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Minireview

Molecules and Cells

Transcriptional Regulation of the AP-1 and Nrf2 Target Gene Sulfiredoxin

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"Two-cysteine" peroxiredoxins are antioxidant enzymes that exert a cytoprotective effect in many models of oxidative stress. However, under highly oxidizing conditions they can be inactivated through hyperoxidation of their peroxidatic active site cysteine residue. Sulfiredoxin can reverse this hyperoxidation, thus reactivating peroxiredoxins. Here we review recent investigations that have shed further light on sulfiredoxin's role and regulation. Studies have revealed sulfiredoxin to be a dynamically regulated gene whose transcription is induced by a variety of signals and stimuli. Sulfiredoxin expression is regulated by the transcription factor AP-1, which mediates its up-regulation by synaptic activity in neurons, resulting in protection against oxidative stress. Furthermore, sulfiredoxin has been identified as a new member of the family of genes regulated by Nuclear factor erythroid 2-related factor (Nrf2) via a conserved *cis*-acting antioxidant response element (ARE). As such, sulfiredoxin is likely to contribute to the net antioxidative effect of small molecule activators of Nrf2. As discussed here, the proximal AP-1 site of the sulfiredoxin promoter is embedded within the ARE, as is common with Nrf2 target genes. Other recent studies have shown that sulfiredoxin induction via Nrf2 may form an important part of the protective response to oxidative stress in the lung, preventing peroxiredoxin hyperoxidation and, in certain cases, subsequent degradation. We illustrate here that sulfiredoxin can be rapidly induced *in vivo* by administration of CDDO-TFEA, a synthetic triterpenoid inducer of endogenous Nrf2, which may offer a way of reversing peroxiredoxin hyperoxidation *in vivo* following chronic or acute oxidative stress.

INTRODUCTION

Peroxiredoxins (Prxs) are a ubiquitous family of peroxidases with cytoprotective and antioxidative effects (Immenschuh and Baumgart-Vogt, 2005). The "two-cysteins" (2-Cys) Prxs are the predominant Prx subfamily, comprising Prx I-IV (Wood et al., 2003) and have an important antioxidative role in diverse cell systems (Immenschuh and Baumgart-Vogt, 2005; Rhee et al., 2005; Wood et al., 2003). For example, in neuronal cells Prxs are protective against Aβ toxicity (Yao et al., 2007), excitotoxicity (Hattori et al., 2003), oxygen-glucose deprivation (Boulos et al., 2007), peroxide (Fang et al., 2007; Sanchez-Font et al., 2003), and MPP^+ toxicity (Qu et al., 2007). 2-Cys Prxs contain a peroxidatic cysteine residue, oxidized by peroxides to cysteine sulfenic acid (-SOH). Cys-SOH then forms a disulfide bond with the resolving cysteine, which is in turn reduced by thioredoxin (Wood et al., 2003). Sometimes, under increased oxidative stress, Prx-SOH is further oxidized by peroxide to sulfinic ($-SO_2H$) acid, causing inactivation of peroxidase activity (Rhee et al., 2007). Prx-SO_2H is not a substrate for the resolving cysteine and cannot be reduced by thioredoxin. As such, Prx hyperoxidation to Prx-SO_2H was thought to be irreversible. Subsequently, it has been found that Prx-SO_2H can be reduced back to the catalytically active thiol form by two ATP-dependent reductases, sulfiredoxin (Biteau et al., 2003; Chang et al., 2004) and sestrin 2 (Budanov et al., 2004). However, recent doubt has been cast on the ability of sestrin 2 to catalyze this reaction (Rhee et al., 2009). Sulfiredoxin acts by catalysing the ATP-dependent formation of a sulfinic acid phosphoric ester on Prx which is then reduced by thiol equivalents such as thioredoxin (Jeong et al., 2006; Jonsson et al., 2008a; 2008b; Rhee et al., 2007). Sulfiredoxin has also been shown to have an additional enzymic activity: the reversal of glutathionylation (Findlay et al., 2006)

Sulfiredoxin is an AP-1 target gene

The first report of direct transcriptional regulation of the sulfiredoxin promoter involved a microarray-based search for glucose/cAMP regulated genes in Min6 insulin-secreting cells (Glauser et al., 2007). Bioinformatics revealed a large number of potential AP-1 target genes in the population of up-regulated genes, which included sulfiredoxin. AP-1 regulation of the sulfiredoxin promoter was subsequently demonstrated (Glauser et al., 2007).

At the same time, our interest in sulfiredoxin arose through our investigation into the regulation of intrinsic antioxidant defences in neurons. We found that synaptic activity, acting via NMDA receptor (NMDAR) signaling, boosted antioxidant defences through a coordinated pattern of gene expression that

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included the up-regulation of sulfiredoxin. Both sulfiredoxin and sestrin 2 were induced by synaptic activity, which also promoted the reduction of hyperoxidized peroxiredoxins (Papadia et al., 2008). Simultaneous knock-down of sulfiredoxin and sestrin 2 promoted neuronal vulnerability of neurons to oxidative stress (Papadia et al., 2008). In the light of recent studies it may be that induction of sulfiredoxin is the more significant to neuroprotection than sestrin 2 (Rhee et al., 2009). Study of the transcriptional regulation of sulfiredoxin in neurons revealed that it could be induced by AP-1. Furthermore, we pin-pointed the sites of regulation to two *cis*-acting AP-1 consensus sites (Papadia et al., 2008). Mutation of each AP-1 site in turn reduced transcriptional activation of sulfiredoxin by synaptic activity, and mutation of both sites abolished induction completely (Papadia et al., 2008). The proximal AP-1 site is completely conserved in diverse mammalian species such as rodents, rats and cows, and humans. However, the distal site, while well-conserved for the most part, has been lost from the primate lineage. As such, AP-1 responsiveness of sulfiredoxin in humans may rely on this single site.

The direct regulation of sulfiredoxin by AP-1 acting via these two sites was confirmed in the context of mouse epidermal cells. Here it was shown that 12-*O*tetradecanoylphorbol-13-acetate (TPA)-mediated induction of sulfiredoxin was stimulated by AP-1 acting on these sites (Wei et al., 2008). Expression of the widely-used inhibitor of AP-1 mediated gene expression, TAM67 (a dominant-negative form of c-Jun (Brown et al., 1993)) both inhibited synaptic activity-dependent induction of the sulfiredoxin promoter in neurons (Soriano et al., 2008) as well as its induction by TPA in mouse JB6 cells (Wei et al., 2008).

Sulfiredoxin is an Nrf2 target gene

A known defence against oxidative insults is the induction of a group of genes encoding antioxidative and drug-metabolizing enzymes (Kensler et al., 2007). These genes are induced by a variety of small thiol-active molecules including the potent chemopreventive agent 3H-1,2-dithiole-3-thione (D3T) (Kensler et al., 2007; Nguyen et al., 2004). Transcriptional regulation of this group of genes is mediated by a *cis*-acting promoter element termed the antioxidant response element (ARE), which recruits the transcription factor Nuclear factor erythroid 2-related factor (Nrf2) as a heterodimer with small Maf proteins (Zhang, 2006). Nrf2 levels are constitutively low due to being targeted for degradation by Kelch like ECH-associated protein (Keap)-1. Under conditions of oxidative stress, Nrf2 degradation is slowed and Nrf2 accumulates in the nucleus and activates ARE-containing genes, with a net antioxidative effect (Nguyen et al., 2004). Small molecule activators of Nrf2 such as D3T also act by interfering with Keap1-mediated degradation. Activation of Nrf2 and induction of ARE-driven defences is implicated in protecting against a variety of diseases in many organs and tissues, including autoimmune diseases, cancer, cardiovascular, neurodegenerative disease and ischemia (Giudice and Montella, 2006; Lee et al., 2005; Shih et al., 2005; Zhang, 2006).

We found that in cortical neurons, expression of Nrf2 rendered them highly resistant to peroxide-induced apoptosis in a cell-autonomous manner (Soriano et al., 2008). Moreover, treatment with the Nrf2 activator D3T inhibited the formation of inactivated, hyperoxidized peroxiredoxins following oxidative trauma, and protected neurons against oxidative stress. In both neurons and glia, Nrf2 expression and treatment with chemopreventive Nrf2 activators, including D3T, sulforaphane and tBHQ, up-regulated expression of sulfiredoxin (Soriano et al., 2008). Analysis of the rat sulfiredoxin promoter revealed a sequence near to the transcription start site (TCACCCTGAGTCAGCG) which resembled an ARE. This includes a near-perfect match for the established consensus (TMAnnRTGA(Y/G)nnnGCR) (Wasserman and Fahl, 1997) with the additional inclusion of two cytosine residues found to be additionally important for ARE activity ((Nioi et al., 2003), TMACnRTGAYnCnGCR). This sequence is remarkably well-conserved across mammalian species as diverse as dolphins, mice and primates (Fig. 1).

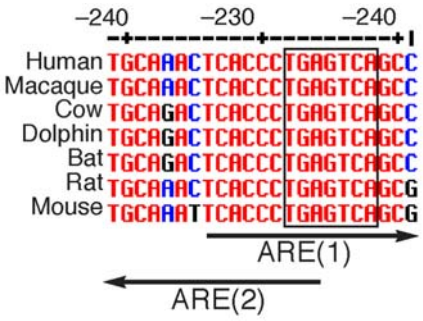

Fig. 1. Schematic showing the high conservation of the Nrf2-responsive region of the mammalian sulfiredoxin promoter. ARE(1) and ARE(2) identified by Soriano et al. (2008) and Singh et al. (2009) respectively. Numbers indicate the position of the ARE relative to the transcription start site in humans. Note that position is also well conserved [ARE position is at -232 (humans) -256 (rats), -211 (mice)]. Red letters indicate maximum conservation. Boxed region indicates AP-1 response element (see text for further details).

In a paper published very shortly after ours, Biswal and co-workers also convincingly show that sulfiredoxin expression is regulated by Nrf2 by a *cis*-acting ARE (Singh et al., 2009). They found that sulfiredoxin expression was induced in the lung in response to cigarette smoke in a Nrf2-dependent manner. Through overexpression and knock-down experiments they demonstrated that sulfiredoxin played an important role in promoting resistance of lung epithelial cells to peroxide-induced cell death.

Interestingly, the ARE proposed in this study is in a slightly different position, running in the opposite orientation to the one we proposed, and offset by seven nucleotides (Fig. 1). This motif, found by using a shorter consensus (RTGA(Y/G) nnnGCR) as a probe, is conserved across many mammals, except mice. This sequence also includes a TMAnn motif in the correct position, though neither of the two additional cytosine residues. In both studies (Singh et al., 2009; Soriano et al., 2008), point mutations made to each ARE would be predicted to impair the function of the other ARE. In all likelihood, both AREs are functional.

The sulfiredoxin ARE contains an AP-1 site: target for both chemopreventive drugs and tumour-promoting compounds

Another interesting facet of sulfiredoxin regulation is that its Nrf2- and AP-1- responsiveness is contained within the same sequence. The proximal, conserved AP-1 site (TGAGTCA) is contained within the ARE site that we recently identified (TCACCC-TGAGTCAGCG, (Soriano et al., 2008)). Several AREs such as those in the promoters of human *NQO1* and *HMOX1* contain AP-1 like sequences and can respond to AP-1-activating stimuli, as well as Nrf2 (Nguyen et al., 2004). The composite ARE/AP-1 site on the sulfiredoxin promoter enables it to respond both to small molecule Nrf2 activators (Soriano et al., 2008) as well

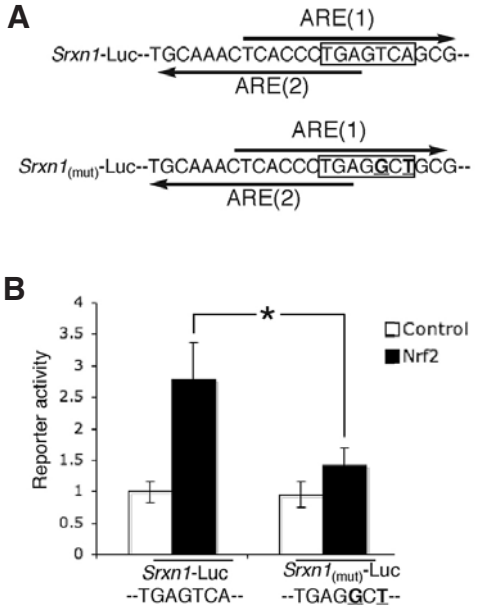

Fig. 2. Mutation of residues supposedly specific to the AP-1 site influence Nrf2-responsiveness of the sulfiredoxin ARE/AP-1 composite element. (A) Schematic showing the mutations made to the consensus AP-1 site embedded within the ARE identified by Soriano et al. (2008). (B) The mutations performed reduce the Nrf2-responsiveness of the sulfiredoxin promoter. Average of four independent experiments is shown. Mutagenesis, transfection and luciferase assays were all performed as described (Papadia et al., 2008). *P < 0.05, Paired Student *T*-test.

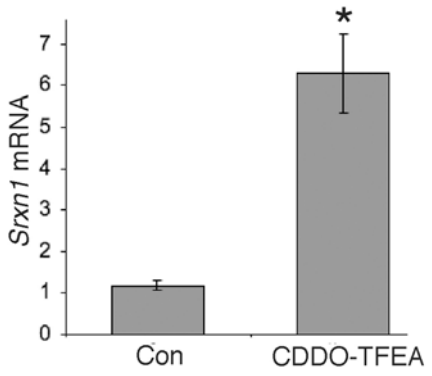

Fig. 3. Sulfiredoxin expression can be induced in vivo by the Nrf2 activator CDDO-TFEA. CDDO-TFEA (10% DMSO, 10% Cremophor-EL, 80% PBS) or vehicle only was injected intraperitoneally into adult mice at a dose of 20 μmol/kg. At 6 h following injection, the animals were sacrificed and lungs harvested (n = 4 for control and CDDO-TFEA). RNA was extracted and subjected to qPCR analysis for *Srxn1* expression as described (Soriano et al., 2008). Expression of *Srxn1* was normalized to GAPDH levels. *P < 0.05, Student *T*-test.

as synaptic activity (Papadia et al., 2008). A previous study had indicated that residues within the AP-1 consensus, but outside the traditional ARE consensus, may contribute to Nrf2-responsiveness (Nioi et al., 2003). Indeed, we find that mutation of the 5th and 7th residues of the AP-1 site in the sulfiredoxin promoter (to TCACCCTGAG**GCT**GCG, mutated residues in bold) had the effect of reducing Nrf2-responsiveness (Fig. 2). These residues were thought to be non-required 'n' residues within the ARE consensus but clearly influence the efficacy of the sulfiredoxin ARE. Note that these residues are outside the ARE identified by Biswal and coworkers, so residual Nrf2-responsiveness could be due to that ARE, as well as residual activity of the mutated ARE.

An apparent paradox associated with genes responsive to both Nrf2 and AP-1 is that while the former are targets of chemopreventive compounds, the latter is a target of certain tumor-promoting agents, such as TPA (Wei et al., 2008). Indeed, in the context of TPA stimulation, sulfiredoxin expression via AP-1 was found to be involved in cellular transformation (Wei et al., 2008). Thus, while sulfiredoxin may contribute to the chemopreventive effects of Nrf2 activating compounds that act to detoxify reactive intermediates of carcinogens, and boost antioxidant defenses, in the context of global AP-1 activation, its antioxidant properties seem to have a different effect.

Pharmacological manipulation of sulfiredoxin *in vivo*

In addition to the aforementioned report of up-regulation of sulfiredoxin in the lung by cigarette smoke via Nrf2 (Singh et al., 2009), a further study also demonstrated Nrf2-dependent induction of sulfiredoxin expression in the lung-this time in response to hyperoxia (Bae et al., 2009). Hyperoxia induced the hyperoxidation of mitochondrial Prx III and promoted the degradation of Prx III in Nrf2-deficient mice that failed to respond to hyperoxia with an induction of sulfiredoxin. This raises the possibility that in the absence of sulfiredoxin, hyperoxidized Prx III is vulnerable to proteolysis. The importance of sulfiredoxin's role at the mitochondria was further illuminated by another recent study (Noh et al., 2009). It was demonstrated that sulfiredoxin translocates from the cytoplasm to mitochondria in response to oxidative stress, where it promotes the reduction of hyperoxidized Prx III. Furthermore, mitochondrially targeted sulfiredoxin was found to be anti-apoptotic, protecting mitochondria from oxidative damage and loss of membrane potential (Noh et al., 2009).

These recent studies support the notion that sulfiredoxin is an important part of the protective response against oxidative stress in the lung (Bae et al., 2009; Singh et al., 2009), a response which also involves the induction of other antioxidative Nrf2 target genes (Kensler et al., 2007). Perhaps significantly, sulfiredoxin levels are depleted in patients with advanced chronic obstructive pulmonary disorder (Singh et al., 2009). This raises the possibility that pharmaceutical up-regulation of sulfiredoxin expression may represent a therapeutic strategy. To investigate this, we treated mice with a known inducer of Nrf2: a synthetic triterpenoid called 1[2-Cyano-3,12-dioxool-eana-1,9(11)-dien-28-oyl] trifluoroethylamide (CDDO-TFEA (Yates et al., 2007)), derivatives of which have been found to have potent cytoprotective, chemopreventive and anti-inflammatory effects (Liby et al., 2007). CDDO-TFEA was administered intraperitoneally to adult rats which resulted in the rapid induction of sulfiredoxin expression in the lung. A 6-fold induction of expression was observed at only 6 h post-administration (Fig. 3). Induction in the liver was even stronger (around 20-fold, data not shown) Thus, pharmaceutical induction of sulfiredoxin in the lung is achievable, and may slow the progression of chronic oxidative lung disorders, in concert with other Nrf2 target genes.

CONCLUSIONS

The regulation of sulfiredoxin by two overlapping AREs facilitates

its rapid transcriptional induction by both oxidative stress and small molecule activators of Nrf2. This Nrf2-responsiveness is observed in a variety of tissue types and is likely to be highly conserved within mammals. Sulfiredoxin is likely to be an important contributor to the cytoprotective and chemopreventive effects of Nrf2 activation.

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