diseases including degenerative diseases of the central nervous system

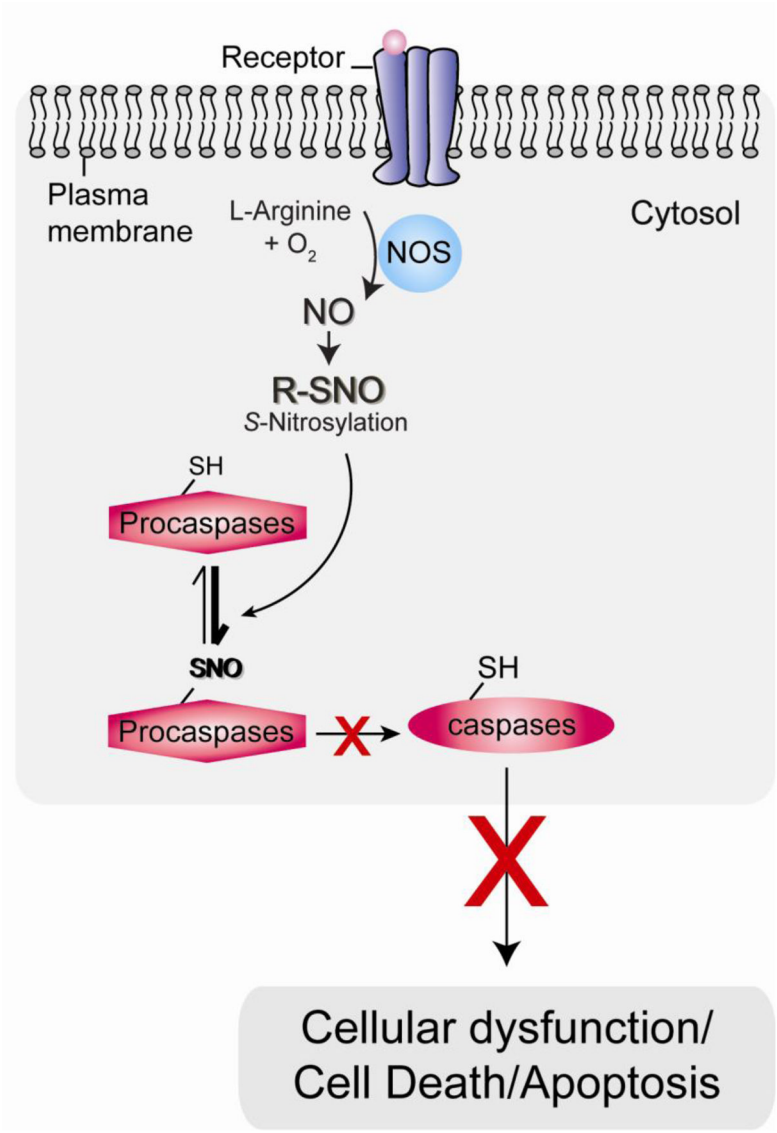

Fig. 1. Anti-cell death mechanism associated with NO and protein *S*-nitrosylation: caspase inactivation and anti-apoptotic effects

Under basal conditions, nitric oxide synthase (NOS) activity is low and basal levels of nitric oxide (NO) contribute to anti-cell death mechanisms. For example, low dose of NO, *S*-nitrosylates (SNO) procaspases/caspases and inhibits their activities.

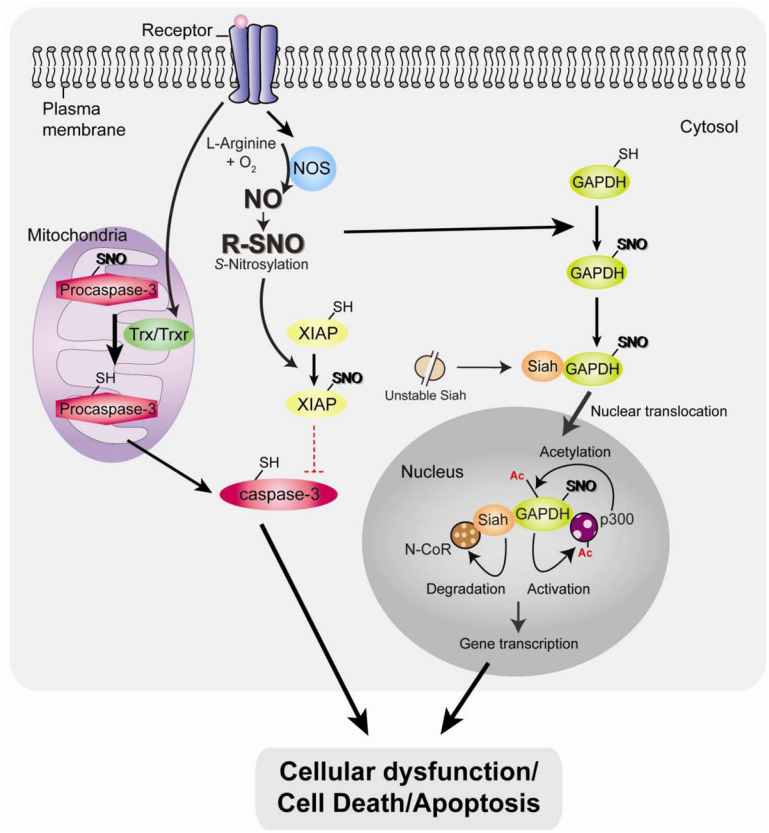

Fig. 2. Pro-cell death mechanisms associated with NO and protein *S*-nitrosylation: caspase activation and nuclear translocation of GAPDH

Under stressed condition, activation of thioredoxin (Trx)/Trx reductase (TrxR) system (specifically in mitochondria) leads to procaspase3 denitrosylation, resulting in caspase-3 activation and apoptosis. In addition, NO inactivates the E3 ligase activity of X-linked inhibitor of apoptosis (XIAP) via *S*-nitrosylation (SNO), thus stabilizing caspases. Excessive nitrosative stress stimulates the formation of NO, which *S*-nitrosylates glyceraldehyde-3-phosphate dehydrogenase (GAPDH) enabling it to bind and stabilize Siah. Siah's nuclear localization signal mediates nuclear translocation of the GAPDH-Siah complex. Stabilized Siah in the protein complex with *S*-nitrosylated GAPDH facilitate degradation of nuclear co-repressor N-CoR. Nuclear translocated GAPDH is further acetylated at by the histone acetyltransferase p300 via direct protein interaction, which in turn stimulates the catalytic activity of p300. Both of these mechanisms by the nuclear GAPDH-Siah complex regulate gene expression, which results in cellular dysfunction/cell death/apoptosis.

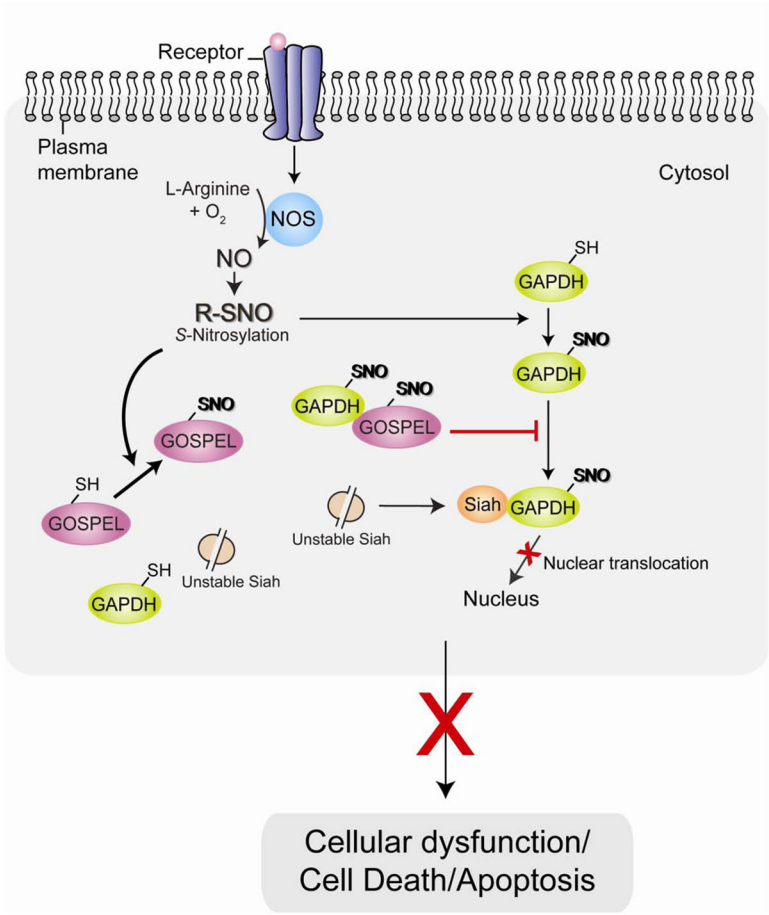

Fig. 3. GOSPEL as the regulator of the cell death mechanism associated with GAPDH nuclear translocation

GOSPEL (GAPDH's competitor Of Siah Protein Enhances Life) was recently identified as a physiological inhibitor against GAPDH-Siah binding. At the initial phase of nitrosative stress when NO levels are low, *S*-nitrosylation (SNO) of GOSPEL augments binding of GOSPEL and GAPDH, competing with Siah for binding to GAPDH, leading to retention of GAPDH in the cytosol and preventing its nuclear translocation and inhibiting cell death.

Table 1

S-Nitrosylation of protein targets implicated in neurodegenerative diseases.

Protein targets	Neurodegenerative disease relevance	Reference
Dynamin-related protein 1 (Drp1)	Alzheimer's disease	[85]
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	Alzheimer's disease	[86]
Heat shock protein 90 (HSP90)	Alzheimer's disease	[100,101]
Matrix metalloproteinase 9 (MMP-9)	Stroke	[80,102,103]
Parkin	Parkinson's disease, Alzheimer's disease	[78,81,91]
Peroxiredoxin 2 (Prx2)	Alzheimer's disease, Parkinson's disease	[84,95,96]
Phosphatase and tensin homolog (PTEN)	Alzheimer's disease, Parkinson's disease, Stroke	[87,106,108]
Protein disulfide isomerase (PDI)	Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis	[88,92]
X-linked inhibitor of apoptosis (XIAP)	Alzheimer's disease, Parkinson's disease	[50,62,93]