Redox Biology 2 (2014) 1023–1028

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Mini Review

Role of sulfiredoxin in systemic diseases influenced by oxidative stress

Asha Ramesh [a,*], Sheeja S. Varghese [a], Jayakumar Doraiswamy [a], Sankari Malaiappan [a]

[a] Department of Periodontics, Saveetha Dental College and Hospitals, 162, Poonamallee High Road, Vellappanchavadi, Chennai, Tamil Nadu 600077, India

ARTICLE INFO

Article history:
Received 9 August 2014
Received in revised form
2 September 2014
Accepted 3 September 2014
Available online 16 September 2014

Keywords:
Sulfiredoxin
Antioxidant
Oxidative stress
Reactive oxygen species
Systemic diseases

ABSTRACT

Sulfiredoxin is a recently discovered member of the oxidoreductases family which plays a crucial role in thiol homoeostasis when under oxidative stress. A myriad of systemic disorders have oxidative stress and reactive oxygen species as the key components in their etiopathogenesis. Recent studies have evaluated the role of this enzyme in oxidative stress mediated diseases such as atherosclerosis, chronic obstructive pulmonary disease and a wide array of carcinomas. Its action is responsible for the normal functioning of cells under oxidative stress and the promotion of cell survival in cancerous cells. This review will highlight the cumulative effects of sulfiredoxin in various systemic disorders with a strong emphasis on its target activity and the factors influencing its expression in such conditions.

Contents

Overview-sulfiredoxin

Sulfiredoxin, a redox protein was discovered by Sun et al. in 1994 [1]. It was characterized initially in mouse epidermal JB6 cells, progressing from early to late stages of carcinogenesis. Sulfiredoxin causes activation of the mammalian peroxiredoxins, a cluster of 6 enzymes, of which it specifically acts on 2-Cys peroxiredoxins [Prx I–IV]. The peroxiredoxins are inactivated by the hyperoxidation caused due to the accumulation of hydrogen peroxide and other free radicals, thereby resulting in a molecular switch mechanism [2]. Sulfiredoxin is primarily located in the cytosol and it gets translocated to the mitochondria during increased oxidative burden [3]. Phosphorylation of the peroxiredoxin moiety is the first chemical step which can occur either by a direct transfer of the gamma phosphate of ATP to the peroxiredoxin molecule or through sulfiredoxin acting as a phosphorylated intermediate [4].

Transcriptional regulation of sulfiredoxin expression is mediated through activator protein-1 and nuclear factor erythroid-2 related factor-2 pathways. Sulfiredoxin as an AP-1 target gene was first reported in a microarray based research for glucose/cAMP regulated genes in Min6 insulin secreting cells [5]. A study on the transcriptional regulation of sulfiredoxin in neurons pinpointed the sites of regulation to two cis-acting AP-1 consensus sites [6]. The AP-1 inhibitor, TAM67 (a dominant-negative form of c-Jun) inhibited the synaptic-activity dependent induction of the

Abbreviations: Prx, peroxiredoxin; COPD, chronic obstructive pulmonary disease; TLR, toll like receptor; Nlrp3, NOD-like receptor family, pyrin domain-containing-3; Nrf2, nuclear factor erythroid 2-related factor 2; LPS, lipopolysaccharide; RANKL, receptor activator of nuclear factor kappa β ligand; RANK, receptor activator of nuclear factor kappa β

* Corresponding author.
E-mail addresses: ash.periopg@gmail.com (A. Ramesh), drsheeja@rediffmail.com (S.S. Varghese), principaldental@saveetha.com (J. Doraiswamy), msankari@gmail.com (S. Malaiappan).

http://dx.doi.org/10.1016/j.redox.2014.09.002

sulfiredoxin promoter in neurons [7]; as well as its induction by TPA (12-O tetradecanoylphorbol-13-acetate) in mouse JB6 cells [8].

A cis-acting promoter element called antioxidant response element (ARE) recruits transcription factors such as Nrf2 and maf proteins during oxidative stress. They regulate a group of genes encoding antioxidative enzymes like sulfiredoxin and drug metabolizing enzymes. The Nrf2 pathway was ascertained with studies using Nrf2 activators such as 3H-1,2-dithiole-3-thione (D3T), sulforaphane, which showed a significant induction in the enzyme expression.

An interesting facet of sulfiredoxin is that the AP-1 and Nrf2 responsiveness is contained within the same sequence i.e the proximal conserved AP-1 site is contained within the ARE site. The apparent contradiction is that AP-1 is a target for tumour promoting agents like TPA [8], whereas Nrf2 is a target for chemopreventive compounds. So sulfiredoxin, as an Nrf2 activator has chemopreventive effects due to its antioxidant property; on the other hand, it has a diametrically opposite effect via the AP-1 pathway [9].

Sulfiredoxin causes reduction of the cysteine sulfinic acid moiety of the peroxiredoxin enzyme back to its stable thiol state. The reaction involves the utilization of ATP and magnesium by sulfiredoxin in order to repair the enzyme. Since the inactivation is caused by an increase in the ROS levels, hydrogen peroxide performs its role as an intracellular cell signalling agent. This results in the activation of sulfiredoxin which in turn exerts its action on peroxiredoxins to efficiently neutralize the hydrogen peroxide molecules and attenuate intra-cellular oxidative stress. Peroxiredoxins also exist as dimers, decamers and high molecular weight complexes, of which the highest chaperone activity is seen in the latter two forms. Hyperoxidation results in the formation of decamers and high molecular weight complexes, thereby increasing the molecular chaperone activity of this enzyme. Reversal of the hyperoxidation invokes a molecular switch mechanism from chaperone to peroxidase activity, thereby terminating the signalling function of hydrogen peroxide and at the same time protecting the cells from oxidative damage caused by its accumulation [10].

Modification of protein cysteine residues by disulphide bond formation with glutathione (glutathionylation) is a reversible post-translational modification of utmost importance in cell signalling events following oxidative or nitrosative stress. It acts as a protective mechanism for proteins from undergoing terminal modifications, when exposed to oxidative stress. When the environment becomes more reducing, deglutathionylation takes place by removal of the glutathione moiety from the protein, either in an enzymatic or non-enzymatic manner. Glutathione, with two cysteine residues takes part in both the reactions. Sulfiredoxin possesses only one cysteine residue and highlights its advantage by not getting glutathionylated during the process [11]. So the other biologically relevant function of sulfiredoxin is deglutathionylation of proteins such as peroxiredoxin, actin and protein tytosine phosphatase 1B [12].

Systemic diseases and oxidative stress

Increased oxidative stress is the major etiopathogenic factor in various systemic diseases such as diabetes mellitus, obesity, atherosclerosis, hypertension, neurodegenerative disorders, inflammatory bone diseases like rheumatoid arthritis and periodontitis. The environmental or noxious stimuli from certain micro organisms could contribute to the oxidative burden imposed on these tissues.

Sulfiredoxin levels in health and disease

The assessed diseased states for this enzyme included atherosclerosis [13], chronic obstructive pulmonary disease [14] and a wide array of carcinomatous lesions. The more invasive squamous cell carcinoma, basal cell carcinoma to the less invasive small cell and large cell lung carcinoma were reviewed for the levels of sulfiredoxin.

Certain studies showed that there is a similarity in the expression of sulfiredoxin levels in a set of squamous cell [8,15] and adenocarcinomas respectively [15,16]. Renal carcinoma and the tumour adjacent renal epithelium cell lines were evaluated for sulfiredoxin mRNA expression. The tumour cell lines showed a significant increase in the target protein expression when compared to the latter [49].

Correlation of immunohistochemical staining results of human cross sectional studies revealed significantly high sulfiredoxin positivity in squamous cell carcinoma (88.1%), basal cell carcinoma (74.4%), melanoma (65.2%) followed by adenocarcinoma (55%), large cell carcinoma (22.2%) and small cell carcinoma (9.1%). The rise in sulfiredoxin positivity can be directly associated with the invasive nature and the metastatic potential of the carcinoma. The current findings can be explained by the fact that this protein has been shown to increase the cell motility and invasion, which will be elaborately discussed under the factors influenced by sulfiredoxin. This increased expression might have a potential value in the diagnosis, prevention or treatment of these tumours. In benign tumours such as papilloma (33%), condyloma (0%), dermato-fibro sarcoma (0%), there is a decline in the levels of sulfiredoxin. Mild sulfiredoxin positivity has been observed in chronic inflammatory conditions (7.7%). Immunohistochemically, the localization of the sulfiredoxin protein was towards the basal cell layer of the dermis in chronic inflammation [8].

Since the lungs are the target organs of the majority of the oxidative insult, robust antioxidant functioning is required for homoeostasis. In an in vivo study, a significant decrease in the sulfiredoxin expression in lungs with chronic obstructive pulmonary disease was observed in comparison to healthy tissue samples. This implied that the increase in oxidative stress in COPD lungs could not be efficiently neutralized by the action of sulfiredoxin. Low levels of sulfiredoxin results in impaired hydrogen peroxide detoxification, thereby resulting in exarcebated oxidative burden to the lungs [14].

Atherosclerosis is the major aetiological factor underlying myocardial infarction and stroke. Nrf2, with its target genes like sulfiredoxin has been implicated in the advanced stages of atheromatous plaque formation [13]. This redox protein can play a crucial role in the pathogenesis of the disease which requires an interplay between oxidative stress and inflammatory response. Plaque associated macrophages can undergo pro (M1) and anti-inflammatory (M2) polarization based on the environmental signals [17]. High levels of sulfiredoxin could be attributed to the increased generation of reactive oxygen species due to the transition of M2–M1 subset of macrophages, which are pro-inflammatory and essential for atherogenesis. The macrophages later develop into foam cells in the atheroma plaques. Also, Nrf2 is required to support the inflammatory reaction in the plaque, by cholesterol crystal induced Nlrp3 inflammasome activation [18], mediated by mitochondrial ROS production [19]. Hence this interrelationship is essential for the development of atherosclerosis.

The erythrocytes have an in-built oxidative stress response network due to the auto-oxidation of haemoglobin. They can also take up the oxidative stress from other tissues and diffuse it. Thus sulfiredoxin performs its role as an antioxidant and the intrinsic store remains constant even through the aging phases of the red blood cells [20].