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The good Samaritan glutathione-*S*-transferase P1: An evolving relationship in nitric oxide metabolism mediated by the direct interactions between multiple effector molecules

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ABSTRACT

Glutathione-*S*-transferases (GSTs) are phase II detoxification isozymes that conjugate glutathione (GSH) to xenobiotics and also suppress redox stress. It was suggested that GSTs have evolved not to enhance their GSH affinity, but to better interact with and metabolize cytotoxic nitric oxide (NO). The interactions between NO and GSTs involve their ability to bind and store NO as dinitrosyl-dithiol iron complexes (DNICs) within cells. Additionally, the association of GSTP1 with inducible nitric oxide synthase (iNOS) results in its inhibition. The function of NO in vasodilation together with studies associating *GSTM1* or *GSTT1* null genotypes with pre-eclampsia, additionally suggests an intriguing connection between NO and GSTs. Furthermore, suppression of c-Jun *N*-terminal kinase (JNK) activity occurs upon increased levels of GSTP1 or NO that decreases transcription of JNK target genes such as *c-Jun* and *c-Fos*, which inhibit apoptosis. This latter effect is mediated by the direct association of GSTs with MAPK proteins. GSTP1 can also inhibit nuclear factor kappa B (NF-κB) signaling through its interactions with IKKβ and Iκα, resulting in decreased iNOS expression and the stimulation of apoptosis. It can be suggested that the inhibitory activity of GSTP1 within the JNK and NF-κB pathways may be involved in crosstalk between survival and apoptosis pathways and modulating NO-mediated ROS generation. These studies highlight an innovative role of GSTs in NO metabolism through their interaction with multiple effector proteins, with GSTP1 functioning as a "good Samaritan" within each pathway to promote favorable cellular conditions and NO levels.

1. Introduction

Traditionally, nitric oxide (NO) has been reported to play a role in a plethora of biological functions [1–24]. These processes include cell signaling [1–6], neurotransmission [7–9], carcinogenesis [10,11], the immune response [12–14], macrophage-induced suppression of tumor cell growth [15–18], and in the regulation of vasodilation [1,19–23]. Considering the multiple functions of NO, studies have explored its generation and potential metabolism through its relationship with various proteins [1,16,18,19,24–28].

One intriguing molecular interaction is between NO and the glutathione-*S*-transferase (GST) family of proteins [24,25,27–30]. These interactions include: **(1)** the binding dinitrosyl-dithiol iron complexes (DNICs) composed of NO, glutathione (GSH), and iron to specific GST family members (GSTP, GSTA, and GSTM) [25,26,30]; **(2)** the interaction between GSTP1 and the glutathione transporter, multi-drug resistance-related protein 1 (MRP1), to act as an integrated transport and storage system for DNICs [28,29,31]; and **(3)** the direct association of GSTP1 with inducible NO synthase (iNOS) to inhibit NO generation [24].

These latter studies suggest an intriguing role of GSTs in NO metabolism, which is accentuated by the interactions of GSTs with other proteins that play critical roles in cellular signaling, proliferation, apoptosis, and differentiation [32–39]. In fact, notable effects include the inhibitory activity of GSTP1 within the c-Jun *N*-terminal kinase (JNK) and nuclear factor kappa B (NF-κB) pathways and GSTP1 may be involved in crosstalk between survival and apoptosis pathways and modulating NO-mediated reactive oxygen species (ROS) generation. As such, GSTs through their role in metabolizing NO and their direct interactions with multiple proteins could act as a novel conduit for

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coupling disparate pathways. This review will examine this concept and propose novel mechanisms by which GSTs function to challenge the paradigm that they only act to eliminate toxins *via* glutathionylation.

2. Impact of NO cytotoxicity and evolution of the GST superfamily

GSTs play roles in phase II detoxification isozymes that are ubiquitously expressed in almost all living organisms, being characterized into three families: microsomal, mitochondrial, and cytosolic [40,41]. The canonical function of the GSTs is to protect proteins from reactive electrophiles by catalysing their conjugation to glutathione (GSH). This family of proteins has key functions in cellular protection, including modulating cellular and oxidative stress, and act synergistically as both enzymes and ligandins to catalyze the conjugation of GSH to toxins [42–44]. While GSTs have similar characteristics and functions, cytosolic GSTs are divided into 16 gene-independent GST classes by sequence homology, substrate specificity, inhibitor sensitivity, and immunological properties [45,46]. The central feature of GSTs in GSH activation is facilitated by Tyr, Ser, or Cys residues within their active sites [45,46].

Evolutionarily, the active site of the GST class of enzymes has changed over time [46,47]. This progression in GST structure involves a change to the crucial cysteine residue (β and Ω classes) observed in the more ancient GSTs, to a serine residue (θ, τ, δ, ε and φ classes), and more recently, to a tyrosine residue (α (GSTA), μ (GSTM), π (GSTP), and Σ (GSTE) classes) [46,47]. It should also be stated that there are a number of GST isotypes within each class *e.g.*, GSTP1, GSTP2, *etc.* [46,47]. Bocedi and colleagues examining 42 different GSTs identified that each of these proteins demonstrated similar affinities for GSH, with efficient activation of the GSH sulfhydryl group [27]. Considering their results, these authors suggested that the Cys/Ser/Tyr evolution of the active site does not appear relevant to fulfill this function [27]. Instead, it was suggested that GSTs evolved to protect cells from the cytotoxicity of NO *via* DNIC binding [27].

This latter suggestion has arisen because the most common NO adduct in cells is present as DNICs [48]. The DNICs are spontaneously formed transition metal complexes composed of NO, iron, and a thiolate ligand (*i.e.*, glutathione or cysteine), with these complexes having cytotoxic activity [49–51]. The remaining two coordination sites around the iron atom (iron is hexacoordinate) are probably completed with other ligands such as water, etc. When bound to GSTs as DNICs, the half-life of NO is increased from less than a second to 4–8 h, depending on the GST isotype [25,27]. Generally, it is known that DNIC formation in solution increases the half-life of NO from less than a second to 1–2 h [48,52–54]. Bocedi et al. discovered that the more evolutionarily evolved Tyr-based GSTs displayed a very marked affinity for DNICs (K_d $< 10^{-9}$ M) to sequester NO [27]. In contrast, the less evolved Ser- and Cys-based GSTs exhibited significantly lower affinities for DNICs (10^2–10^4 times lower), which led to inefficient binding [27].

The above conclusion was supported by an earlier investigation from the same laboratory that solved a crystal structure for a DNIC bound to GSTP1-1 [25]. It was demonstrated that Tyr-7 within the GSTP1-1 active site was crucial for binding DNICs in the form of a dinitrosyl-diglutathionyl iron complex [25]. This structure demonstrated that Tyr-7 within GSTP1 binds to the iron atom through its phenolate group, and in so doing displaces one of the GSH ligands [25]. As such, in GSTP1 the iron atom is coordinated by Tyr-7, GSH, and the two NO molecules [25] (Fig. 1).

The half-lives of these GST-DNIC complexes within human placenta and rat liver homogenates were approximately 8 h when DNICs were bound to GST-P1-1 [55]. In contrast, DNICs bound to GST-A and GSTM had half-lives of 4.5 h [55]. The enhanced binding affinity of GSTP1-1 for DNICs relative to other Tyr-based GSTs (GSTA1 and GSTM1) may suggest a more prominent relationship of GSTP1 in NO metabolism [27]. A later study by the same laboratories revealed that 20% of these DNIC-GST complexes were associated with subcellular components, including the nucleus, which may indicate a protective mechanism against DNA damage [56]. On the other hand, the less evolved bacterial Cys-based GSTs demonstrate low affinity for DNICs and it was suggested that this may contribute to the sensitivity of bacteria to NO [27].

3. Nitric oxide storage and transport in cells are mediated by GST P1-1 and MRP1 *via* DNICs

The multi-functional properties of GSTs, particularly in

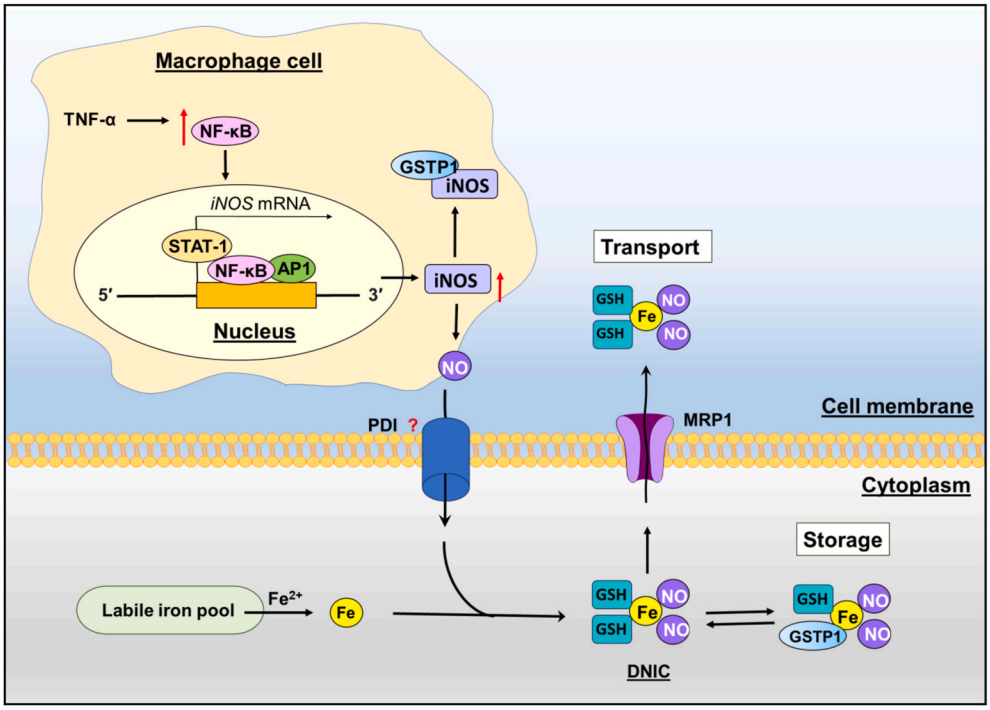

Fig. 1. MRP1 and GSTP1-mediated transport and storage of NO as DNICs. Cytokines such as TNFα activates the NF-κB pathway leading to the transactivation of iNOS that generates intracellular NO within murine macrophages. Intracellular iron in the labile iron pool can spontaneously complex with NO and GSH, leading to DNIC formation. The DNICs can be reversibly bound and stored by GSTP1 and transported out of cells by the GSH transporter, MRP1. As such, GSTP1 and MRP1 form a functional unit that can protect cells from the cytotoxicity of NO as DNICs. Protein disulfide isomerase (PDI) may play a role in NO transport across the membrane [62]. However, no functional studies have indicated an integrated role of PDI with GSTP1 and MRP1.

detoxification, may be key to NO regulation and metabolism [57–59]. As mentioned above, the complexation of GSTs (A1, M1, and P1) to DNICs extends the half-life of 'free NO' [55]. The functional roles of these GST-DNIC complexes are not well understood, and some studies have suggested that GSTs may act as storage enzymes for NO or play a key role in detoxifying this radical [28,31]. This observation is supported by studies that demonstrated that GSTA1 could stabilize glutathione reductase from irreversible inhibition by DNICs [26]. When the DNIC concentration exceeded the binding capacity of the GST enzymes, glutathione reductase activity was inhibited by DNICs [26].

Our laboratory has proposed a model for NO trafficking in cells where DNICs act as a common currency for the transport and storage of NO, which is mediated by GSTP1-1 and the GSH transporter, MRP1 (Fig. 1) [28,31,60]. This mechanism extends the findings that GSTs can protect cells from the cytotoxic activity of NO [61] and suggests that GSTs function as a storage protein for DNICs that are then transported out of the cell by MRP1 [28,31]. Initial studies using stably transfected MRP1 hyper-expressing MCF7-VP breast cancer cells and its relevant control cell-type (MCF7-WT) stably transfected to overexpress GSTA1-1, GSTM1-1, or GSTP1-1, reported a marked decrease in NO-mediated iron release (as DNICs) by MRP1 following GSTP1-1 overexpression only [31]. These results suggested that the increased affinity of GSTP1 for DNICs compared to the other GST isotypes may be associated with its ability to mediate the storage of DNICs in tumor cells. The decreased NO-mediated iron release from cells observed during GSTP1-1 overexpression was shown *via* electron paramagnetic resonance (EPR) and fast-pressure liquid chromatography to be the result of increased DNIC-GST P1-1 complex formation [31].

It was suggested by this later study that the GSTP1-1-DNIC complexes may function as a 'storage sink' for NO within cells and that GSTP1-DNIC binding prevents NO-mediated iron release [31]. Collectively, these investigations propose a model for NO trafficking in cells where GSTP1 sequesters NO, iron, and GSH in the form of DNICs to inhibit DNIC transport out of tumor cells by MRP1 [31]. Of relevance, the enzyme protein disulfide isomerase (PDI) has been reported to play a role in NO transport across the membrane into cells [62], again suggesting that there are specific protein-mediated mechanisms of NO trafficking in cells (Fig. 1).

Subsequent studies demonstrated that both GSTP1 and MRP1 were up-regulated in NO-generating murine macrophage-like cell-types (RAW264.7 and J774) after activation with lipopolysaccharide and interferon-γ [28]. In support of the proposed mechanism in Fig. 1, these studies in macrophage models also demonstrated that inhibition of Mrp1 transport activity *via* either pharmacological inhibition using MK571 or after silencing *Mrp1* expression using *Mrp1* siRNA resulted in decreased NO-induced iron-59 release from cells [28]. Furthermore, *Mrp1* silencing also resulted in DNIC accumulation within macrophages [28], suggesting that MRP1 was involved in transporting DNICs out of cells.

The synergistic relationship between MRP1 and GSTP1 was evidenced by the enhanced efflux of iron-59 (as DNICs) from the cells following *Gstp1* silencing [28]. Viability studies corroborated the protective function of MRP1 and GSTP1 expression, as silencing of *Mrp1* or *Gstp1* expression led to a significant decrease in cellular viability [28]. These data are consistent with the aforementioned study using human MCF7 cells that demonstrated cells hyper-expressing GSTP1 and MRP1 were resistant to exogenous NO [31]. Furthermore, silencing of *nuclear factor-erythroid 2-related factor 2* (*Nrf2*), a transcriptional regulator of *MRP1* and *GSTP1*, reduced cellular viability by 60–80% after a 4–24 h incubation [28]. The decreased viability of the macrophages after silencing *Gstp1* or *Mrp1* was prevented by the NOS inhibitor, L-NAME [28].

An investigation examining rat hepatocytes and liver homogenates identified DNIC complexes bound to GSTA [55]. In these studies, GSTA exhibited extraordinarily high affinity (K_d 10^{-10} M) for DNICs [55]. Taking into account that Tyr-based GST enzymes bind DNICs with slightly differing affinities (K_d 10^{-9} to 10^{-10} M) [25,30] and that GSTA is highly expressed in hepatocytes (0.3 mM concentration) [55], it may be that different GST enzymes are necessary for protection against NO cytotoxicity within different cell-types. Further investigations using a variety of physiologically relevant cell-types that express multiple GST isoforms are required to understand how GST enzymes interact with DNICs and MRP1. Nonetheless, the well-known coordinate role of MRP1 and GST in the detoxification of substrates such as cytotoxic drugs [57,58,63], also extends to NO present in cells as DNICs [64].

Consistent with the interaction of DNICs with GSTs, it is interesting to discuss studies demonstrating the association between the *GSTM1* and *GSTT1* null genotype and NO-related disorders, including preeclampsia, hypertension, and atherogenesis [65–68]. A 2018 study of 104 patients with preeclampsia and 200 healthy controls identified a highly significant ($p < 0.001$) association between the *GSTM1* null genotype and the development of preeclampsia [68]. Although the risk of developing preeclampsia was higher for patients with the *GSTT1* genotype, it was not significant [68]. However, the risk of developing preeclampsia with a combined *GSTM1* and *GSTT1* genotype was much higher relative to the *GSTM1* null genotype alone [68]. These results are similar to another study in Mexican mestizo populations that demonstrated that patients with the combined *GSTM1/GSTT1* deletion genotype conferred a marginally higher risk of preeclampsia *versus* the controls [67]. An analogous association was also demonstrated for the individual *GSTM1* and *GSTT1* null genotypes and the risk of developing preeclampsia [67].

Furthermore, data comprising 12 studies with a total of 2040 cases and 2462 controls revealed a significant association between the *GSTM1* and *GSTT1* null genotype and the risk of hypertension [66]. Case studies on the incidence of atherosclerosis in Serbian populations found that the *GSTM1* null genotype was significantly more frequent in atherosclerotic patients than in controls (52.0% *versus* 34.1%), with a 2-fold increase in the risk of developing atherosclerosis [65]. It was shown that both *GSTM1* and *GSTT1* genes had a protective effect against atherosclerosis, while deletion of both genes led to a robust atherosclerosis risk [65].

Collectively, given the strong correlation between GSTs and the development of preeclampsia, hypertension, and atherogenesis, further research is required to investigate the role of the MRP1 and GST system in endothelial cells to examine its role in the regulation of vasodilation.

4. GSTP1 associates with iNOS and decreases its stability and protein level

It has been previously reported that GSTP1 levels are increased in response to lipopolysaccharide (LPS) stimulation in macrophage-like cells [28], and that GSTP1 overexpression in cells suppressed the excessive generation of pro-inflammatory factors and iNOS expression [69]. Moreover, studies have demonstrated that GSTP1 can decrease iNOS protein levels in macrophage-like cells, with GSTP1 expression also decreasing the effects of the acute inflammatory response to LPS *in vivo* in mice [69,70].

Considering the roles of iNOS in mediating the inflammatory response [71–73] and the reported interactions between GSTP1 and NO [25,28,30,31,55,61,74], an intriguing recent study has reported the direct interaction between GSTP1 and iNOS [24]. These studies demonstrated that overexpression of GSTP1, but not GSTM1 or the GSTP1 mutant that possesses an inactive catalytic site (Y7F), decreased iNOS protein levels following LPS stimulation of RAW264.7 macrophages [24]. Knockdown of *GSTP1* using shRNA also demonstrated that inhibition of GSTP1 expression increased iNOS levels in activated RAW264.7 cells [24]. To understand how GSTP1 impacts iNOS levels, HEK293 cells were co-transfected with iNOS and GSTP1 and pre-incubated with the protein synthesis inhibitor, cycloheximide [24]. These studies demonstrated lower iNOS protein levels in GSTP1 overexpressing cells upon cycloheximide treatment, suggesting a decrease in iNOS half-life [24]. Collectively, these results suggested that GSTP1 expression may promote iNOS protein degradation [24].

Intriguingly, immunoprecipitation of GSTP1 and iNOS in activated

RAW264.7 cells stably expressing GSTP1 demonstrated that GSTP1 directly binds iNOS [24]. These results were replicated in HEK293 cells under overexpression conditions [24]. Moreover, co-transfection of HEK293 cells with the catalytically inactive GSTP1 mutant (Y7F) and iNOS demonstrated interactions between iNOS and the GSTP1 mutant [24]. These data suggested that the binding of GSTP1 to iNOS is independent of catalytic activity. It is of note that iNOS is composed of two catalytic units, the *C*-terminal reductase, and the *N*-terminal oxygenase domains [75]. On the other hand, GSTs are dimers, with each monomer containing two substrate-binding sites, namely the GSH-binding site (G-site) and the xenobiotic substrate-binding site (H-site) [76]. Mapping of the iNOS and GSTP1 domains using immunoprecipitation revealed that the oxygenase domain of iNOS, but not the reductase domain, was required for iNOS-GSTP1 binding [24]. Additionally, the G-site of GSTP1, but not the H-site domain, was required for GSTP1-iNOS binding [24].

Docking of GSTP1 with iNOS by Cao et al. using the program, ZDock, predicted their interaction, and it was suggested that Tyr7, Phe8, Val32, Val33, Glu36, Lys190, and Asn200 of GSTP1, and Tyr78, Arg80, Lys97, and Glu154 of iNOS were involved [24]. This observation is of interest, as studies that solved the crystal structure of a DNIC bound to GSTP1 demonstrated that Tyr-7 was directly involved in its binding [25].

Similar docking studies using the more sophisticated high ambiguity driven protein-protein docking (HADDOCK 2.4) server [77,78]

(A)

	Positive control	Negative control	Test	
	E2A + HPR	P21 + EGFR	iNOS-GSTP1	iNOS-GSTA1
			Mouse species	
HADDOCK score	-34.4 +/- 2.3	27.7+/-6.7	-97.6 +/- 4.7	-64.7 +/- 5.7
van der Waals energy	-100.3 +/- 13.4	69.2 +/- 9.5	-55.8 +/- 3.7	-35.4 +/- 4.2
Desolvation energy	-18.3 +/- 1.9	20.5 +/- 1.7	3.3 +/- 2.9	64.4 +/- 39.8
Z-Score	-2.1	1.3	-2.4	-1.4

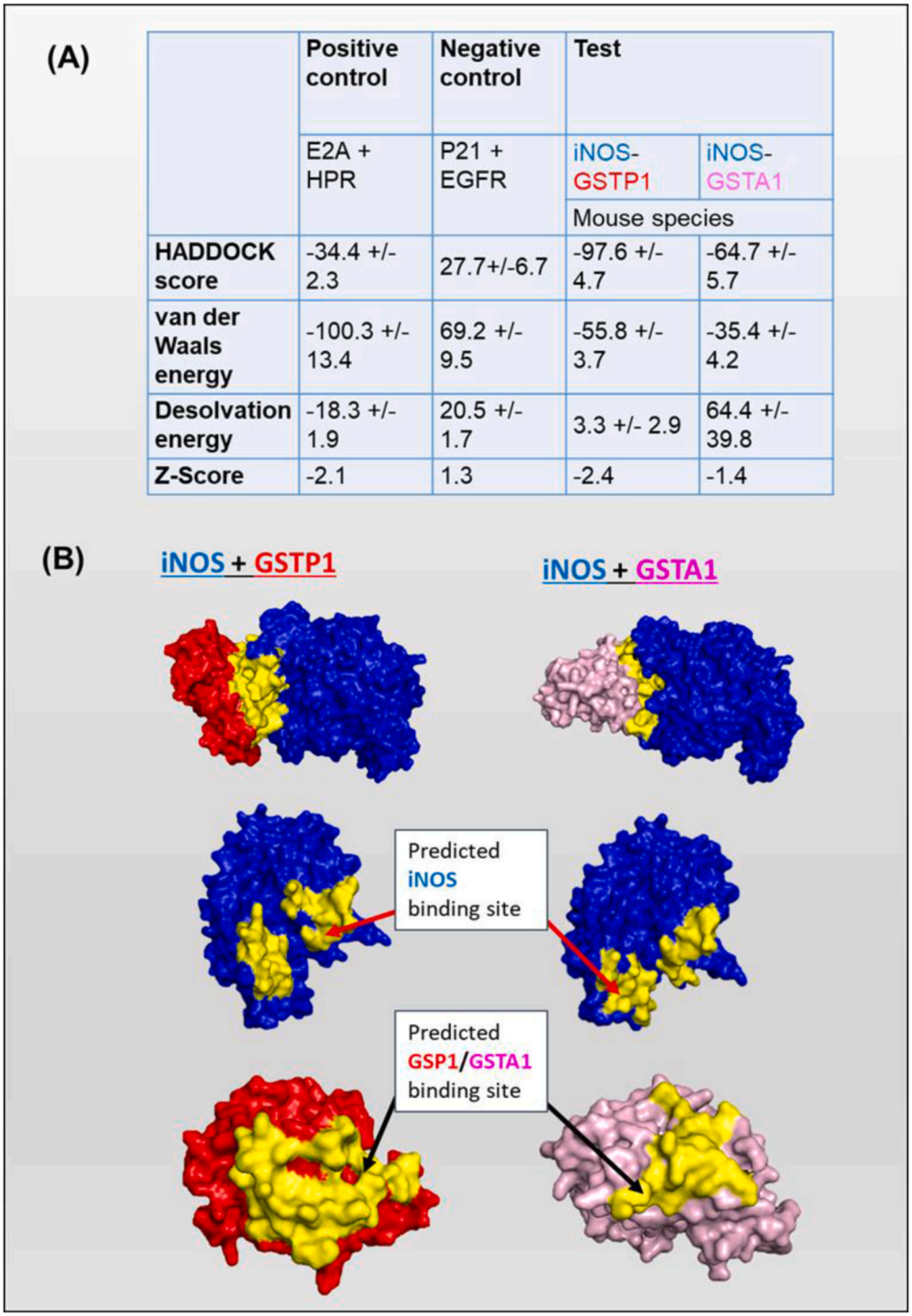

Fig. 2. A, B. Docking of iNOS and GSTP1 via the HADDOCK docking server [77,78] suggests an association between these proteins, confirming a previous experimental and docking study with GSTP1 [24]. A novel interaction of iNOS and GSTA1 was also demonstrated using the HADDOCK server and suggested similar interaction sites as observed for iNOS and GSTP1. The tabulated positive and negative controls are interactions of E2A with HPR and p21 with EGFR, respectively, and are suggested control interactions by the docking server [78, 106].

confirmed the association of GSTP1 and iNOS (Fig. 2). This program results in a HADDOCK score, which is a weighted sum of multiple energy terms that predicts the potential association between proteins [77,78]. The HADDOCK score generated for the iNOS-GSTP1 interaction (−97.6) was more favorable than the positive control interaction of the proteins E2A and HPR (−34.4), or the negative control interaction between p21 and EGFR (+27.7; Fig. 2). Analogously, the van der Waals energy, desolvation energy, and Z-score from HADDOCK all indicated a potential association between iNOS and GSTP1 (Fig. 2).

Additional docking studies using HADDOCK and GSTA1 also demonstrated a strong potential binding between GSTA1 and iNOS (Fig. 2), with a HADDOCK score of −64.7. While this value is slightly lower than that predicted for the GSTP1-iNOS interaction (Fig. 2), it suggests further binding studies would be valuable in understanding the relationship between GSTA1 and iNOS. Due to the absence of a crystal structure for mouse GSTM1, no docking of this protein to iNOS could be achieved.

4.1. *GSTP1 regulates iNOS monomer/dimer level*

Dimerization of NOS is required for NO generation and inhibitors of dimerization suppress iNOS activity and promote its *S*-nitrosylation and degradation [79,80]. Considering this, the regulation of iNOS dimerization by GSTP1 has been investigated in activated macrophages [24]. It was discovered that GSTP1, but not GSTM1 or mutant GSTP1 (Y7F), significantly decreased iNOS dimer levels relative to the monomer [24]. Furthermore, *GSTP1* knockdown in activated RAW264.7 cells increased iNOS dimer levels [24]. Together, these studies suggest that GSTP1 may be able to promote the *S*-nitrosylation of iNOS that leads to its degradation.

4.2. *GSTP1 expression increases S-nitrosylation and ubiquitination of iNOS*

While *iNOS is* robustly transcriptionally regulated by NF-κB, post-translational modifications such as *S*-nitrosylation and ubiquitination may also modulate iNOS protein levels [24,81–83]. Of interest, NO has been shown to inhibit iNOS dimer stability through *S*-nitrosylation of the zinc-binding tetrathiolate cysteines in iNOS, resulting in the release of zinc and the generation of inactive monomers [83].

Considering the role of GSTP1 in decreasing iNOS stability, the impact of GSTP1 on the *S*-nitrosylation and ubiquitination of iNOS has recently been investigated in activated RAW264.7 cells and GSTP1-overexpressing HEK293 cells [24]. This study demonstrated that GSTP1 overexpression significantly increased the level of *S*-nitrosylated iNOS and that *GSTP1* knockdown resulted in a decrease in *S*-nitrosylated iNOS [24]. It has also been reported that ubiquitination of iNOS is necessary for its degradation [81] and that GSTP1 facilitates iNOS ubiquitination upon treatment of cells with the proteosome inhibitor, MG132 [24].

Collectively, these studies suggest that GSTP1 modulates the post-translational regulation of iNOS. However, the regulation of iNOS by GSTP1 may also occur at the transcriptional level through the inhibition of NF-κB [35], and this is described below.

5. NF-κB is a key redox regulator of iNOS induction and GST isoform expression

Central to the regulation of NO is the induction of the transcription factor, NF-κB, which is responsible for modulating several pro-survival, pro-inflammatory, and immune-regulatory pathways [84–86], including the expression of cytokines and iNOS [85,87,88]. In this pathway, pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin (IL)-1, as well as other agents, such as LPS, can activate NF-κB transcriptional activity *via* the trimeric IκB kinase (IKK) complex [89] (Fig. 3).

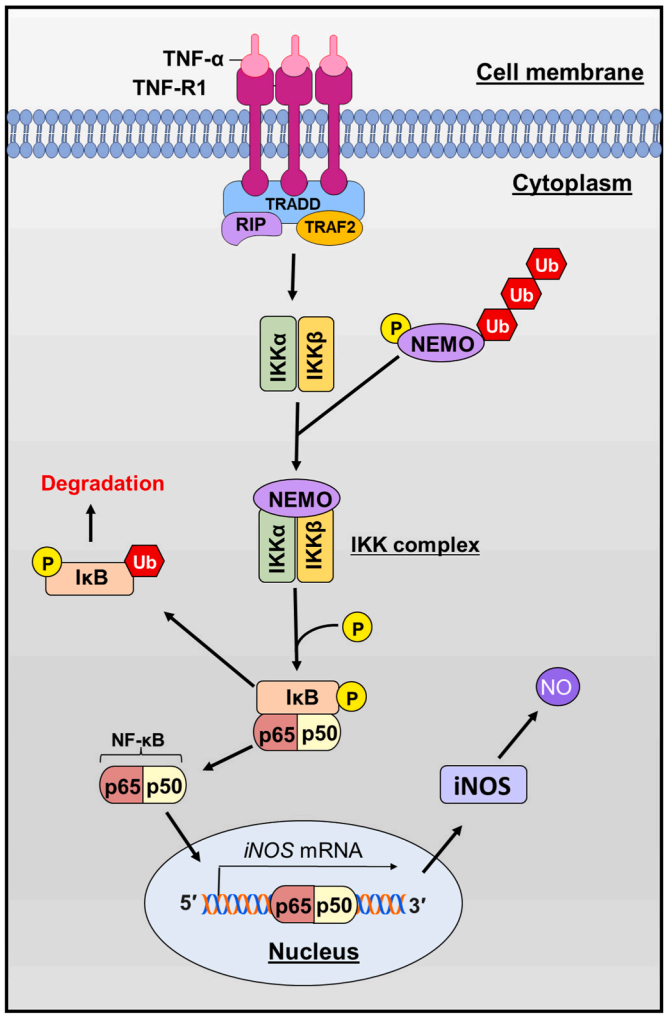

Fig. 3. Canonical NF-κB signaling *via* the IKK complex and IκB, and subsequent induction of iNOS transcription. The binding of TNFα to the TNF receptor 1 (TNF-R1) activates downstream signaling *via* the TRADD, RIP, and TRAF2 complex. Subsequently, this activated complex promotes the NF-κB IKK complex, consisting of NEMO, IKKα, and IKKβ. The IKK complex can then phosphorylate the NF-κB inhibitor, IκB, targeting it for ubiquitination and degradation. The liberation of the NF-κB transcriptional complex (composed of p65 and p50) from IκB can then translocate to the nucleus to transcribe target genes, *e.g.*, *iNOS*.

The IKK complex consists of two homologous catalytic subunits, IKKα and IKKβ, and the regulatory subunit, NF-κB essential modulator (NEMO) [89–92]. Once activated, IKKβ can induce the phosphorylation and subsequent degradation of the "inhibitor of KB" (IκB) by the IKK complex [89–92]. The IκB protein consists of 3 major isoforms, IκBα, IκBβ, and IκBε, and functions to specifically inhibit the NF-κB dimers, p50 and p65 [89,93]. Once phosphorylated, IκB proteins are degraded, and p50 and p65 can translocate to the nucleus and promote target gene transcription, including *iNOS* [94–96] (Fig. 3).

Considering the significance of NF-κB in regulating cellular responses, several mechanisms, including oxidant-dependent modifications, regulate NF-κB activation and its down-stream targets [84,97]. The redox-sensitive cysteine thiols on some proteins are highly susceptible to such oxidative modifications including *S*-nitrosylation [98–101], *S*-glutathionylation [35,102–106], sulfenic acid formation [35,36,107,108], and the generation of disulfide bonds [36,109–111]. Multiple studies have demonstrated that NF-κB is modified *via* *S*-glutathionylation (the conjugation of GSH with cysteine residues) [98–101]. Additionally, *S*-glutathionylation of IKKβ impedes its kinase activity and

the induction of downstream pro-inflammatory responses [35,102,103,105].

Considering the function of GSTP1 in *S*-glutathionylation [112], a recent study has investigated the role of GSTP1 in NF-κB activation and pro-inflammatory cytokine production in epithelial cells exposed to LPS [35]. This latter study using unstimulated lung epithelial cells (C10 cells), demonstrated that GSTP1 became directly associated with IκBα and resulted in NF-κB inhibition [35]. However, upon exposure to LPS, there was a rapid decrease in the IκBα and GSTP1 interaction and an increased association of GSTP1 with IKKβ, along with enhanced IKKβ *S*-glutathionylation [35]. This observation was supported by the decreased *S*-glutathionylation of IKKβ observed after siRNA-mediated knockdown of *GSTP1* in LPS-stimulated cells [35]. Knockdown of *GSTP1* also promoted NF-κB nuclear translocation, transcriptional activity, and pro-inflammatory cytokine production, demonstrating the inhibitory activity of GSTP1 on IKKβ [35]. Similar results to that observed with the knockdown strategy were achieved using the isotype-selective inhibitor of GSTP, TLK117 [35]. Incubation of RAW264.7 macrophage-like cells with LPS has been demonstrated to increase NF-κB, p65, and iNOS expression and lead to elevated NO levels [113].

Several studies have indicated that NO prevents the phosphorylation and degradation of IκBα [114,115] and can inhibit IKKβ activity *via* its *S*-nitrosylation [98]. These data indicate a feedback system mediated by NO and assisted *via* the inhibitory binding by GSTP1 [35]. Furthermore, as described above, it is of interest that GSTP1 also directly associates with iNOS [24], a key downstream effector of the NF-κB pathway [98]. The inhibitory binding activity of GSTs, either to: **(1)** iNOS; **(2)** NF-κB regulators (IκBα and IKKβ); or **(3)** in terms of GSTP1 directly binding DNICs [25,28,31], demonstrates a broad functional role of GSTP1 in regulating the activity of NO itself and NO-related pathways.

Intriguingly, it has been reported that GSTP1 also physically associates with TRAF-2 [33,34,116], which is a critical upstream activator of transcription factors such as NF-κB [117–119] (Fig. 3). It was demonstrated that GSTP1 overexpression inhibited TRAF2-induced activation of its downstream targets, JNK and p38, but not NF-κB *in vivo* and *in vitro* [33]. However, the GSTP1-induced inhibition of AP1, another key TRAF2 downstream target, has not yet been investigated. Considering the role of AP1 in activating iNOS transcription [120], studies exploring the effect of GSTP1-TRAF2 binding on AP1 activation could highlight another regulatory mechanism of GSTP1 that inhibits NO metabolism. However, the ability of GSTP1 to directly bind JNK could have significant implications on cellular NO generation [32,116,119,121] and is described below.

6. The potential coordinate suppression of JNK by GSTs and NO

The genomic and physiological response of cells to changes in their environment is induced by multiple pathways, such as the mitogen-activated protein kinase (MAPK) pathway that relays, amplifies, and integrates signals from extracellular stimuli [122–124]. As part of the MAPK pathway, JNK signaling is predominantly regulated by environmental stress, such as oxidative insults (*e.g.*, ROS) or cytokines [32,39,125–130]. Central to this pathway is the phosphorylation and activation of JNK and its downstream targets, c-Jun and c-Fos, which form the AP1 transcriptional complex [131–133]. The AP-1 complex has central roles in apoptosis, proliferation, and the transcription of essential target genes [133–136]. Of relevance, another key regulator of the JNK pathway is GSTP1, which binds to JNK and prevents its activation [32,39,119,121,125,126,137,138].

6.1. GST inhibition of the JNK pathway and potential negative feedback systems

The GSTP1-mediated inhibition of JNK is well established [32,32,34,116,121,139]. Studies by Adler et al. have purified a complex composed of GSTP1, c-Jun, and JNK that exhibited a dose-dependent inhibition of JNK activity by GSTP1 [32]. Moreover, an investigation using mouse embryo fibroblasts from *Gstp*-null mice demonstrated a high basal level of JNK activity that was decreased by forced expression of *Gstp* cDNA [139]. It has also been discovered using purified recombinant proteins and fluorescence resonance energy transfer (FRET) studies that the *C*-terminus of JNK is crucial for the JNK-GSTP1 protein-protein interaction [121].

Studies conducted by Colman and colleagues examined this GSTP1-JNK interaction by assessing the binding of GSTP1 to the JNK1 and JNK2 isoforms [138]. It was reported that GSTP1 preferentially bound the active form of JNK1 [138]. However, the interaction of GSTP1 with unphosphorylated JNK1 required the JNK substrate, ATF2 [138]. The same study demonstrated that GSTP1-1 directly interacted with ATF2 and suggested that the GSTP1-mediated inhibition of JNK could be explained by the competition of GSTP1 with active JNK for ATF2 [138]. These latter results conflict with investigations demonstrating a direct interaction with GSTP1 and non-activated JNK [32,121,125,140].

GSTP1 exists in its monomeric and dimeric forms, which are in equilibrium [39,141]. Recent investigations showed that GSTP1 is a downstream target of epidermal growth factor receptor (EGFR). Intriguingly, phosphorylation of tyrosine-3, -7, and -198 in GSTP1 by this receptor tyrosine kinase shifts the GSTP1 dimer-monomer equilibrium to the monomer [39] (Fig. 4). This shift in equilibrium results in a >2.5-fold decrease in JNK downstream signaling, as GSTP1 binds JNK in monomeric form, suppressing its activity [39] (Fig. 4). Other reports have demonstrated similar inhibition of JNK downstream signaling by GSTP1. Forced expression of GSTP1 in mouse fibroblast cells (3T3-4A) decreases JNK phosphorylation, which coincides with a decline in JNK activity, increased c-Jun ubiquitination, and decreased c-Jun-mediated transcriptional activity [32].

When exposed to oxidative stress, the cysteine residues of GSTP1 are oxidized and form intra- and inter-subunit disulfide bonds between Cys47, Cys101, and other cysteine residues, resulting in GSTP1 oligomerization and dissociation of JNK (Fig. 4) [39,121,126,142]. Then, JNK can be phosphorylated to activate c-Jun and AP1 [32,121,134]. Studies have also shown inactivation of GSTP1 *via* tyrosine nitration from RNS agents such as peroxynitrite and tetranitromethane, which suggests that RNS may also induce GSTP1 oligomerization [143].

GSTs are largely transcriptionally regulated by the transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2), *via* antioxidant response elements (AREs) located within the promoter and enhancer regions of the *GST* gene [144–146]. Expression of GSTP1 is regulated by an ARE within the *GSTP1* enhancer, *GPE1* [144,145]. Intriguingly, both Nrf2 and the down-stream target of JNK, c-Jun, have been shown in rat liver cells to transactivate *GSTP1* expression *via GPE1* [145]. This coordinate regulation of GSTP1 expression by Nrf2 and activated c-Jun suggests potential negative feedback on JNK mediated by the direct binding of GSTP1 to JNK. It can also be suggested that GSTP1 functions as a sensor for oxidative stress in these pathways.

Studies have also demonstrated that the *C*-terminal of GSTM1 directly associates with the *N*-terminal region of apoptosis signal-regulating kinase 1 (ASK1), which is an activator of c-Jun [38,147]. It was reported that GSTM1-1 suppressed stress-stimulated ASK1 activity in human 293 embryonic kidney cells, and this was independent of GSTM1 glutathione-conjugating activity (Fig. 4). Moreover, interactions between ASK1 and GSTM1 inhibited ASK1-dependent apoptotic cell death [38]. Considering this, GSTA1 also binds JNK, with this being associated with the suppression of its signaling and apoptosis in Caco-2 cells [37]. While studies exploring the direct relationship of GSTM1 and GSTA1 with JNK signaling pathways are limited, the central roles of GSTs in detoxification and modulating oxidative stress suggest these GSTs may be novel regulators of the JNK pathway along with GSTP1 (Fig. 4).

GSTP1-1 can interfere with the MAPK pathway not only through its interaction with JNK, but also at the TRAF2 level by blocking the

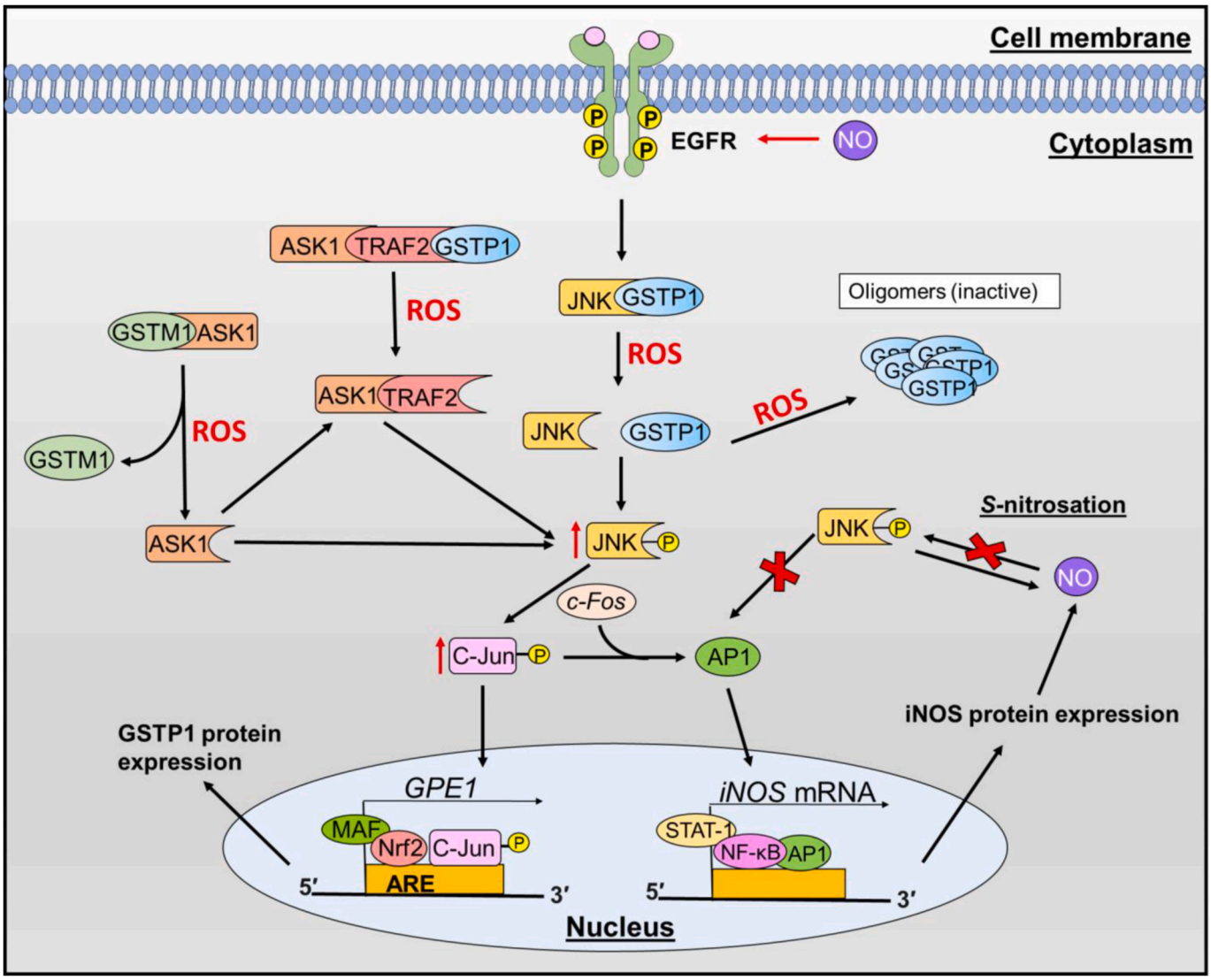

Fig. 4. Coordinate GSTP and iNOS mRNA expression mediated by ROS-induced activation of the JNK signaling pathway and the subsequent expression of target genes. Phosphorylation and activation of EGFR result in the monomerization of GSTP1, which then binds JNK and inhibits its activity and subsequent downstream signaling. Oxidative stress promotes GSTP1 oligomerization that then results in the liberation of JNK and the activation of its downstream targets, c-Jun and AP1. Subsequently, c-Jun can transactivate the GSTP1 enhancer, GPE1, resulting in elevated GSTP1 expression, indicating a potential negative feedback mechanism for inhibiting JNK activity. On the other hand, AP1 enhances iNOS transcription, increasing its protein levels and, consequently, NO generation. Considering that NO inhibits JNK through S-nitrosation that then inhibits AP1 transcriptional activity, the generation of NO may act as a negative feedback on JNK and NO generation via iNOS.

upstream signal transduction that leads to JNK and p38 phosphorylation [33]. TRAF2 is an important signal transducer for many TNF receptor superfamily members [118,148,149]. The release of TRAF2 into the cytoplasm leads to the activation of MAPKs that mediate opposite effects [148]. As previously mentioned, another vital protein-protein interaction of GSTP1 in the JNK pathway is the association of GSTP1 with the TRAF domain of TRAF2 [33,34,116]. It has been demonstrated that GSTP1 physically binds to TRAF2 (Fig. 4) and that GSTP1 overexpression results in TRAF2-induced inhibition of JNK and p38 activation [33]. The same study reported that GSTP1 inhibited ASK1 activation and TRAF2-ASK1-induced signaling [33]. This observation again highlights the prominent role of GSTP1 in cellular signaling through its direct interaction with multiple proteins (Fig. 4). In particular, the downstream impact of GSTP1-mediated inhibition of JNK and p38 is of interest in terms of NO metabolism, as p38 [150–152] and JNK [153,154] induce NOS expression. Of interest, there are several reports indicating regulation of the MAPK pathway by NO [155–158].

6.2. NO and NO derivatives as mediators of the JNK pathway

Similarly to GSTP1, studies have revealed that endogenously produced NO can suppress JNK activation *via S*-nitrosation in BV-2 murine microglial cells, RAW264.7 cells, and rat alveolar macrophage cells (Fig. 4) [155]. In these studies, IFN-γ-induced suppression of JNK1 activation was prevented by N^G-nitro-L-arginine, a NO synthase inhibitor [155]. Moreover, the NO donor, *S*-nitroso-*N*-acetyl-DL-penicillamine (SNAP), was also able to suppress the activation of JNK1 *in vivo* [155]. Further studies demonstrated that IFN-γ-induced NO production in RAW264.7 cells increased the *S*-nitrosation of JNK1 at Cys^{116}. This observation is of interest given the involvement of Cys^{116} in the thiol-mediated redox regulation of JNK1 [159].

It was later discovered that NO could inhibit all three JNK isotypes *via* a thiol-mediated redox mechanism [158]. This inhibition is reversible and could modify JNK and its kinase properties while still allowing the phosphorylation of JNK by SAPK/Erk kinase (SEK1) [158]. It was suggested that NO-mediated inhibition of JNK, unlike that mediated by

GSTP1, occurred by suppressing the interaction between JNK and c-Jun [158]. These studies are supported by more recent reports that show a NO-mediated increase in serum deprivation-induced apoptosis of meniscal cells *via* the inactivation of JNK [160]. Some data also indicates that *S*-nitrosation may suppress the JNK activator, ASK1 [161].

Additional complexity regarding the effects of NO on these signaling pathways is demonstrated by studies demonstrating that the DNA-binding activity of c-Jun may be suppressed by physiological levels of *S*-nitrosoglutathione, which can modify specific cysteine residues within c-Jun's DNA-binding site [162]. The binding site of another down-stream target of JNK, AP-1 (composed of c-Jun and c-Fos), is also suppressed *via* the modification of conserved cysteine residues in the c-Jun- and c-Fos-binding domain by NO [163]. Although it is suggested that NO functions to inactivate the JNK pathway *via S*-nitrosation of JNK itself, studies examining the impact of NO donors and NO derivatives such as reactive nitrogen species (RNS) suggest a more complex relationship.

While ROS and RNS are generally considered as "radical species," RNS possess distinctive chemical and biological properties that facilitate the *S*-nitrosation and nitration of target molecules [164]. Considering this, RNS can exert oxidative activity *via* species such as peroxynitrite, which is produced by the reaction of NO and superoxide [165]. Conflicting with the research above, studies have shown that exogenous NO donors, such as sodium nitroprusside (SNP), *S*-nitrosoglutathione, and diethylamine NONOate, exert similar effects as ROS and can activate JNK [166–168]. These results are corroborated by reports of JNK activation following increased iNOS levels induced by serum deprivation of PC12 pheochromocytoma cells [169].

Of interest, the generation of NO and superoxide ($O_2^{\cdot-}$) are necessary for activating JNK by shear stress in endothelial cells [170]. Increased shear stress increases tyrosine nitration, a common marker for RNS generation, which was suppressed by NO scavengers and inhibitors [170]. Incubating these cells with peroxynitrite also resulted in JNK activation [170].

Considering the suppression and activation of the JNK pathways by RNS, it is possible that their effect on JNK activity is dependent on the specific RNS species, their concentration, the cell-type, and the cellular redox state [155,158,161,164,166,166–169,171–175]. JNK appears to be effectively inactivated by *S*-nitrosation induced by endogenous NO [155,158]. However, in cells that are exposed to increased levels of shear stress and ROS, RNS seems to instead induce JNK activation [164]. These results suggest that RNS may function as a signaling molecule in the activation and suppression of JNK, and this is dependent on the redox state of the cell [155,158,161,164,166,166–169,171–175]. This relationship of NO to the JNK pathway may be linked to the regulatory activities of GSTP1 in this pathway.

6.3. *The coordinate regulation by GSTP1 and NO of the JNK pathway and its implications*

As illustrated in Fig. 4 and as described above, GSTs and NO play integral roles in the activation or suppression of the JNK pathway. Considering the GSTP1- and GSTM1-mediated inhibition of JNK and its down-stream targets, AP1 and p38 [69], which transcriptionally activate iNOS [120,150], an underlying regulatory mechanism of iNOS by GSTs may exist. Given the mechanisms of GSTP1 in suppressing NO generation [24,35], it can be suggested that GSTs inhibit JNK activation to maintain favorable NO levels for apoptosis. This hypothesis is supported by the feedback mechanism of NO, in which RNS can induce JNK activation and the subsequent activation of transcription factors that increase iNOS transcription [120,133,134,153,164]. In contrast, iNOS-mediated generation of NO can inhibit JNK activation [155,158,171], and this is supported by the positive feedback of GSTP1 *via* c-Jun, which can promote GSTP1 expression, and hence, the inhibition of the JNK pathway [144,145]. These feedback systems for NO inhibition and activation can be associated with broader GSTP1-mediated suppression of NO signaling in survival and apoptosis pathways (Section 7).

7. The interplay of GSTP1 in inhibiting apoptosis and survival pathways that induce NO

As mentioned above, high ROS and RNS levels are toxic and can result in non-specific DNA, protein, and lipid damage within the cell [36,176,177]. The response to such insults is to promote the expression of antioxidants such as the GSTs to alleviate oxidative stress [36,178,179]. However, when the cell has endured significant damage, apoptosis can occur. Thus, the cell can flux between apoptosis and survival responses depending on the cellular state [36,180–182], which may be regulated by GSTP1. To understand the potential connection of GSTP1 with the opposing pathways of survival and apoptosis, the interplay between ROS and the NF-κB and JNK pathways is first briefly described below.

There are two central pathways involved in apoptosis: the death receptor (extrinsic) and the mitochondrial (intrinsic) pathways, which both require caspase activity [183]. The role of NF-κB in these pathways is to inhibit apoptosis [36,182,183]. The relevance of this function of NF-κB is supported by the embryonic lethality and liver degeneration observed in mice lacking the RelA component of NF-κB [184]. Furthermore, other studies expound on the importance of IKKβ and IKKγ in preventing embryonic liver apoptosis [185–187]. On the other hand, activated JNK can promote apoptosis *via* c-Jun/AP1 mediated expression of pro-apoptotic genes or by translocating to the mitochondria [36,188]. Within mitochondria, JNK can phosphorylate Bcl2 to inhibit its anti-apoptotic activity [188]. Additionally, JNK can also stimulate the release of cytochrome *c* from the mitochondrial inner membrane, which initiates the activation of the caspase-9-dependent caspase cascade to induce apoptosis [188].

Several feedback mechanisms have been identified between ROS, caspases, JNK, and the NF-κB pathway [180,182]. The expression of anti-apoptotic genes such as Bcl-2 and caspase inhibitors are induced by NF-κB [189,190]. Moreover, NF-κB can transactivate multiple antioxidant genes, including *manganese superoxide dismutase* (*MnSOD*), *Cu, Zn superoxide dismutase* (*SOD1*), *ferritin heavy chain* (*FHC*), *thioredoxin 1* (*TRX1*), *TRX2*, *GSTP1*, *metallothionein-3* (*MT3*), *NAD(P)H quinone dehydrogenase 1* (*NQO1*), *heme oxygenase* 1 (*HO-1)*, *glutathione peroxidase 1* (*Gpx1*), and *dihydrodiol dehydrogenase* (*DDH1*) [36]. In fact, NF-κB activation results in the inhibition of prolonged JNK activation, probably *via* the assuagement of ROS due to the up-regulation of anti-oxidant targets and other activities [36,180,191,192]. However, the inhibition of NF-κB stimulates apoptosis [185–187].

In view of the studies above demonstrating the association of GSTP1 with JNK, TRAF2, IKKβ, and IKβa in the JNK and NF-κB pathways (Section 5-6), a new hypothesis can be proposed (Fig. 5). It can be speculated that the inhibitory activity of GSTP1 on the NF-κB *versus* JNK pathways may be mediated by NO and other ROS through their ability to induce GSTP1 oligomerization leading to the release of JNK [39,121,126,142]. The liberation of JNK then results in its activation and the induction of apoptosis [32,116,119,125,126,137,138,140,188] (Fig. 5).

It has been proposed that ROS behaves as a bridging molecule in NF-κB and JNK crosstalk [36,193]. Under normal physiological conditions, ROS is attenuated by activating the expression of the antioxidants mentioned above *e.g.*, SOD1, HO-1, GSTP1, *etc*. However, the excessive production of mitochondrial ROS can instead instigate JNK apoptotic pathways and induce the prolonged activation of JNK [180,188]. In addition to mitochondrial ROS, NO can also stimulate apoptosis at high concentrations. In our proposed mechanism (Fig. 5), GSTP1 inhibits the NF-κB pathway under conditions of excess ROS to favor apoptosis through prolonged JNK activation and the NF-κB-mediated inhibition of iNOS transcription. This suggestion is supported by GSTP1 dissociation from JNK and the subsequent oligomerization of GSTP1 *via* ROS [39,121,126,142] (Fig. 5). Although these latter studies demonstrate GSTP1 oligomerizes with ROS, this has only been observed regarding the GSTP1-JNK interaction [39,121,126,142].

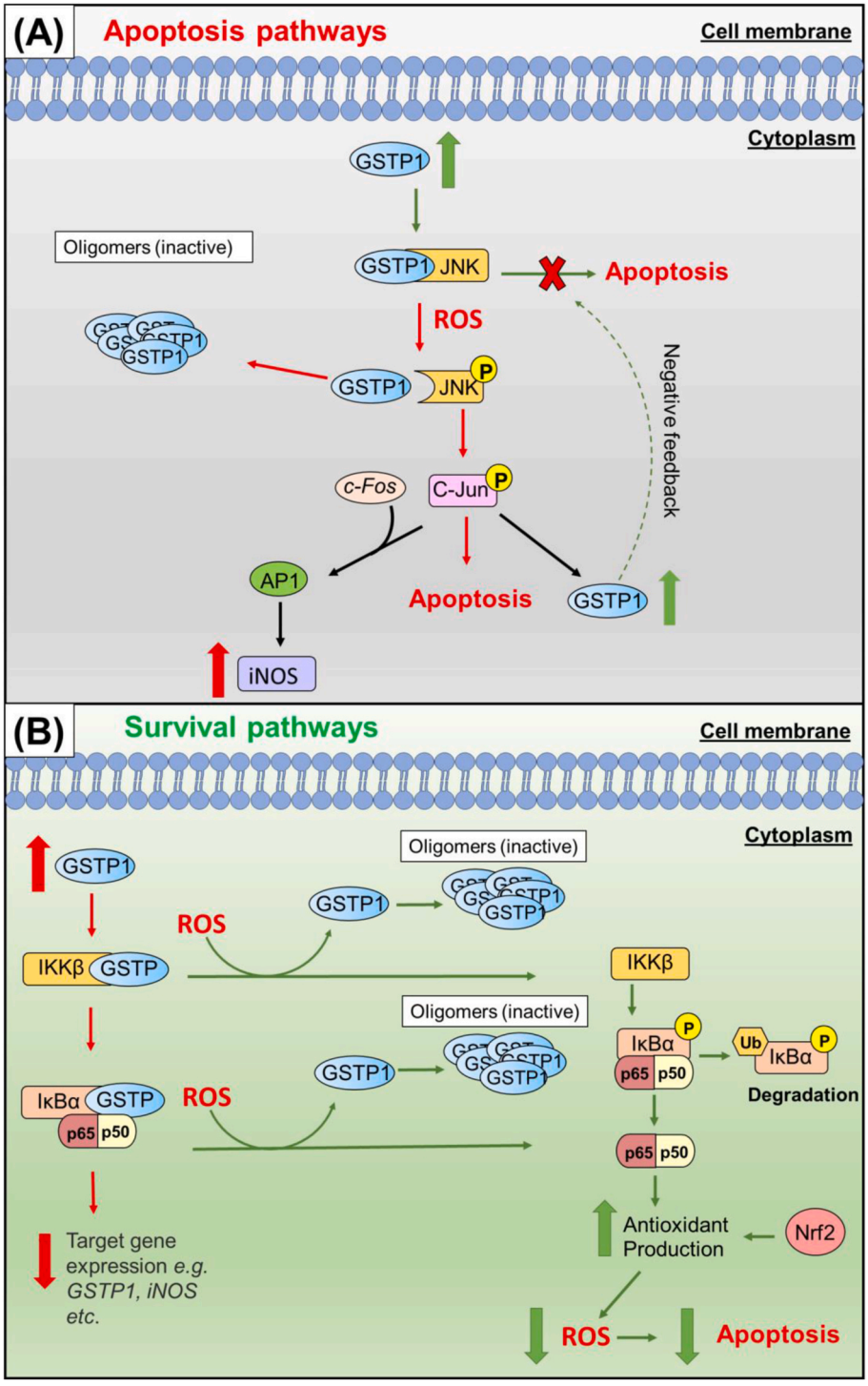

Fig. 5. The proposed interplay between apoptosis and survival pathways and the dual function of GSTP1. (A) Elevated GSTP1 levels result in the increased binding of GSTP1 to JNK and inhibition of this apoptosis pathway. This mechanism is activated upon the induction of excessive ROS, which oxidizes cysteines in GSTP1, resulting in oligomerization and inactivation, and also JNK liberation. JNK can then be phosphorylated, resulting in the up-regulation of its downstream targets, c-Jun and AP1, to induce apoptosis. Notably, AP1 can also function to increase iNOS transactivation. Furthermore, c-Jun can promote the transcription of *GSTP1*, indicating a potential negative feedback to inhibit JNK activity. **(B)** GSTP1 can bind both IKKβ and IκBα for inhibition of NF-κB-mediated transcription of target genes involved in alleviating oxidative stress, *e.g., GSTP1*. It is suggested that the generation of ROS will promote the dissociation of GSTP1 from IKKβ and IκBa, resulting in the phosphorylation and degradation of IκBa and the release of the NF-κB complex. Activation of this pathway will promote cellular survival through increased antioxidant production and the alleviation of ROS, which can then decrease ROS-induced JNK-mediated signaling. The oscillation between these pathways may be mediated by the ROS-dependent binding of GSTP1 to other proteins (*e.g.*, IKKB), considering that every pathway results in a negative feedback mechanism to suppress GSTP1 expression.

Additionally, investigations examining the endogenous production of GSTP1 *via* the Nrf2 pathway after it is activated by ROS [145,146] suggest that under redox stress, there is sufficient GSTP1 to inhibit the NF-κB pathway. As stated above, NF-κB can function to halt prolonged JNK activation *via* JNK/NF-κB crosstalk and by decreasing ROS levels [36,180,191,192]. This decrease in oxidative stress is achieved by the transcription up-regulation of antioxidants that can scavenge ROS [36,146,180,191,192], likely preventing the oligomerization of GSTP1. The generation of GSTP1 within both these pathways may favor the inhibition of apoptosis pathways through GSTP1-mediated inhibition of TRAF2, ASK1, and JNK.

It has been suggested that TNF-α may play a crucial role in the crosstalk between JNK and NF-κB pathways through the selective activation and inhibition of NF-κB signaling, which prevents prolonged JNK activity [36,180,193,194]. This mechanism may be linked to the GSTP1-NO relationship, as GSTP1 can inhibit activation of LPS-induced MAPKs, including JNK and p38, as well as NF-κB in RAW264.7 cells [69]. This inhibition *via* GSTP1 resulted in decreased TNF-α and NO generation, highlighting yet another regulatory mechanism of NO by GSTP1. It is further proposed that GSTP1 may act as a molecular switch for LPS-induced ROS [69].

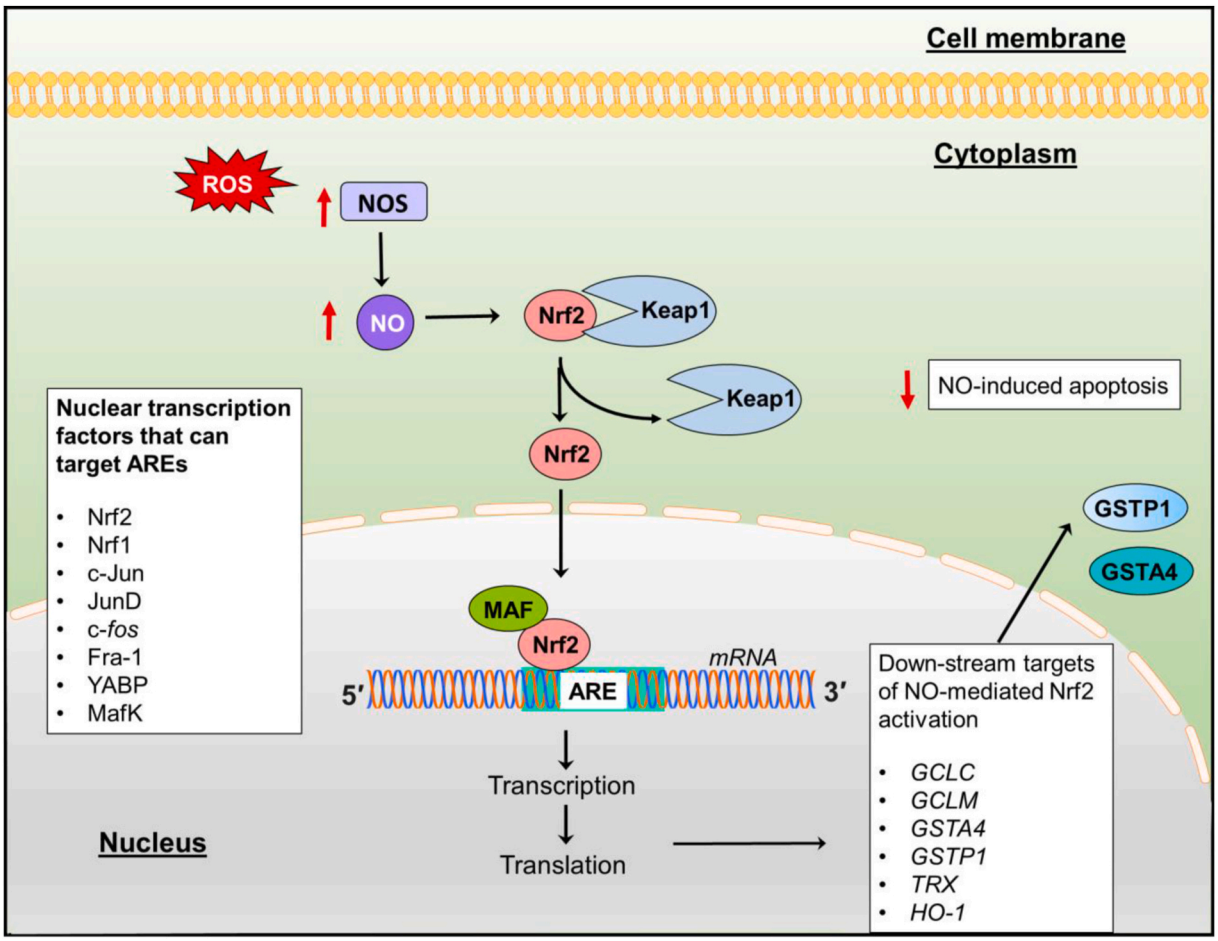

Fig. 6. NO-mediated nuclear translocation of Nrf2 and transcriptional up-regulation of genes containing AREs in their promoters. It has been demonstrated that NO can induce the dissociation of the transcription factor, Nrf2, from Keap1, potentially via S-nitrosylation of their cysteine residues, leading to increased Nrf2 nuclear translocation. This NO-mediated translocation of Nrf2 increases the transcription of genes possessing AREs in their promoters, namely: GCLC, GCLM, GSTA4, GSTP1, and TRX. The up-regulation of these genes combats NO-induced cytotoxicity and apoptosis. Of note, other nuclear transcription factors (e.g., c-Jun) can also target AREs, although to a lesser extent than Nrf2.

8. NO-induced transcriptional up-regulation of protective genes by Nrf2 *via* AREs

The physiological effect of NO on inducing apoptosis largely depends on the concentration of NO and the cell-type [5,195–201]. The current predominant view is that high NO concentrations exert cytotoxic effects by reacting with superoxide to generate RNS such as peroxynitrite, which results in non-specific DNA, protein, and lipid damage [5,202]. Such effects can promote the activation of downstream signaling pathways and gene expression, including the Nrf2 pathway [178,203] (Fig. 6). It is well established that Nrf2 transcriptionally activates genes encoding detoxification enzymes through associating with AREs located within the promoter and enhancer regions of genes including *GSTs A, M*, and *P* [144–146,204,205].

Under physiological conditions, Nrf2 activity is inhibited by the binding of Keap1, which leads to the proteasomal degradation of Nrf2 (Fig. 6.) [206,207]. In the presence of ROS/RNS, Keap1 is inactivated by the oxidation of key cysteine sulfhydryl groups leading to the translocation of Nrf2 to the nucleus for the activation of ARE-mediated gene expression [146,178,208]. It has been proposed that cysteine residues within Keap1 are sensors for phase 2 enzyme induction and protection of cells from ROS [209–212]. In fact, *S*-nitrosation of these cysteine residues by NO may explain the NO-induced dissociation of Keap1 from Nrf2 and subsequent nuclear translocation of Nrf2 [213]. It has also been demonstrated that exposure of neuroblastoma cells to NO resulted in a marked increase in the transcription of the ARE-regulated genes, *GCLC*, *GCLM*, *GSTP1*, and *HO-1*, and a moderate increase of *GSTA4* and *TRX* levels, to combat NO-induced apoptosis (Fig. 6) [178]. A similar study demonstrated that the role of NO in activating MAPK pathways in endothelial cells was linked to the ability of NO to increase Nrf2 translocation to the nucleus and its transactivation of *HO-1* [214].

Considering the roles of GSTs in modulating NO levels and transcription discussed above, the increased translocation of Nrf2 to the nucleus and the subsequent increase in GSTP1 expression may be a response to inhibit NO-mediated cytotoxicity. It can be collectively suggested that high NO concentrations increase the transactivation of AREs by Nrf2 to promote cytoprotection against NO *via* GSTP1 expression (Fig. 6). Other nuclear transcription factors, including Nrf1, c-Jun, JunD, *c-Fos*, Fra-1, YABP, MafK, and AP-1, can also bind and regulate AREs [146,179,215–220] and potentially the expression of GSTP1. As previously mentioned, Nrf2 and c-Jun have been shown to transactivate the ARE within the *GPE1* promoter of GSTP1 [145]. Hence, GSTP1 expression is modulated by a number of transcription factors, with Nrf2 being a significant regulator.

9. Summary

Traditionally, the GSTs are well-known antioxidants that catalyze glutathionylation of xenobiotics, including anti-cancer drugs to prevent their cytotoxicity. It has been suggested that GSTs evolved from

possessing a serine or cysteine in their catalytic site to having a tyrosine residue that interacts with NO as DNICs. Studies conducted by our laboratory demonstrated that the interaction of GSTP1 with MRP1 facilitates the storage and transport of NO as DNICs that protects macrophages from NO cytotoxicity (Fig. 1). More recently, it has been discovered that GSTP1 directly associates with iNOS resulting in its inhibition, suggesting GSTP1 acts as a regulatory nexus in NO metabolism. These interactions may explain many studies demonstrating a strong correlation between preeclampsia, hypertension, and atherogenesis with *GSTM1* or *GSTT1* null genotypes.

Other key associations of GSTP1 can be identified in the NF-κB and JNK pathways (Figs. 3–5), where GSTP1 interacts with proteins to inhibit NO generation by iNOS and to maintain sufficient cellular levels of NO to mediate survival or apoptosis pathways. Considering this, it is suggested that GSTP1 functions as a "molecular switch" between survival and apoptosis and also for NO generation. The common functional role of GSTP1 throughout its interactions and pathways discussed herein is that this protein acts as a good Samaritan for maintaining cellular viability. This role is particularly facilitated by the ability of GSTP1 to interact directly with NO as DNICs, or indirectly through its ability to bind iNOS and other proteins in the JNK and NF-κB pathways.

While the direct association of GSTP1 with many regulatory proteins has been documented, it remains unclear how it fluxes between all these molecules and the factors that regulate these interactions to enable cellular death or survival. Although the impact of ROS on GSTP1 activity is well documented in the pro-apoptotic JNK pathway (Fig. 4), further studies are required to elucidate its effect on the anti-apoptotic NF-κB pathway and the crosstalk between these processes (Fig. 5). For instance, it has been demonstrated that high ROS levels lead to GSTP1 oligomerization. However, it is unclear if this influences the NF-κB pathway. Based on previous studies indicating that GSTP1 oligomerization leads to its inactivity and, subsequently, JNK activation to induce apoptosis, it can be speculated that the following events will also occur. These include: **(1)** the binding of GSTP1 to inhibit the NF-κB pathway *via* its interactions with Iκα and IKKβ, leading to prolonged JNK activation that induces apoptosis; **(2)** increased c-Jun activation and subsequent transactivation of the *GPE1* enhancer region of *GSTP1*; and **(3)** ROS-mediated activation of Nrf2 to up-regulate antioxidant response genes such as *GSTP1*. The combined product of these protective responses is the alleviation of redox stress due to the up-regulation of GSTP1 and other antioxidant proteins that leads to the binding of nascent GSTP1 to JNK, which then inhibits its apoptotic activity.

In conclusion, considering the functions of GSTs in detoxification and the roles of NO in cell signaling and cytotoxic effector functions, the interactions of GSTs with multiple effector proteins highlight an innovative role of GSTs in NO metabolism. Future studies examining these GST interactions and their impact on the function of NO will be valuable in understanding the potentially expanding roles of GSTP1as a good Samaritan.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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