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REVIEW

Nucleoredoxin Vis-à-Vis a Novel Thioredoxin in Regulating Oxidative Stress in Plants: A Review

Soham Hazra[1] · Avishek Chatterjee[2] · Somnath Bhattacharyya[3] · Poulomi Sen[4]

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Abstract Unavoidable biotic and abiotic stresses-led reactive oxygen species (ROS) generation has a profound negative impact on cellular intergradations. To impede the harmful effects of ROS, plant cells follow a multileveled complex network system of antioxidants, thus maintaining the cellular redox homeostasis. Report suggests plants having better antioxidative system show better performance under oxidative stress. Low molecular weight nucleoredoxin (NRX) is a nuclear thioredoxin (TRX) system with oxidoreductase capacity which can protect the cellular components like DNA, RNA or protein by protecting antioxidative enzymes like catalases. In response to the adverse environmental conditions, plant cells generate more ROS as a result of signal-led cellular defense mechanism. NRX plays a significant role in regulating the redox balance of the cell. Furthermore, for stress breeding during the process of developing stress-resistant varieties favorable alleles of NRX can be introgressed into elite breeding lines of different crops. This review describes the causes of oxidative stress, ROS production, major classes of ROS, role of ROS on plant growth and development, functional details of plant NRX and recent updates on plant NRX in different crops, especially in alleviating stress-incurred damages. NRX will be helpful in the progress toward developing varieties suitable for climate-resilient agriculture.

Keywords ROS · Antioxidant · Oxidative stress · Nucleoredoxin · DNA · RNA

Introduction

Reactive oxygen species (ROS) are produced in cell organelles such as chloroplasts, mitochondria and peroxisomes as a result of unavoidable aerobic metabolic processes like photosynthesis, respiration and photorespiration [77, 83]. Owing to their highly reactive nature, ROS can induce a series of unwanted chemical reactions affecting cellular integrity [7]. Cells have their own ROS-scavenging mechanisms [150] by contributing unpaired electrons; low molecular weight compounds known as antioxidants balance out these dangerous free radicals and unstable compounds [101]. The term “oxidative burst” refers to the excessive ROS generation occurring at the site of invasion under biotic or abiotic stresses as a result of cellular signaling during fast defense mechanisms [16, 140]. A wide range of developmental and stress-related processes are associated with the cellular accumulation of ROS [140, 141]. Fascinatingly, plants have developed the capability of utilizing oxidative stress (or ROS production) for various functions, viz. signaling and detecting different stresses, controlling growth, determining polarity and recognizing hormones and regulatory substances like amino acids and purines. They also play a

✉ Poulomi Sen
poulomisen6121991@gmail.com

[1] Department of Agriculture, Brainware University, Barasat, Kolkata, West Bengal, India

[2] School of Agriculture, Swami Vivekananda University, Barrackpore, West Bengal, India

[3] Crop Research Unit, Department of Genetics and Plant Breeding, Bidhan Chandra Krishi Viswavidyalaya, Mohanpur, Nadia, West Bengal 741252, India

[4] Department of Genetics and Plant Breeding, School of Agricultural Sciences, Sister Nivedita University, NewTown, West Bengal, India

pivotal role in gravitropic reactions and several other activities not directly associated with stress or oxidation [88]. Antioxidants aid in defending cells against the harmful effects of oxidative stress. Oxidative stress occurs when the amount of cellular ROS outweighs the amount of antioxidants due to the deregulation of the ROS-scavenging process causing cellular modifications and potential damage that might lead to cell death [113, 128]. Conversely, when ROS levels are minimal, the cell is in a reduced state. In this state, ROS can function as secondary messengers involved in processes like stem cell upkeep, cell division and differentiation, organ development and responses to living organisms and environmental factors [49, 179].

In fungi, animals, plants and microorganisms, low molecular weight (12 kDa) proteins named thioredoxins (TRX) are found to be involved in regulating cellular redox balance. TRXs are recognized as ancient redox regulators found in both prokaryotes and eukaryotes. They serve as oxidoreductases, facilitating the reduction of disulfide bonds in a variety of target proteins, thereby controlling physiological and biological processes [148]. Multigenic TRX superfamily includes conventional TRX, nucleoredoxin (NRX), glutaredoxin (GRX) and protein disulfide isomerase [142]. These proteins exhibit a shared structural feature known as the "Thioredoxin Fold" (Fig. 1), characterized by a stacked arrangement of five β-sheets encircled by four α-helices [122]. Members of TRX are found in almost all cellular compartments. Cytoplasmic TRX genes, lacking nucleus localizing signals, have been studied widely, but the existence of a nuclear TRX system has remained difficult to ascertain over an extended period. In most of the eukaryotes, NRX is the most predominant nuclear TRX. NRX exhibits substantial similarity in sequence to TRX. However, its homology is even more pronounced with tryparedoxin (TryX), a protein belonging to the TRX family that was initially discovered in parasite trypanos. NRX has been less studied compared to other thioredoxins. Recently, two NRXs have been characterized in Arabidopsis [22]. NRX possesses a conserved TRX domain and a catalytic motif essential for oxidoreductase activity. Notably, among the two identified NRXs, only NRX1 is subject to reduction by cytosolic NADPH-dependent thioredoxin reductase A (NTRA), whereas NRX2 does not exhibit this behavior. In plant cells under oxidative stress, the oxidoreductase nucleoredoxin (NRX) specifically interacts with enzymes involved in key hydrogen peroxide (H_2O_2)-scavenging pathways, such as catalases [73, 86]. NRX shows promising potential as a central redox regulator that plays a pivotal role in regulating various cellular processes, as well as serves as a crucial node for multiple redox-sensitive signaling pathways and their related pathologies [73]. Biotic and abiotic stresses are modern threats to the yield stability of different crops [123]. Abiotic stresses like sudden rise or fall in temperature or change in rainfall also cause drastic yield loss [59]. In few pockets of the world these stresses turn into yield reducing disasters. To keep pace with the increasing population, development of biotic and abiotic stress-tolerant varieties is on high demand since last few decades. As every stress always passes through oxidative stress, NRX can be considered as a potential contributor toward stress breeding.

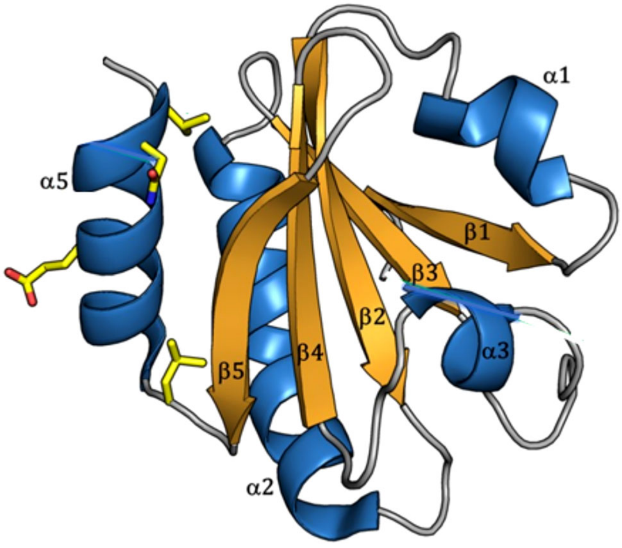


Fig. 1 Structural feature of TRX superfamily showing "Thioredoxin Fold"

This review is intended to discuss the basic idea about oxidative stress, ROS generation process and their scavenging mechanism, role of ROS on plant growth and current knowledge about the principle of balancing the redox potential of a plant cell mainly by nucleoredoxin. Additionally, this review also looks into the up-to-date research works about NRX in different crops and takes a modest attempt in describing newfangled future opportunities about NRX as an effective tool in resistant breeding.

Oxidative Stress

The term "Oxidative stress" was initially used by [152]. Oxidative stress is a biological state that arises when the generation of reactive oxygen species (ROS) exceeds the capacity of the body's antioxidant defense systems and is characterized by an imbalance between the harmful free radical generation and the ability of the cell to nullify them [8, 130]. It occurs when there is an excess of reactive oxygen species (ROS) in the cells, leading to damage of lipids, proteins and DNA. The toxicity of ROS has driven the evolution of intricate systems of both non-enzymatic and enzymatic signal-led detoxification mechanisms in plants [3]. Elevated levels of reactive nitrogen species (RNS) like NO, peroxynitrite ($ONOO^-$) and nitrosoglutathione (GSNO) in cells may also lead to nitrosative stress [151, 166].

Reactive Oxygen Species (ROS)

ROS are partially reduced forms of atmospheric oxygen (O_2) [143]. O_2 derivatives are considered to be the oldest stress generator of this planet [35]. ROS can be either free radicals (highly reactive atoms with an unpaired electron in their outer shell) like superoxide ($O_2^{\bullet -}$), hydroxyl ($HO^{\bullet}$), peroxyl ($RO_2^{\bullet -}$), hydroperoxyl ($HO_2^{\bullet}$) and alkoxyl ($RO^{\bullet}$) radicals or not free radicals, for example, hydrogen peroxide (H_2O_2), organic peroxides (ROOH) and hydroxide ion (OH^-) [129].

Under normal growing conditions, the generation of reactive oxygen intermediates (ROIs) within plant cells is typically minimal [74], with an estimated rate of $240\ \mu M\ s^{-1}{}^{1}O^{2-}$ and a steady-state concentration of approximately $0.5\ \mu M$ H_2O_2 specifically within the chloroplasts [27, 57]. Insurmountable biotic and abiotic stresses lead to enhanced production of ROS during the process of defense, programmed cell death or systemic signaling. First oxidative burst was reported in potato tubers inoculated by the pathogen *Phytopthera infestans* [34]. ROS generation is further amplified in the presence of iron, copper or manganese like free metals [1]. NADPH oxidase enzyme is one of the major enzymes involved in ROS generation like conversion of oxygen into superoxide by a one-electron transfer process, facilitated by NADPH [149].

Few of the major ROS agents are described below.

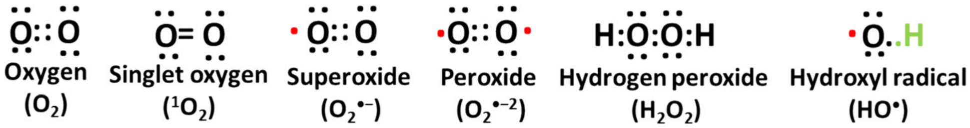
a. Singlet oxygen (${}^1O_2$)*:* Two oxygen atoms (O) share a double bond in the stable diatomic molecule that makes up molecular oxygen in its natural state. Two unpaired electrons in two different orbitals define singlet oxygen (Fig. 2). Due to the antibonding molecular orbitals that these two electrons occupy, the configuration is unstable [15, 85]. Recent research aided by highly selective singlet oxygen sensor green (SOSG) suggests that ${}^1O_{2,}$ usually generated in chloroplast PSII, is much more stable than previously thought and it can even diffuse beyond chloroplasts even up to the cell wall of a plant cell [36, 43, 108].

b. Superoxide ($O2^{\bullet -}$)*:* The oxygen atom (O), which has an extra electron occupying the outer p-orbital, has a negative charge on the superoxide ion [60, 85]. During oxidative phosphorylation or photosynthesis, electrons can leave the electron transport chain, producing superoxide as a byproduct under non-stress condition. Stresses like cd^+, salinity, pathogen attack, herbicides or xenobiotics may enhance its generation in peroxisomes by following two mechanisms: (1) mediated by xanthine oxidase in the cellular matrix and (2) NADH: ferricyanide reductase, cytochrome b and monodehydroascorbate reductase-mediated synthesis in the membrane of peroxisomes [30, 135]. As a consequence of aquatic environment acclimatization, rice roots and stems are the major organs for $O2^{\bullet -}$ production [176]. Superoxide also takes part in plant stem cell regulation [179], and overproduction of it may lead to cell death [56].

c. Hydrogen peroxide (H_2O_2)*:* In addition to the production of superoxide during cellular respiration, superoxide dismutase (SOD) also converts superoxide to hydrogen peroxide [23]. In the peroxisomes during photorespiration, as well as in reaction to pathogen attacks and other abiotic stresses, NADPH oxidase (also known as respiratory burst oxidase (RBO)) enzymes produce hydrogen peroxide [41, 85, 149, 169]. Respiratory burst oxidase homologues (RBOH) gene family codes for NADPH oxidase and it is omnipresent in all sequenced plants [58, 76, 82, 160, 162, 173]. Lines with overexpression of RBOH genes have shown a heightened level of stress responses [44, 160]. Aquaporins located on plasma membrane can mediate a long-distance transport of H_2O_2 [9, 175]. H_2O_2 also takes part in cell differentiation, senescence, cell wall formation, hormonal regulated growth and development, signaling, programmed cell death, etc. [80, 111, 114, 179].

d. Hydroxyl radical ($HO^{\cdot}$)*:* The hydroxyl radical consists of one oxygen atom (O) bound to one hydrogen atom (H). It has an unpaired electron which is a highly reactive chemical species [105]. Several reactions like Fenton reaction or Haber–Weiss reaction generate hydroxyl radical by typical conversion of H_2O_2 in presence of O_2 and Fe^{2+} ion or superoxide radicals, respectively (Fig. 3). Singlet oxygen can also react with water to produce hydroxyl radicals through a type II photosensitization reaction [85]. This ROS is generally effective at its generation site, and it can eventually affect single-stranded DNA and polysaccharides leading to loosening of cell wall

Fig. 2 ROS atomic structure with unpaired electron



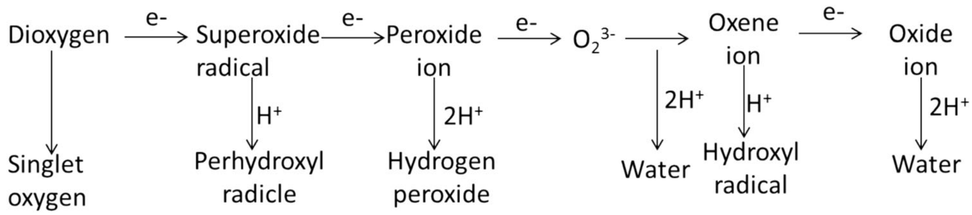


Fig. 3 Sequential generation of ROS by reduction of ground state oxygen

[64, 80]. Regulation of seed germination and viability has been well reviewed by [95].

Table 1 represents the half-life and diffusion distance of the ROS agents.

Damages Caused by ROS on Cellular Macromolecules

Several pathways involved in ROS-induced cell damages have been described in earlier reports [98, 105]. ROS directly affects DNA, RNA, lipids, proteins and carbohydrates [56]. However, when present in greater amounts, they react, harm a variety of biomolecules and ultimately cause programmed cell death (PCD) [112, 127]. The occurrence of protein oxidation and nitrosylation, including the formation of carbonyl groups, nitration and nitrotyrosine, has the potential to have a negative impact on numerous enzymatic processes and growth factors, leading to significant cellular dysfunction [153].

Cell death is also caused by peroxidation of mainly phospholipids (main component of cell membrane) due to sphingomyelinase activation (Fig. 4) [46]. Products of lipid peroxidation may also oxidize amino acids for example 4-hydroxynonenal and malondialdehyde are known to affect lysine or histidine [32]. The most common protein oxidation type is carbonylation of amino acids such as Cys and Met [100]. The oxidation of the majority of amino acids is commonly viewed as a pathophysiological process, whereas the oxidation of sulfur-containing amino acids is believed to serve a regulatory function by modeling the protein folding. Oxidation of nucleic acids accompanied with premature aging and DNA strand breaks leads to necrosis [7, 113]. Hydroxyl radicals play a significant role in damaging polynucleic acids. They interact with them by attaching to the double bonds of nucleotide bases and removing H^+ from the C–H bonds of 2-deoxyribose and the methyl group of thymine [177]. Along with nuclear ROS protection system, cytosolic ascorbate peroxidase and catalase play a crucial role in protection of DNA from ROS [177]. As carbohydrates are the major organic constituent of a plant cell, oxidation of it may also potentially facilitate deterioration of cell health. $HO^{\cdot}$ induced breakdown of pectin and xyloglucan may cause cell wall loosening, cell expansion and even early ripening of fruits [47, 48].

Table 1 Half-life and diffusion distance of the ROS agents

ROS	Half-life	Diffusion distance
$^1O_2$	1.4 µsec	0.8 µm
H_2O_2	1 ms	1 µm
O_2^{-}	1 s	8 mm
$^{\bullet}OH$	1–0.01 µsec	0.5 µm

The extent of these alterations and the cell's capacity to repair such damages play a crucial role in determining whether the consequences are going to be adaptive or maladaptive [149].

ROS-Scavenging Mechanism

It is an obligation to the plants to effectively manage excessive ROS production to uphold cellular redox homeostasis. Consequently, elevated ROS levels are detected and tightly regulated by a range of ROS-scavenging mechanisms. Antioxidants neutralize free radicals by donating one electron without undergoing any destructive conversion into radicals, thereby stabilizing them and preventing damage of cells [117, 139]. Superoxide dismutase (SOD), glutathione peroxidase (GPX), dehydroascorbate reductases (DHARs), ascorbate peroxidase (APX) and catalase (CAT) are major ROS-scavenging enzymatic antioxidants reported in plant cells [62, 134, 145], and the balance among their activities is crucial for determining superoxide radicals and hydrogen peroxide level in plant cells [81, 172]. Superoxide dismutases are metalloproteins involved in converting superoxide free radical ($O_2^{\bullet-}$) to molecular oxygen and H_2O_2 [13]. CAT is used for ROS removal and APX functions as fine modulator of ROI signaling. Reduced CAT activity is mostly compensated by enhanced APX and GPX activity in plants. The signaling processes followed by different enzymatic antioxidants have been described by researchers [38]. Different monosaccharides and disaccharides such as maltose, sucrose, etc., sometimes behave like ROS scavengers [25].

Plant defense mechanism against oxidative stress is also dependent on high concentration of ascorbic acid and

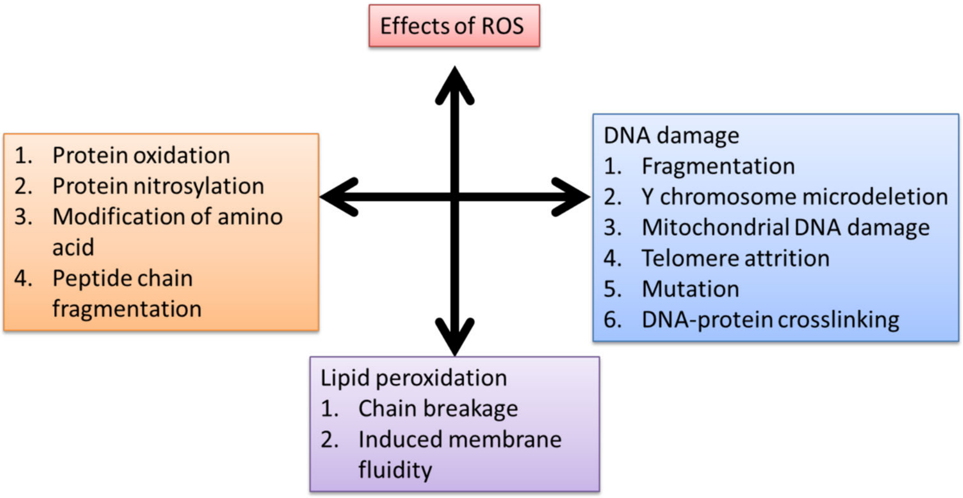


Fig. 4 Molecular damages caused by ROS

glutathione in cellular compartments [61]. High reduced peroxide ratio of glutathione and ascorbic acid in cell is maintained by dehydroascorbate reductase (DHAR), glutathione reductase (GR) and monodehydroascorbate reductase (MDAR) involving NADPH as H^+ donor [6]. However, overproduction of glutathione in chloroplasts may also cause oxidative stress due to altered redox state [26, 63, 165]. Synthesis of less sensitive lipid and protein isoforms in plant cells and a shield composed of layer of dead cells may reduce the aggressiveness of ROS [33, 116].

ROS Avoiding Mechanism

Mechanisms like leaf curling, leaf movement, hidden stomata, C_4 or CAM metabolism and rearrangement of the photosynthetic apparatus or alternative channeling of the electrons during ETS of photosynthesis or respiration by enzymes like alternative oxidases (AOXs) can reduce ROS production by either preventing electrons from reducing O_2 into O_2^- or by reducing O_2 level in cell [14, 125].

Locations of ROS-scavenging system in a plant cell are furnished in Table 2.

ROS Mediated Plant Growth and Development Regulation

The presence of H_2O_2 in the meristematic tissues of roots confers to cell division, whereas O2$^{\bullet-}$ promotes cell elongation [37]. Balance between O2$^{\bullet-}$ to H_2O_2 in cell tip plays an inevitable role in deciding whether a cell will divide or elongate. This balance is highly dependent on the expression of a transcription factor, UPBEAT1 (UPB1) [164]. ROS along with hormones, Brassinosteroids (BRs) and auxin signaling can conjointly regulate root growth [102, 157, 158]. The excessive buildup of ROS-mediated oxidized glutathione within root apical cells results in abnormal growth which can be partially restored to the normal phenotype by applying reduced glutathione externally [178]. $O_2^{\bullet-}$ concentration in shoot apical meristem is antagonistically controlled by H_2O_2. Increased levels of $O_2^{\bullet-}$ in stem cells trigger the expression of WUSCHEL gene, supporting stem cell functions. On the other hand, the accumulation of H_2O_2 in the peripheral zone encourages cell differentiation [179]. A thioredoxin, DCC1 can regulate ROS levels in cell leading to an altered bud and shoot regeneration rate in Arabidopsis [182]. The buildup of H_2O_2 stimulates the expression of the WRKY53 gene, which is essential for the onset of leaf senescence [184]. WRKY genes have been reported to be overexpressed in heat stress tolerant wheat genotypes [19]. If $O_2^{\bullet-}$ levels are suppressed, tuber sprouting takes longer. However, when potato tubers are exposed to external H_2O_2, their dormancy is broken [99]. In rice, the homeobox gene MADS3 is demonstrated to be crucial for the development of stamens during the early stages of floral growth. During advanced stages of anther development, MADS3 oversees ROS balance. Irregular expression of MADS3 leads to an increase in $O_2^{\bullet-}$ levels and results in pollen sterility [71]. Auxin-mediated overexpression of ROS-related genes may also lead to an activation of RSL4, therefore consequently affecting root hair growth [103, 109]. Excessive IAA can cause a buildup of ROS in the apical spikelet, culminating in cell death within rice panicles [126]. Hypersensitive response (HR) due to pathogen invasion is also triggered through ROS accumulation [31]. Under biotic stress, ROS can kill the pathogen directly or sometimes the spread of the pathogen can be restricted by thickening the cell wall [121, 170].

Table 2 Locations of ROS-scavenging system in a plant cell

Location	ROS	Enzymatic antioxidants	Non-enzymatic antioxidants	Regeneration of reduced forms
Nucleus	H_2O_2	PRX	Ascorbate, Glutathion	GR, GRX, TRX, NTR
Chloroplast	$^1O_2$		Carotenoid,Tocopherol	NTR, DHAR, GR, GRX, TRX, MDAR
	$O2^{\bullet-}$	Cu Zn SOD, Fe SOD	Ascorbate, Glutathion	
	H_2O_2	APX, PRX		
Peroxisomes	H_2O_2	CAT, APX		MDAR, GR
	$O2^{\bullet-}$	Cu Zn SOD, Fe SOD	Ascorbate, Glutathion	
Mitochondria	H_2O_2	APX, PRX		TRX, GR, NTR, MDAR, GRX
	$O2^{\bullet-}$	Cu Zn SOD, Mn SOD	Ascorbate, Glutathion	
Cytosol	H_2O_2	APX, PRX		NTR, DHAR, GR, GRX, TRX, MDAR
	$O2^{\bullet-}$	Cu Zn SOD	Ascorbate, Glutathion	

Abbreviations used: PRX, peroxiredoxin; CAT, Catalase; APX, ascorbate peroxidase; SOD, superoxide dismutase; GR, glutathione reductase; GRX, glutaredoxin; NTR, NADPH-thioredoxin reductase; TRX, thioredoxin; MDAR, monodehydroascorbate reductase; DHAR, dehydroascorbate reductase

A notable research gap persists in comprehending the intricate dynamics of oxidative stress, reactive oxygen species (ROS) and the mechanisms involved in scavenging ROS. While significant strides have been made in understanding the detrimental effects of oxidative stress on cellular function and its implications for various diseases, gaps remain in elucidating the precise mechanisms governing ROS production and detoxification. Furthermore, future research in this field could explore the role of proteins such as TRX and novel redox-sensitive proteins like NRX in ROS regulation. Understanding how these proteins function as ROS sensors and regulators could offer valuable insights into developing targeted therapies for oxidative stress-related disorders. Additionally, exploring the potential crosstalk between TRX and NRX pathways could uncover novel therapeutic strategies for managing oxidative stress and its associated pathologies.

Thioredoxin (TRX)

TRX was initially discovered involving its role as an electron donor facilitating ribonucleotide reductase activity, which is crucial for DNA synthesis in *Escherichia coli* [20]. TRX is a compact protein weighing ∼ 12 kDa and is conserved across various species in both prokaryotes and eukaryotes [2]. TRX contains a preserved WCGPC (Trp–Cys–Gly–Pro–Cys) sequence motif, and the oxidoreductase activity is directly associated with the two cysteine residues (Cys32 and Cys35 in human TRX1). Several proteins have been identified as targets for the oxidoreductase function of TRX viz., peroxiredoxin (Prx), ribonucleotide reductase and methionine sulfoxide reductase [10].

Types of conventional TRX, viz., m, f, x, y and z, are localized in plastids and they are said to be involved in light dependent metabolisms using the ferredoxin (Fdx)/thioredoxin reductase system (FTR), whereas TRX h and o types are prevalent in mitochondria and cytosols and they use the NAD(P)H-dependent thioredoxin reductases (NTR) [5, 54, 94, 110, 144]. Later co-localization of NTR, TRX h system in the nucleus of aleurone and scutellum cells of wheat seeds has been established [131].

Members of TRX Family

This extensive family of TRX, encompassing both glutathione peroxidases and Prx with an extended TRX-like domain [174], can be categorized into multiple subgroups,

TRX1

TRX1, a pivotal member of the TRX family, orchestrates a vital ROS-neutralization cascade involving NADPH, TrxR, TRX and Prx. Its functions encompass reducing Prx, mitigating H_2O_2 and safeguarding cells from oxidative stress by rectifying disulfide bonds in cellular proteins [69]. TRX1 also serves as an electron donor for enzymes, primarily located in the cytosol, and modulates redox status in the nucleus [65]. Additionally, it functions extracellularly, acting as an adult T-cell leukemia-derived factor and secreted from cells during stress conditions [154].

TRX2

Expressed in diverse tissues, such as heart, skeletal muscle, cerebellum, adrenal gland and testis, TRX2 is a mitochondrial protein with oxidoreductase activity. It actively regulates redox status and inhibits ASK1-induced apoptosis in cells and mice, leading to significant apoptosis in TRX2-deficient conditions [119, 155].

Glutaredoxin (GRX)

GRX was initially identified in *Escherichia coli* as a glutathione-dependent electron donor for ribonucleotide reductase [67]. In contrast to TRX, which utilizes NADPH, glutathione reductase and glutathione, GRX directly utilizes glutathione as a hydrogen donor. Mammals possess three GRX proteins—GRX1, GRX2 and GRX5—while *Saccharomyces cerevisiae* harbors GRX3 and GRX4 [136]. GRX1 and GRX2 exhibit oxidoreductase activity with TCPYC and SCYSC catalytic motifs, respectively [70]. GRX5 is crucial for yeast and zebrafish viability, contributing to mitochondrial biogenesis of Fe–S clusters [137]. GRX2, which is mostly found in mitochondria and is also partially found in the nucleus, is crucial for the synthesis of Fe–S clusters and has a unique function in protecting cells against reactive oxygen species (ROS) [97].

TRX-Related Protein 14 and 32 (TRP14 and TRP32)

TRP14, comprising of a ROS-sensitive Cys residue and WCPDC catalytic motif, exhibits TRX-like oxidoreductase activity, directly neutralizing H_2O_2 [68]. Widely expressed in tissues and cell lines, TRP14 plays a role in regulating TNF-α-induced NF-κB signaling and apoptosis. Unlike TRX, it does not bind ASK1, LC8/PIN, a dynein light chain protein, and exhibits interactions with IβB and Bim [132].

TRP32 was co-purified with a mammalian STE-20-like (MST) catalytic fragment responsible for phosphorylating FOXO, a transcription factor linked to cell proliferation and longevity [92]. Despite the absence of co-immunoprecipitation between TRP32 and MST, there is a potential role for TRP32 in modulating MST kinase activity under oxidative stress, possibly through the modulation of Cys residues [93].

Protein Disulfide Isomerase (PDI)

PDIs constitute a substantial family of TRX-like proteins involved in overseeing protein folding and oxidation in the extracellular milieu. Comprising 18 members, PDIs play a pivotal role in ensuring accurate protein folding and regulating endoplasmic reticulum (ER) reactions [40, 171]. Despite their significance, the complete spectrum of their functions remains incompletely elucidated.

Sperm-Specific TRX (SpTRX)

Three SpTRX proteins, namely SpTRX1, 2 and 3, are identified as TRX homologs exclusively expressed in the testis. SpTRX1, characterized by 23 repeats of a 15-amino acid sequence, demonstrates notable catalytic activity in insulin reduction. In contrast, SpTRX2 features three NDP-kinase domains but lacks detectable oxidoreductase or TRX-like activity, suggesting a potential requirement for cofactors for enzymatic function.

Nucleoredoxin (NRX)

Nucleoredoxin (NRX, NXN or Red-1) was initially identified by Kurooka and gropus [89]. The discovery of the NRX gene occurred during an investigation around the nude (Foxn1, Whn or Hfh11) gene locus. Though NRX is functionally similar to conventional TRX, it possesses slightly different TRX domain [104]. The primary distinction lies in their structural composition. Conventional thioredoxin (TRX) comprises a single domain, whereas NRX is a multidomain protein [146, 147, 168]. Given its sequence similarity to TRX protein and its predominant nuclear localization upon ectopic expression in COS-7 cells, it was aptly named as nucleoredoxin. Later its presence in cytosol and subcellular localization was confirmed [51].

NRX-an Oxidoreductase

Nucleoredoxin (NRX) belongs to the superfamily thioredoxins (TRX) which includes thiol-oxidoreductase enzymes crucial for cellular redox homeostasis by converting thiol and disulfide reversibly [73].Table 3 represents the description of NRX sub families of plants. These enzymes have two active cysteine (cys) molecules separated by two amino acids (–CXXC–) and conserved active sites, WCG/PPC [106]. Trp residues preceding the catalyting cys molecules are important for TRX stability [138].

During protein-to-protein interaction, the thiol group of the cys residue at the N-terminal of NRX is deprotonated and forms a disulfide bond with the cys residue of the substrate protein through a nucleophilic attack on the substrate protein known as dithiol mechanism [104, 107, 167]. This is followed by the formation of an intermediate NRX-substrate complex. The thiol group of cys present on the C-terminal of NRX forms a disulfide bond with its N-terminal cys residue thus releasing the substrate protein. Subsequently, the disulfide bond within NRX undergoes cyclic reduction facilitated by an enzyme known as TRX reductase (TRXrd) with the help of

Table 3 Description of NRX subfamilies of plants

Category	TRX domain number	1st TRX domain	2nd TRX domain	3rd TRX domain
Type I	3	WCG/PPC (typical redox active sites)	Atypical	WCG/PPC(typical redox active sites)
Type II	2	WYP/AK/PC (Atypical redox active sites)	W/R/HCL/A/V/RPC/G (Atypical redox active sites)	_
Type III	2	WCRPC (typical redox active sites)	WCPPC/F/S (typical redox active sites)	_

NADPH [39, 52]. These cys residues in TRX domain are very important in oligomerization of the protein that is needed for structural switching [78, 124] (Fig. 5). Post-translational modifications like reversible S-nitrosation (attachment of nitroso group to cysteine thiols) of different TRX proteins are also considered to have a profound effect on protein structure and function in cellular signaling pathways [75]. Involvement of NRX in modulating the activity of phosphofructokinase 1 (PFK1) during glucose metabolism leading to a balance in glycolysis and pentose phosphate pathways has been established [50].

Structure of NRX

The NRX proteins, ubiquitously present in species like humans and mice, exhibit a remarkable 99% identity and consist of 435 amino acid residues. Orthologues are found in diverse vertebrates, including dogs, rats and red monkeys. Notably, NRX's TRX-like domain shares significant similarity with tryparedoxin (TryX), an oxidoreductase identified in trypanosomatid [118]. In mammalian NRX, the N-terminal region harbors another TryX-homologous segment, displaying higher homology to TryX than to TRX. This region features the WCPPC motif, implicated in TRX oxidoreductase activity. Furthermore, a conserved Cys residue, forming a CXXXXXC motif preceding LSAPC, distinguishes NRX, aligning with other proteins involved in thiol-disulfide exchange reactions [45]. The C-terminal region of mammalian NRX bears an acidic region akin to the b-domain of PDI proteins, lacking catalytic function but crucial for substrate recognition [84]. PDI domain is replaced by a divergent C1 (DC1) domain in plant NRX.

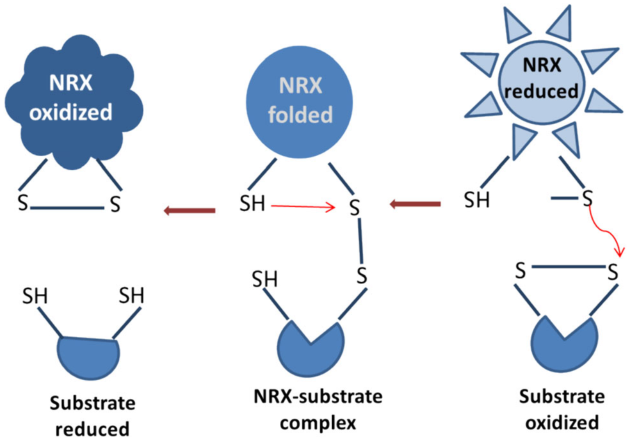


Fig. 5 Oxidoreductase activity of NRX

In nematodes like *Caenorhabditis elegans*, a number of NRX (TryX)-like proteins (WormBase: www.wormbase.org) are thought to have a role in lifespan regulation by redox-dependently regulating FOXO through β-catenin. Common motifs include WCGPC and WCPPC in both domains. These proteins share a single TryX-like domain; distinct from the mammalian NRX structure, the presence and function of oxidoreductase activity remain undisclosed [42].

Laughner and his group [90] have documented the presence of NRX in maize (*Zea mays* L.), viz. zNRX. zNRX possess three TryX-like domains, each resembling the two TryX-like domains observed in mammalian NRX. The most closely related TryX-like domain in zNRX shares 49% similarity with the central TryX-like domain found in human NRX. Both N-terminal and C-terminal TryX-like domains of zNRX exhibit WCPPC motifs. Moreover, zNRX demonstrates notable oxidoreductase activity against insulin, albeit less potent compared to that of *Escherichia coli*. Immunostaining of sections from maize kernels using an anti-zNRX antibody revealed that zNRX is primarily situated within the nucleus of the kernel. Western and Northern blot analyses demonstrated that zNRX is highly concentrated in maize kernels, while its expression is relatively lower in leaves, epicotyls, stems and roots. Besides zNRX, NRX-like proteins have been identified in cork oak (*Quercus suber*), muskmelon (*Cucurmis melo*), wheat (Triticum aestivum), cotton (*Gossipium sp*), tomato (*Solanum lycopersicum*), cucumber (*Cucumis sativus*), pumpkin *(Cucurbita moschata)* rice (*Oryza sativa*) and *Arabidopsis thaliana* (Table 4). Due to the distinct domain structures of zNRX as compared to mammalian NRX, it might be more appropriate to classify them as separate proteins within the same family. A line diagram of the NRX proteins of various species is shown in Fig. 6 [104]. Given that zNRX is known to localize in the nucleus, it is plausible that plant NRX-related proteins could be involved in regulating transcriptional activity, similar to the reported function of mammalian NRX. Unlike mammalian NRX, plants like grapevine, rice or poplar harbor multiple NRX which suggests multiple duplications in the gene [91]. By studying the comparative organization of NRX from most angiosperms, NRX of plants can be categorized into three sub families based on amino acid sequence and TRX domain number. Interestingly, it was observed that all three NRX proteins possess an intron located precisely 18 amino acids upstream of each TRX active domain [104].

Role of NRX in Animal Cell

In animal body, reports suggest that NRX interacts with several proteins—disheveled (DVL), protein phosphatase 2A (PP2A), phosphofructokinase-1 (PFK1), translocation protein SEC63 homolog (SEC63), MYD88, flightless-I (FLII) and calcium/calmodulin-dependent protein kinase II type alpha (CAMK2A)-regulating crucial cellular processes [163, 167]. Its involvement spans proliferation, organogenesis, cell cycle, glycolysis, immunity, motility and more. Associated with pathologies including cancer, liver diseases, obesity and neurodegenerative disorders, NRX emerges as a key redox regulator with implications in diverse signaling pathways and associated diseases [73].

NRX Against Oxidative Stress in Plant Cells

Abiotic Stress

Enhanced expressions of NRX along with CAT genes impart resistance to water stress in heterografts in cucumber and pumpkin [28]. Maize NRX possesses three TRX-like domains. Notably, the first and third domains contain the characteristic active site WCPPC found in typical TRX-like domains. Additionally, the third domain of NRX demonstrates the capability to reduce disulfide bonds in vitro [90]. The newly discovered NRX gene from wheat (*Triticum aestivum* L.) was initially cloned and described to have a role in conferring drought resistance by Zhang et al. in 2014 [181]. Additionally, they reported molecular markers associated with drought resistance. The various domains of wheat NRX1-D (TaNRX1-D) have been comprehensively investigated. The TaNRX1-D protein from wheat consists of three TRX domains. Specifically, domain 1 encompasses the WCPPC motif, domain 2 contains GYPPV, and domain 3 contains WCGPC. However, domain 2 does not possess a similar active site which supports its weakest reducing capacity [21]. For elucidating the molecular mechanism of TaNRX1 in drought resistance of wheat, interaction of NRX1 with three candidate proteins, protein disulfide isomerase (TaPDI), TaTRX-h and protein phosphatase 2A catalytic subunit (TaPP2Ac) was investigated and upon analysis they showed to have a positive regulation over drought stress [156]. Contribution of TaNRX1 to drought resistance was further explored by developing transgenic lines by RNA interference (RNAi) or NRX1 overexpression [183]. Antioxidant content like catalase, superoxide dismutase and peroxidase, sugar, proline, leaf chlorophyll content, carbon assimilation, water retention capacity, etc., are enhanced in NRX1 overexpressing lines contributing to drought resistance. Even multiple stress-related transcription factors like WRKY, MYB and bHLH are also positively regulated in the NRX1 overexpressing lines suggesting a strong correlation and interaction among them [183]. Under tremendous oxidative stress condition with increased amount of H_2O_2, NRX1 protects major ROS-scavenging enzymatic antioxidants like catalases. Thus, plants with wild-type NRX1 always show resistance to oxidative stress whereas mutants with nrx1 seem to be highly prone to it [86]. The impact of cys residues in the TRX domain for oligomerization of AtNRX1 has been examined by cys to ser substitution mutants at C55S, C58S, C375S and C378S positions [79]. Impact of NRX1 on thermo tolerance in tomato (*Solanum lycopersicum* L.) has been investigated and through clustered regularly interspaced short palindromic repeats (CRISPR/Cas9)-mediated mutations it has been proved that the mutants exhibit a remarkable susceptibility to heat stress, resulting in elevated levels of electrolyte leakage, malondialdehyde content and H_2O_2 concentration in comparison to the wild-type counterpart. In addition, NRX1 also seems to be a major regulator of antioxidant coding transcription factors and Heat Shock Proteins (HSPs) under tremendous abiotic stress like crippling heat [17]. Through bioinformatic analysis, a total of 35 TRX genes were detected in the entire genome of foxtail millet (*Setaria italica*) [180]. Phylogenetic examination categorized these 35 SiTRXs into 13 distinct types. Subsequent characterization included the investigation of their chromosome distribution, gene structure, cis-elements and conserved protein motifs. A structural analysis of TRX family members led to the identification of three nucleoredoxin (NRX) members. Assessment of the expression patterns of foxtail millet's SiNRX members under various abiotic stresses revealed diverse stress-response behaviors. Moreover, subcellular localization studies indicated that SiNRXs were present in the nucleus, cytoplasm and membrane. Further experiments showed that

Table 4 Cropwise accession numbers of NRX

Crop	Gene name	Accession number
Arabidopsis lyrata	AlNRX1	AFH64402
	AlNRX2	EFH43567
Arabidopsis thaliana	AtNRX1	AEE33684
	AtNRX2	AEE85880
Cucumis melo	CmNRX1	AAU04767
Gossypium hirsutum	GhNRX1	CotAD_56209
Gossypium barbadense	GbNRX1	KT372889
Medicago truncatula	MtNRX1	ACJ85567
	MtNRX2	XP_003603818
	MtNRX3	XP_003603563
Oryza sativa	OsNRX1a	NP_001050329
	OsNRX1b	AAU89249
	OsNRX1c	EEC75442
	OsNRX1d	NP_001050331
	OsNRX2	NP_001044503
	OsNRX3	EEC77960
Picea sitchensis	PsNRX1	ABK25413
	PsNRX2-3	ABK25089
Populus trichocarpa	PtNRX1a	XP_002314537
	PtNRX1b	XP_002314534
	PtNRX1c	XP_002314533
	PtNRX1d	EEF00707
	PtNRX1e,	XP_002314535
	PtNRX2	XP_002306954
	PtNRX3	XP_002330779
Ricinus communis	RcNRX1	XP_002525368
	RcNRX2	XP_002510593
Sorghum bicolor	SbNRX1	XP_002467709
	SbNRX2	XP_002467708
	SbNRX3	XP_002448495
Solanum lycopersicum	SlNRX1	Solyc05g005470
	SlNRX2	Solyc05g005460
Selaginella moellendorffii	SmNRX1	EFJ30324
Vitis vinifera	VvNRX1a	XP_002263480
	VvNRX1b	CBI28536
	VvNRX1c	XP_002262828
	VvNRX1d	XP_002262857
	VvNRX1e	XP_002264954
	VvNRX2	XP_002285895
	VvNRX3	CBI20806
Zea mays	ZmNRX1b	NP_001130856
	ZmNRX2	NP_001131397

overexpression of SiNRX1 in Arabidopsis enhanced its tolerance to drought and salt stresses, resulting in increased survival rates and improved growth performance [180] (Fig. 7).

Biotic Stress

In eukaryotes NRX is very common except unicellular green algae (Ostreococcus) or yeast. The expression of

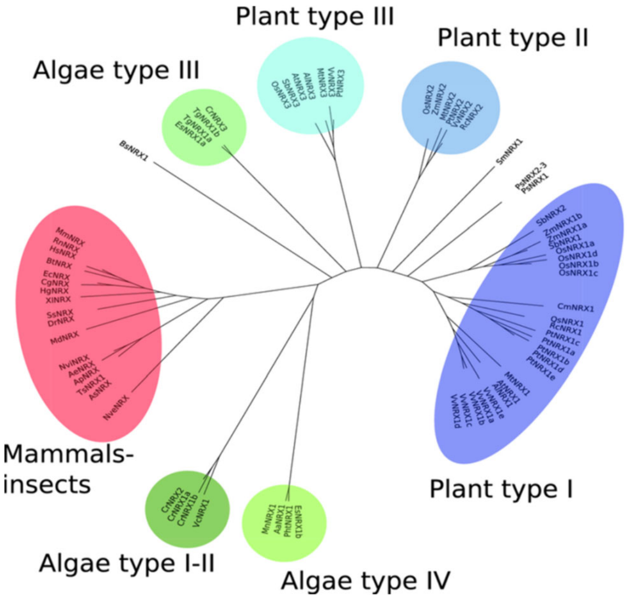


Fig. 6 Phylogenetic Tree of NRX. Aa, *Aureococcus anophagefferens*; Ap, *Acyrthosiphon pisum*; As, *Ascaris suum*; Ae, *Acromyrmex echinatior*; Al, *Arabidopisis lyrata*; At, *Arabidopsis thaliana*; Bs, *Bodo saltans*; Bt, *Bos taurus*; Cg, *Cricetulus griseus*; Cm, *Cucumis melo*; Cr, *Chlamydomonas reinhardtii*; Dr, *Danio rerio*; Ec, *Equus caballus*; Es, *Ectocarpus siliculosus*; Hg, *Heterocephalus glaber*; Hs, *Homo sapiens*; Md, *Monodelphis domestica*; Mm, *Mus musculus*; Mn, *Micromonas sp. RCC299*; Mt, *Medicago truncatula*; Nve, *Nematostella vectensis*; Nvi, *Nasonia vitripennis*; Os, *Oryza sativa*; Pht, *Phaeodactylum tricornutum CCAP 1055/1*; Ps, *Picea sitchensis*; Pt, *Populus trichocarpa*; Qs, *Quersus suber*; Rc, *Ricinus communis*; Rn, *Rattus norvegicus*; Sb, *Sorghum bicolor*; Sm, *Selaginella moellendorffii*; Ss, *Salmo salar*; Tg, *Toxoplasma gondii*; Ts, *Trichinella spiralis*; Vc, *Volvox carteri f. nagariensis*; Vv, *Vitis vinifera*; Xl, *Xenopus laevis*; Zm, *Zea mais* [104]

NRX-1 gene is induced by salicylate (SA) in grapevine conferring resistance against downy mildew disease caused by *Plasmopara viticola* [53]. Two distinct genes within the nuclear genome of *Arabidopsis thaliana*, sharing less than 30% amino acid sequence similarity encoding AtNRX1 and AtNRX2 with disulfide reduction capacity were identified, categorizing them into the Type I and Type III subgroups. Their presence has also been tested positive in cytosol except the nucleolar region. NTRA thioredoxin reductase is said to be the physiological reducer of native NRX1 but not NRX2. While NRX1 has been shown to impact pollen fertility, the involvement of NRX2 in this process has not been substantiated [104]. The involvement of AtNRX1 in the growth of pollen tubes within the pistil has been reported. However, it appears that this role is specific to the in vivo context, as the protein does not exhibit the same effect in vitro suggesting that NRX1 functions by integrating signals from the maternal tissue and providing guidance to the pollen tube as it progresses toward the ovule [133]. AtNRX1 is also associated in the defense mechanism against the fungal pathogen, *Alternaria brassicicola* via jasmonic acid (JA) signaling through affecting the major gene of this pathway PLANT DEFENSIN 1.2 (PDF1.2). AtNRX1 has three TRX domains and two of them harbor WC(G/P)PC in their active site sequence. The third TRX domain has more reduction capacity than the first one but they reduce the substrate sequentially thus suggesting their reliance on each other [86, 104]. In cotton plants (*Gossypium barbadense*) well established evident is available about the contribution of NRX to plant immune response against apoplastic oxidative burst accounted by NADPH oxidases and class III peroxidases [12, 120]. Under tremendous oxidative burst, as an early response to pathogen attack in a plant body a numerous number of ROS production is seen in cellular apoplast region to combat the attack of the microbes through degenerating their nucleic acid, proteins or lipid [159, 161]. Consequently, these apoplastic ROS will either diffuse into the cell membrane leading to different signaling cascades [87, 115] or strengthen the cell wall through oxidative glycoprotein crosslinking or lignin, suberin production [72]. In GbNRX1, out of three TRX active domains flanked by a signal peptide at N-terminal end and cys rich C-terminal domain, first and third domains have typical TRX sequence whereas second one harbors atypical active site. First domain has highest reduction capacity followed by third and second TRX domain. A well-regulated system is indicated by rapid ROS production and its fast dissipation. Reduced disease resistance capacity due to knocking out GbNRX1 gene suggests NRX1 to be a crucial component of maintaining apoplastic redox homeostasis as it also regulates the expression of defense related genes like PR1, PR4 and PR10 or genes

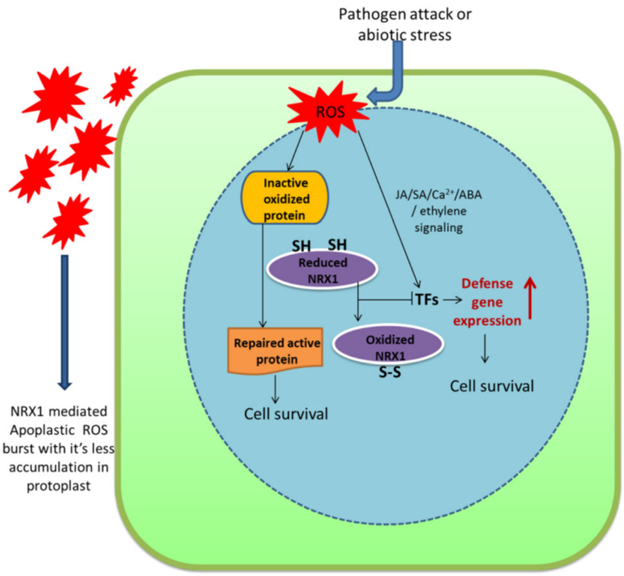


Fig. 7 Oxidoreductase activity of NRX1 against ROS production in plant cell

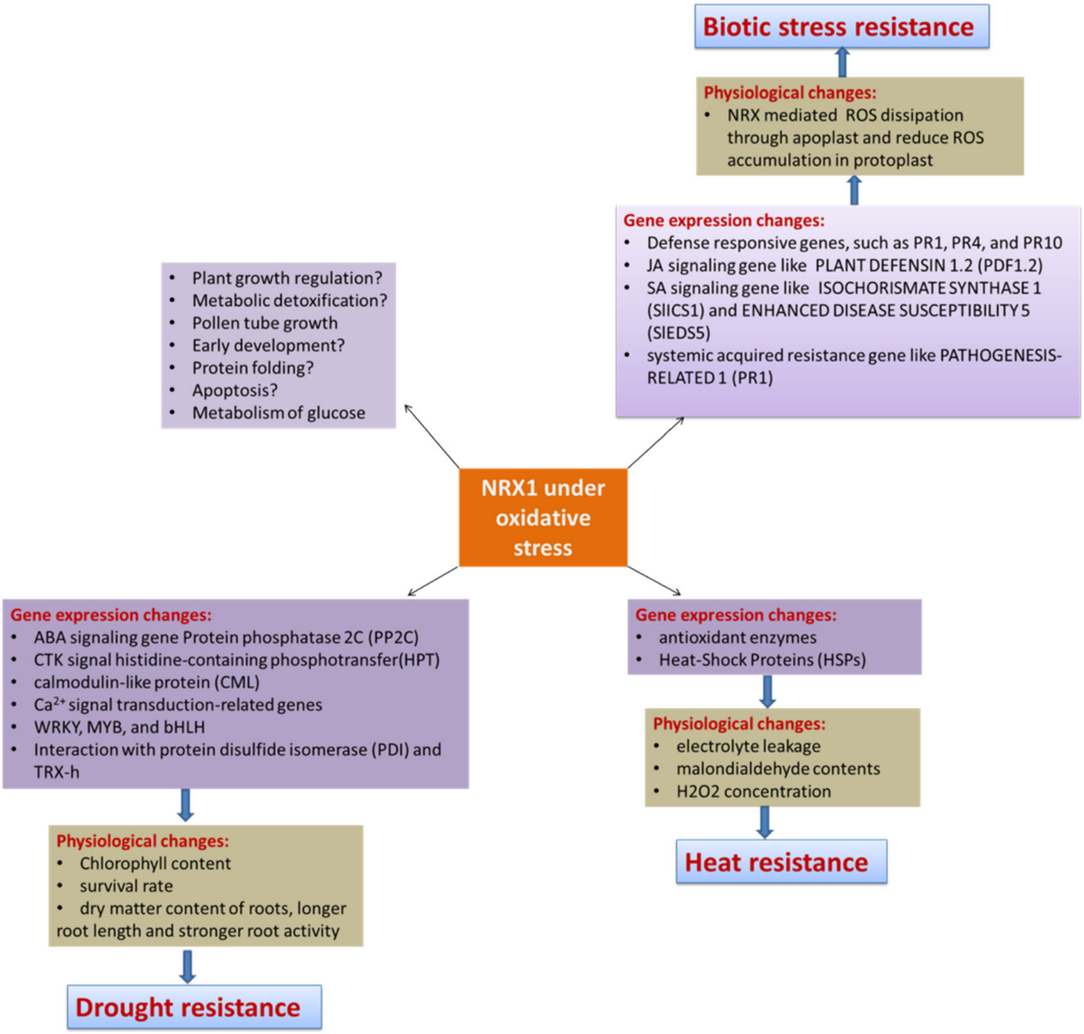


Fig. 8 Pathways followed by NRX1 against oxidative stress

related to carbon metabolism [96]. Evidently tomato NRX1 also affects biotic stress tolerance against bacterial diseases caused by *Pseudomonas syringae* pv. *maculicola (Psm)* ES4326 or fungal diseases caused by *Alternaria brassicicola* in tomato. Findings suggest the NRX1 is also a key regulator of phytohormones like jasmonic acid (JA) and salicylic acid (SA) levels in a cell via controlling the expressions of the genes like ISOCHORISMATE SYNTHASE 1 (SlICS1) and ENHANCED DISEASE SUSCEPTIBILITY 5 (SlEDS5) related to SA biosynthesis [18] (Fig. 8).

Conclusion and Future Perspectives

Enzymatic and non-enzymatic ROS-scavenging mechanisms are very crucial for maintaining cellular integrity under oxidative stress induced by biotic and abiotic stresses. Recent researches on the meta-analysis of publicly accessible rice transcriptomes found that the most differentially expressed genes under abiotic stress are ROS detoxifiers (scavengers) [29]. Current breeding approaches like molecular breeding have played a key role in speed breeding. The most effective strategy for locating and transferring the QTLs linked to the desired characteristic is marker-assisted breeding. In QTL identification and subsequent marker development programs, oxidative stress has received less attention due to the trait's complexity and functional overlap with salt, drought and heat stress. Few particular QTLs were found to be linked to oxidative stress, but several QTLs and markers were found to be linked to heat tolerance, which shares common genes for detoxifying ROS produced by oxidative stress.

Contribution of NRX to regulate redox potential in a cell has been furnished by different researchers in different crops. Though data on plant NRX is scarce, the established proof suggests NRX protein with two "cys" residues separated by two amino acids on active TRX domain is the favorable form for breeding purpose [4, 55]. NRX functions as a redox-sensor for overseeing the Wnt/β-catenin signaling pathway. Reactive oxygen species (ROS) are unavoidable byproducts of cellular respiration and necessitate detoxification, yet cells both generate and utilize ROS to manage diverse cellular functions. It's noteworthy that the Wnt/β-catenin pathway, known for regulating cell proliferation and fate, also participates in ROS utilization. Impact of NRX on different pathogen induced biotic stresses and even in abiotic stresses has been established in different research findings [17, 183]. Certainly a precise integration of proteomics, genomics and molecular biology for allele mining followed by introgression of the favorable NRX allele in a variety will facilitate stress breeding with more precision [24, 180]. Well established data about NRX in animal cells especially in mammals and involvement of mammalian NRX in signal transduction, metabolic pathways in neuron cells or NRX induced transcription factor activation, complex protein to protein interaction also stipulates ample research works to elucidate future studies about plant NRX [66, 167]. Inclusion of more wild relatives or landraces during allele mining and even mutation breeding for creating genetic variation will be helpful for a breeder [11]. Hybridization followed by selection through easy to use molecular markers and high throughput phenotyping will optimize the breeding protocols and this can be deployed in farmers' field against hostile stress situation.

However, research on NRX is still in its initial phase. Many important aspects regarding NRX needs to be further clarified. The specific molecular mechanisms remain uncertain. The idea of redox-dependent regulation of the Wnt/β-catenin pathway, wherein ROS function could be elucidated by NRX, a protein with evolutionarily conserved ROS-reactive cysteine residues that detect intracellular redox states, is fascinating. Further exploration of NRX promises to enhance comprehension of ROS signaling.

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Declarations

Conflict of 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.

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