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# Role of Plasma Membrane Redox Activities in Immune Response Mechanisms

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**Abstract:** *The plasma membrane redox system (PMRS) is an important component of the cell's ability to defend itself against oxidative stress. Many immune signaling pathways are regulated through redox reactions. Biological systems utilize oxidation-reduction reactions to modulate their responses to environmental cues. The role of redox molecules such as NO and ROS as key mediators of immunity has recently gathered a lot of interest and attention. Beyond the chemical interactions of NO and ROS that combine to eradicate pathogens, these redox small molecules are effective immune-modulators that regulate cellular metabolism as well as multiple pro-inflammatory and repair/tissue-restoration pathways. Redox molecules such as peroxide, superoxide, NO, and RNS, once thought to be only toxic, are essential in tissue repair. These species are generated, converted and metabolized during host microbe interaction involving the innate immune system. Cytochrome b558 is the flavin binding component of the NADPH oxidase. NADPH oxidases are key producers of ROS. A variety of RNS and ROS is produced in the acidic milieu of phagosomes, which provide an environment conducive to the redox chemistry, which is the first line in fighting infection. Bacterial cell immune response also involves NO. Thus understanding the plasma membrane redox activities can help unravel the mechanisms of immune response.*

**Keywords:** *Plasma membrane, Redox activities, oxidative stress, NO, ROS, RNS. Nitrous Oxide, Reactive Oxygen Species, Reactive Nitrogen species.*

## I. INTRODUCTION

It is well established, however, that a trans plasma membrane electron transport (TPMET) system or plasma membrane redox system (PMRS) is expressed in every living cell, including bacteria, cyanobacteria, yeasts, algae and all kinds of plant and animal cells(1–4). There are experimental evidences provided by many workers for their direct involvement in several vital physiological and biological functions (5,6). The physiological functions such as many different specialized PMRSs have been described including the ion uptake (7), H<sup>+</sup> excretion (8), thiol reduction (9), light induced absorbance change (10).

Various enzymes forming the specialized PMRSs have been identified in a number of studies conducted (11-13) viz (i) NADH:ascorbate free radical (AFR) oxidoreductase (ii) NADH:ubiquinone (CoQ) oxidoreductase; (iii) superoxide generating NADPH oxidase of defense; (iv) TPMET system in nonphagocytic cells; (v) superoxide generating NADPH oxidases of fertilization; (vi) ferric reductase; (vii) NADH: dichlorophenol-indophenol (DCIP) reductase; (viii) NADH oxidase; (ix) NADH:ferricyanide-reductase

The plasma membrane redox system (PMRS) is an important component of the cell's ability to defend itself against oxidative stress and are modulated during stress(14). The system comprises antioxidants, enzymatic and chemical reductants, and a source of reducing equivalents usually NADPH (15, 16). Major antioxidant systems contained in the plasma membrane include ubiquinone and vitamin E allowing scavenging of damaging free radicals and inhibition of lipid peroxidation (17) Reductases contained in the plasma membrane include cytochrome b5 reductase, NQO1 and an additional cytosolic NADPH CoQ reductase (18). The enzymatic reductases maintain ubiquinone or vitamin E quinone in their hydroquinone forms. Ubiquinol can provide antioxidant protection either alone or in combination with vitamin E or ascorbate (19).

## II. COMPONENTS OF PM REDOX ACTIVITY AND THEIR ROLE IN IMMUNE RESPONSES

In the recent decades many workers have investigated the presence of redox components in purified plasma membrane and this led to conclusion that though the redox activity varies greatly in their location, properties and physiological roles but there is similarity in the nature of redox components. The most common redox components are following:

- 1) *Cytochromes of B Type*: Though cytochromes have been ascertained for their role as redox component in mitochondrial respiratory chain since long time, but their occurrence in plasma membranes was first reported in 1977(20) The light reducible b type cytochromes have been reported (21) Cytochrome b558 is the flavin binding component of the NADPH oxidase (22)
- 2) *Flavins and Flavoproteins*: Flavoproteins function in biological e- transport chain as electrical transducers, enabling e- transfer to proceed from two electron donors such as pyridine nucleotides to one electron acceptors such as quinones or cytochromes. Flavins have been isolated and measured in isolated PM vesicles (23) Exogenous FMN stimulated redox activity of a purified 27 kDa maize PM reductase upon reconstitution (24) suggesting that the enzyme was a flavoprotein. Immunological cross reactivity between spinach PM bound NADH:HCF(III) oxidoreductase and NADH: Cyt b5 reductase, a flavoprotein isolated from potato tuber has been reported (25) The involvement of flavins in these processes has remained an attractive working hypothesis.
- 3) *Quinones*: A duroquinone dependent oxidoreductase was reported in the plasma enriched fractions and the role of quinones in PM bound redox reactions was also suggested (26, 27) Vitamin K3 enhanced the redox activity indicating that quinones may act as electron carriers. (28) Also the experiments based on NAD(P)H:duroquinone, NAD(P)H:HCF(III) oxido reductase activities suggested the role of quinone as electron carrier component of PM redox chain.
- 4) *Other Redox Components*
  - a) The -SH groups located at the plasma membrane are kept in reduced form by plasma membrane redox chains (29) They exist in plasma membrane of human erythrocytes and have shown important role in protecting them against free radical damage by keeping the -SH groups in reduced state. NADH oxidase is an -SH containing enzyme.
  - b) Iron sulfur-proteins play an important role as redox carriers in bacterial plasma membranes (30). Unlike mammalian systems, bacteria use iron sulfur clusters in electron transport. These clusters are located in the periplasmic space and are particularly susceptible to NO's attack. The result is the release of iron into the interior of the cell where it binds to DNA. NO does not penetrate easily to the interior of the bacteria and thus, peroxide, via Fenton chemistry, is required to interact with the bound iron.

#### A. Nature of Electron Donor

Direct and indirect experimental evidence from a number of studies point to NAD(P)H as the intracellular source of electrons in PM linked redox activities (31-33). Many workers were of the view that NADH is the preferred electron donor. This could be due to preferential transfer of electrons from NADPH to NAD<sup>+</sup> which in turn donates to O<sup>2</sup> or any other acceptor with the help of PM bound oxido-reductases (34-36). There is some information on other natural electron donors such as GSH, ascorbate and semi-dehydroascorbate. The involvement of -SH groups in TPMET has been discussed by various workers (37) Ascorbate free radical generated by ascorbate and dehydroascorbate was suggested to be an electron donor (38, 39) The views presented above indicate the involvement of many reductants as physiological electron donors in PM bound redox systems.

### III. NATURE OF ELECTRON ACCEPTOR/ CARRIER

Molecular oxygen is considered to be the physiological electron acceptor in PM bound reactions. But since under certain conditions it is difficult to measure Oxygen consumption in assaying TPMET Activity, therefore artificial electron acceptors are used. The criteria for using any artificial electron acceptor necessitates its high redox potential, sensitivity of extinction co-efficients to redox state, stability, impermeability, non toxicity and that the reduction process should not involve either utilization or release of protons. A variety of electron carriers like Ferric chelates, Ferricyanide and Ascorbate free radical has been used. (40)

### IV. REDOX AND OTHER RELATED ACTIVITIES ASSOCIATED WITH PM

- 1) NADH oxidase: Lin first established NADH oxidase as one of the plant PM bound activities by observing that the rate of oxygen consumption increased three times in corn root protoplasts in presence of NADH.
- 2) NAD(P)H oxidase: Presence of NAD(P)H oxidase activity on the external surface of isolated intact plasma membrane vesicles was also reported.
- 3) NAD(P)H- Acceptor Reductases: Exogenous NAD(P)H increases the rate of ferricyanide reduction (41) as reported in intact tissues, culture grown cells and protoplasts, and also causes the reduction of other electron acceptors like DCPIP, duroquinone and cytochrome c. However due to formation oxygen radicals, particularly in the presence of peroxidases, it was difficult to assess if the oxygen radicals act as intermediate in the electron transfer between these acceptors and NAD(P)H dehydrogenases on the membrane surface or directly.

- 4) Reduction of extracellular Ferricyanide and other  $\text{Fe}^{3+}$  chelates in TPMET(32)
- 5) Proton Transport associated with PM redox activities. The plasma membrane redox systems could be proton pumping and likely to be involved in energisation of solute transport across the plasma membrane of a eukaryotic cell. Many workers have explored the relationship of proton extrusion coupled to the PM bound redox system with PM  $\text{H}^+$ ATPase.(32)

## V. REDOX ACTIVITIES & FORMATION OF ROS

Cellular defense against stress is another key function in which the PMRS is involved and reactive oxygen species (ROS) play a double underlying role in that they can be produced by some of the PMRS enzymes and be protected against by others. The key producers of ROS in many cells are the NOX family of NADPH oxidases.

The protective role of PMRS against ROS is due to its anti oxidant properties. ROS are generated in cells by both enzymatic and nonenzymatic reactions as by-products of redox reactions. AS the ROS is very reactive in nature they are potentially very destructive to cells as they can react with lipids, proteins, or nucleic acids giving rise to severe cell damage. The protection and elimination of these ROS can be done by quenching these radical chain reaction by small molecules which include the ubiquinol/ubiquinone (CoQH<sub>2</sub> /CoQ) redox pair and  $\alpha$ -tocopherol ie vitamin E(35, 37) inside the lipid bilayer, and ascorbate ie vitamin C(38) at the interphase. To be able to sustain the capability of the redox systems to continuously reduce they need to be maintained in the proper redox state which is done by the PMRS. It maintains the adequate antioxidant levels (40).

Two PMRS enzymes, namely an NADH:ascorbate free radical (AFR) oxidoreductase and an NADH:ubiquinone (CoQ) oxidoreductase, have been shown to drive electrons to a semi-oxidized form of ascorbate, ascorbate free radical (AFR), through CoQ, resulting in stabilization of ascorbate.

NADH:AFR oxidoreductase Ascorbate can donate either one or two electrons in redox reactions. Loss of the first electron results in the AFR, which is not very reactive. Upon reaction with mild oxidants such as ferricyanide, the second electron is removed and AFR is converted to a less stable form, dehydroascorbic acid (DHA). Studies have shown that it provides a mechanism for cells to regenerate efficiently extracellular ascorbate from the AFR(41).

The PM NADH:AFR oxidoreductase appears to be distinct from the PM NADH:ferricyanide reductase, implicating the different levels of transplasma membrane electron transport systems that exist for discrete functions(42). The NADH:AFR reductase serves to protect cellular components from free radical-induced damage by a direct quenching of soluble free radicals or scavenging those radicals that initiate lipid peroxidation(43) Membrane-bound tocopheroxyl radicals are reduced by ascorbate to tocopherol, which is a protective agent against peroxidation of polyunsaturated membrane lipids by reducing lipid hydroperoxyl radicals to hydroperoxides(44,45). Anti-oxidant recycling of  $\alpha$ -tocopherol by ascorbate has been observed in liposomes, cellular organelles and erythrocytes(46, 47) The NADH:AFR reductase has a high apparent affinity for both NADH and the AFR.

NADH:CoQ oxidoreductase There are many one- and two-electron reductases in cellular systems capable of reduction of quinones to semiquinones and hydroquinones respectively. NQO1 and NQO2 are the two mammalian forms of the obligate two-electron reductase family termed NAD(P)H:quinone acceptor oxidoreductases (NQO). The NADH:CoQ oxidoreductase is a 34 kDa protein with an internal fragment sequence identical to cytochrome b5 reductase. The role of CoQ in TPMET has been described, using the PMs from the deletion mutant yeast strain coq3D, which is defective in CoQ6 biosynthesis, ( 49, 50), as a source of electrons for transmembrane ascorbate stabilization. At the PM interphase, CoQ maintains ascorbate in the reduced state using cytoplasmic NADH as a unique electron source. Also it can be said that by the catalytic action of NADH:CoQ reductase, NADH drives a one electron reduction of CoQ to its semiquinone radical. Phenoxyl radical of a tocopherol is reduced and generates a tocopherol. (51)

It means CoQ quenches the free radical chain by regenerating tocopherol and scavenges peroxyradical in its hydroquinone form.(9)Thus an internal NADH:CoQ oxidoreductase acts as an electron donor and reduces its final acceptor ascorbate by reduced CoQ acting as a carrier. (51,52).

As a first defensive weapon against pathogens, ROS are also generated by PMRS at the cell surface of certain lineages of cells, a phenomenon known as a respiratory burst(53). The professional phagocytes of the immune system have the ability to produce ROS as microbicidal agents against pathogens.

The enzymes responsible for the production of ROS are a multicomponent inducible NADPH oxidase, that requires assembly at the PM to function as an oxidase, and a myeloperoxidase. Also known as 'respiratory burst oxidases', the activated NADPH oxidases generate tightly controlled and localized oxygen free radical.

This respiratory burst is accompanied by increased oxygen consumption (54) due to the activity of NADPH oxidase Furthermore, the oxygen free radical rapidly dismutates to hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and water.

The  $H_2O_2$  can be transformed by other membrane enzyme systems into other more reactive ROS (such as hydroxyl radical and singlet oxygen). The most prominent of these enzymes is neutrophil myeloperoxidase, which generates hydrochloric acid through the oxidation of  $Cl^-$  by  $H_2O_2$  (55).

The NADPH oxidase of phagocytes (NOX2) is a special and inducible form of ubiquitous PMRS. NOX2 is a transplasma membrane heterodimeric cytochrome b558, composed of a small  $\alpha$ -subunit and a larger  $\beta$ -subunit, associated with two proteins, located in the cytoplasm of unstimulated cells(56). The larger subunit of NOX2 functions as an electron transport chain containing four NADPH binding regions, an FAD binding site, and two heme groups anchored by four histidines.(57) NOX1, NOX3, NOX4, NOX5, Duox1 and Duox2, which are present in non-phagocytic tissues, are all homologs of the larger subunit of NOX2.

In a study to investigate how **cytochrome b5 reductase** (b5R), one of the PM redox enzymes, regulates cellular response under stressed conditions, human neuroblastoma cells transfected with b5R were used for viability and mitochondrial functional assays.(58,59) Cells transfected with b5R exhibited significantly higher levels of the  $NAD^+/NADH$  ratio, consistent with increased levels of b5R activity(60). Overexpression of b5R made cells more resistant to  $H_2O_2$  (oxidative stress), 2-deoxyglucose (metabolic stress), rotenone and antimycin A (energetic stress), and lactacystin (proteotoxic stress), but did not protect cells against  $H_2O_2$  and serum withdrawal. Overexpression of b5R induced higher mitochondrial functions such as ATP production rate, oxygen consumption rate, and activities of complexes I and II, without formation of further reactive oxygen species, consistent with lower levels of oxidative/nitrative damage and resistance to apoptotic cell death.

Unlike mammalian systems, bacteria use **iron sulfur clusters** in electron transport. These clusters are located in the periplasmic space and are particularly susceptible to **NO's** attack. The result is the release of iron into the interior of the cell where it binds to DNA. NO does not penetrate easily to the interior of the bacteria and thus, peroxide, via Fenton chemistry, is required to interact with the bound iron. This process oxidizes DNA and leads to its cleavage. In contrast, NO can diffuse to most parts of mammalian cells, where it serves as an antioxidant. These two basic differences make  $NO/H_2O_2$  a perfect killing combination for *E. coli* and at the same time, protects mammalian cells from ROS-mediated toxicity. (61)

Thiol-based redox sensors, its associated enzymatic detoxification systems and BSH-related regulatory mechanisms in *S. aureus*, which are important for the defense under redox stress conditions has been discussed (62, 63) These thiol switches of *S. aureus* function in protection against redox active disinfectants and antimicrobials, including HOCl, the AGXX antimicrobial surface coating.(64-66)

## VI. SIGNIFICANCE AND FUTURE PROSPECTS

Molecules such as ROS, similar to those produced from ionizing radiation, can be generated in the body and when uncontrolled, can lead to cellular and tissue damage (67, 68)NO/RNS and ROS serve both as immune-toxins as well as immune-modulators. The incoming immune signal initiate the production of NO and ROS to intercept and kill pathogens. NO and ROS also modulates the downstream signaling pathways that lead to the full expression of the immune response. it is critical to understand the NOX system and the roles of other NOX family enzymes as major sources of ROS production at specific sites of injury/inflammation. (69)

Depending on the source of ROS, cell type, and tissue environment, ROS signaling may participate in normal physiological processes or contribute to a maladaptive response that leads to metabolic dysfunction and inflammatory signaling. Diseases associated with elevated inflammatory signaling and metabolic dysfunction such as atherosclerosis, diabetes mellitus, and stroke are associated with an altered redox balance. Understanding the role of ROS signaling in the regulation of metabolic activity, inflammatory activation, and diseases associated with metabolic dysfunction is important in our pursuit of novel therapies to treat these diseases.(70)

A higher  $NAD^+/NADH$  ratio and consequent more efficient mitochondrial functions are induced by the PMRS, enabling them to maintain redox state and energy metabolism under conditions of some energetic stresses. This suggests that b5R can be a target for therapeutic intervention for aging and neurodegenerative diseases. It is suggested that up-regulated PM redox enzymes (e.g., b5R, NQO1) can play a key role in removing abnormal proteins by increasing chaperon proteins during pathogenic processes in AD, PD, and prion disease. Taken together, the studies have indicated that b5R can be a therapeutic target for neurodegenerative diseases focused on the regulation of mitochondrial function. Thus, thiol switches could be novel drug targets for the development of alternative redox-based therapies to combat multi-drug resistant *S. aureus* isolates. Further work is required to improve mitochondrial energy metabolism using other cell culture and animal models.

Overall, the complexity of these reactions reflects on the diverse nature of redox chemistry within a biological setting. The studies on the modulators of PMRS can help unravel the mysteries and mechanisms of the complex immune responses.

**BIBLIOGRAPHY**

- [1] Crane FL, Sun IL, Clark MG, Grebing, Löw H. Transplasmamembrane redox systems in growth and development. *Biochim Biophys Acta* 1985; 811: 233–264.
- [2] Rubinstein B, Luster DG. Plasma membrane redox activity: components and role in plant processes. *Annu Rev Plant Physiol Mol Biol* 1993; 44: 131–155.
- [3] Medina MA, Núñez de Castro I. Plasma membrane redox systems in tumor cells. *Protoplasma* 1995; 184: 268–272.
- [4] Jennifer D. Ly, Alfons Lawen Transplasma membrane electron transport: enzymes involved and biological function. *Redox Report*, Vol. 8, No. 1, 2003
- [5] Forman H. J., Torres M., Fukuto J. (2003) *Signal Transduction by Reactive Oxygen and Nitrogen Species: Pathways and Chemical Principles*, Dordrecht, The Netherlands; Boston, MA, USA, Kluwer Academic Publishers.
- [6] Forman H. J., Torres M., Fukuto J. (2002) Redox signaling. *Mol. Cell. Biochem.* 234-235, 49–62.
- [7] Quinone, MA, Giraldez, Witt F G and Aoaricio P J (1997): Blue light dependent monovalent anion uptake . *Physio. Plant.* 90, 779-785
- [8] Shimazaki, K, Goh, CH and kinoshita t(1991): Involvement of intracellular Ca<sup>2+</sup> in blue light dependent proton pumping in gcp from *vicia faba*. *Physiol plant.* 105, 554-561
- [9] Rubinstein B and Stern AI(1991) Relationship of transplasma redox activity to proton and solute transport by roots of *Zea Mays*. *Plant Physiol.* 80, 805-811.
- [10] Horowitz, BA , Perlman, A and Gressel, A (1990) Induction of trochoderma sporulation by nano second laser pulses: evidence against cryptochrome cycling. *Photochem and photobiol.* 51, 99-104.
- [11] Jennifer D. Ly & Alfons Lawen (2003) Transplasma membrane electron transport: enzymes involved and biological function, *Redox Report*, 8:1, 3-21, DOI: 10.1179 / 135100003125001198
- [12] Villalba JM, Navarro F, Córdoba F et al. Coenzyme Q reductase from liver plasma membrane: purification and role in transplasma-membrane electron transport. *Proc Natl Acad Sci USA* 1995; 92: 4887–4891.
- [13] Santos-Ocaña C, Córdoba F, Crane FL, Clarke CF, Navas P. Coenzyme Q6 and iron reduction are responsible for the extracellular ascorbate stabilization at the plasma membrane of *Saccharomyces cerevisiae*. *J Biol Chem* 1998; 273: 8099–8105.
- [14] Buron MI, Rodriguez-Aguilera JC, Alcain FJ, Navas P. Transplasma membrane redox system in HL-60 cells is modulated during TPA-induced differentiation. *Biochem Biophys Res Commun.* 1993; 192:439–445. doi: 10.1006/bbrc.1993.1434.
- [15] Kagan VE, Tyurina YY. Recycling and redox cycling of phenolic antioxidants. *Ann NY Acad Sci* 1998; 854: 425–434.
- [16] Hyun, D. H., Hernandez, J. O., Mattson, M. P., and de Cabo, R. (2006). The plasma membrane redox system in aging. *Ageing Res. Rev.* 5, 209–220. doi: 10.1016/j.arr.2006.03.005
- [17] Navas, P., Villalba, J. M., and Lenaz, G. (2005). Coenzyme Q-dependent functions of plasma membrane in the aging process. *Age* 27, 139–146. doi: 10.1007/s11357-005-1632-z
- [18] Takahashi, K., Akiba, Y., and Horiguchi, M. (1992). Effect of an antithyroid agent (propylthiouracil) and L-ascorbic acid on mixed-function oxidase and drug metabolism in hepatic microsomes of chickens. *Comp. Biochem. Physiol. C* 102, 73–75. doi: 10.1016/0742-8413(92)90046-A
- [19] Crane, F. L. (2001). Biochemical functions of coenzyme Q10. *J. Am. Coll. Nutr.* 20, 591–598. doi: 10.1080/07315724.2001.10719063
- [20] Brain R, D, freeberg, JA Weiss, CV and Briggs, WR (1977) Blue light induced absorbance changes in membrane fractions from corn and *Neurospora*. *Plant Physiol* 59, 448-452.
- [21] Goldsmith, MHM, Caubergs, RJ, Briggs WR(1980) Light inducible cytochrome reduction in membrane preparation from corn coleoptiles stabilization and spectral characterization of the reaction. *Plant physio.* 66, 1067-1073.
- [22] Breitenbach, M., Rinnerthaler, M., Weber, M. et al. The defense and signaling role of NADPH oxidases in eukaryotic cells. *Wien Med Wochenschr* **168**, 286–299 (2018). <https://doi.org/10.1007/s10354-018-0640-4>
- [23] Warpeha, KMF, Kaufman, LS and Briggs, WR (1992): A flavoprotein may mediate the blue light activated binding of guanosine 5 triphosphate to isolated plasma membranes of *Pisum sativum* L. *Photochem. Photobiol.* 55, 595-603.
- [24] Larson, C., Widell, S and Kjellborn, (1987): Preparation of high purity plasma membranes. *Method Enzymol.* 148, 558-568.
- [25] Askerlund, p and Larsson, C (1991): Trans membrane electron transport in plasma membrane vesicles loaded with an NADH generation system of Ascorbate. *Plant Physiol.* 96, 1178-84.
- [26] Lin, C., Ahmad, M., and Cashmore, A R. (1996): Arabidopsis cryptochrome 1 is a soluble protein mediating blue light dependent regulation of plant growth and development. *Plant J.* 10, 893-902.
- [27] Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. *Biochim Biophys Acta.* 2004;1660:171–199. doi: 10.1016/j.bbame.2003.11.012.
- [28] Arroyo, A., V E Kagam, VA Tyurin, J K Burgess, R do Cabo, P Navas, and J M Villalba. NADH and NADPH-dependent reduction of coenzyme Q at the plasma membrane. *Antioxid Redox Signal.* Summer 2000.
- [29] Crane, F L and Barr, R(1989): Plasma membrane oxidoreductases. *Critical review Plant Sciences.* 8 273-307.
- [30] Crane, FL , Barr, R , Craig, TA and Morre DJ (1988): Plasma membrane electron transport in relation to cell growth and iron uptake. *J Plant Nutr.* 11, 1117-1126.
- [31] Moller, I. M and Crane, F. L.(1990) Redox process in the plasma membrane In the *Plant plasma membrane: Larson C and Moller, I M (eds) pp 93-121, Springer Verlag, Heidelberg.*
- [32] Misra, PC (1991) Transplasma membrane electron transport in plants. *J Bioenerg. Biomembr* 23, 425-441.
- [33] Masih, N and Misra, PC (2001) Ca<sup>2+</sup> Uptake and PM depolarization associated with blue light sensitive exogenous NADH oxidation by *Cuscuta reflexa*. *J Plant Physiol.*
- [34] Buckhout, TJ, Bell, BF, Luster, DG and Chaney, RL (1989): Iron-stress induced redox activity in tomato (*lycopersicon esculentum* Mill.) is localized on the plasma membrane. *Plant Physiol.* 90, 151-156.
- [35] De Luca T, Morre DM, Zhao H, Morre DJ. NAD<sup>+</sup>/NADH and/or CoQ/CoQH<sub>2</sub> ratios from plasma membrane electron transport may determine ceramide and sphingosine-1-phosphate levels accompanying G1 arrest and apoptosis. *BioFactors.* 2005;25:43–60.
- [36] Bienfait, H F and Lutge, U (1988): On the function of two systems that can transfer electrons across the plasma membrane. *Plant Physiol Biochem.* 26, 665-671.

- [37] Villalba JM, Gómez-Díaz C, Navarro F, Navas P. Role of transplasma membrane redox system in cell protection against oxidative stress. *Trends Comp Biochem Physiol* 1996; 2: 65–72.
- [38] Villalba JM, Crane FL, Navas P. Antioxidant role of ubiquinone in animal plasma membrane. In: Asard H, Bérczi A, Caubergs RJ. (eds) *Plasma Membrane Redox Systems and their Role in Biological Stress and Disease*. Dordrecht: Kluwer, 1998; 247–265.
- [39] Kesharwani RK, Singh DV, Misra K, Rizvi SI. Plant polyphenols as electron donors for erythrocyte plasma membrane redox system: validation through in silico approach. *Org Med Chem Lett*. 2012;2:12. doi: 10.1186/2191-2858-2-12.
- [40] Navarro F, Arroyo A, Martín SF et al. Protective role of ubiquinone in vitamin E and selenium-deficient plasma membranes. *Biofactors* 1999; 9: 163–170.
- [41] Alcain FJ, Buron MI, Villalba JM, Navas P. Ascorbate is regenerated by HL-60 cells through the transplasmalemma redox system. *Biochim Biophys Acta* 1991; 1073: 380–385.
- [42] Villalba JM, Canalejo A, Rodríguez-Aguilera JC, Buron MI, Moore DJ, Navas P. NADH-ascorbate free radical and NADH ferricyanide reductase activities represent different levels of plasma membrane electron transport. *J Bioenerg Biomembr* 1993; 25: 411–417
- [43] May JM, Qu Z-C, Cobb CE. Recycling of the ascorbate free radical by human erythrocyte membranes. *Free Radic Biol Med* 2001; 31: 117–124.
- [44] Gómez-Díaz C, Rodríguez-Aguilera JC, Barroso MP et al. Antioxidant ascorbate is stabilized by NADH-coenzyme Q10 reductase in the plasma membrane. *J Bioenerg Biomembr* 1997; 29: 251–257.
- [45] May JM. Is ascorbic acid an antioxidant for the plasma membrane? *FASEB J* 1999; 13: 995–1006.
- [46] Mehlhorn RJ, Sumida S, Packer L. Tocopheroyl radical persistence and tocopherol consumption in liposomes and in vitamin E-enriched rat liver mitochondria and microsomes. *J Biol Chem* 1989; 264: 13448–13452.
- [47] Mendiratta S, Qu Z-C, May JM. Enzyme-dependent ascorbate recycling in human erythrocytes: role of thioredoxin reductase. *Free Radic Biol Med* 1998; 25: 221–228.
- [48] Jimenez-Hidalgo M, Santos-Ocana C, Padilla S, Villalba JM, Lopez-Lluch G, Martin-Montalvo A, Minor RK, Sinclair DA, de Cabo R, Navas P. NQR1 controls lifespan by regulating the promotion of respiratory metabolism in yeast. *Aging Cell*. 2009;8:140–151. doi: 10.1111/j.1474-9726.2009.00461.x.
- [49] Rodríguez-Bies E, Navas P, López-Lluch G (2015) Age-dependent effect of every-other-day feeding and aerobic exercise in ubiquinone levels and related antioxidant activities in mice muscle. *J Gerontol A Biol Sci Med Sci*. 2015 Jan; 70(1):33-43
- [50] David Mantle, Robert A. Heaton and Iain P. Hargreaves: Coenzyme Q10 and Immune Function: An Overview *Antioxidants (Basel)*, 2021 May; 10(5): 759.
- [51] Navarro F, Villalba JM, Crane FL, Mackellar WC, Navas P. A phospholipid-dependent NADH-coenzyme A reductase from liver plasma membrane. *Biochem Biophys Res Commun* 1995; 212: 138–143.
- [52] Baggiolini M, Wymann MP. Turning on the respiratory burst. *Trends Biochem Sci* 1990; 15: 69–72. 41. Baldrige CW, Gerard RW. The extra respiration of phagocytosis. *Am J Physiol* 1933; 103: 235–236.
- [53] Sumimoto H, Miyano K, Takeya R. Molecular composition and regulation of the Nox family NAD(P)H oxidases. *Biochem Biophys Res Commun* 2005; **338**: 677–686.
- [54] Nguyen, GT, Green, ER and Mecas, J: Neutrophils to the ROScue: Mechanism of NADPH oxidase activation and Bacterial Resistance. *Front. Cell. Infect. Microbiol.*, 25 August 2017
- [55] Klebanoff SJ. Myeloperoxidase. *Proc Assoc Am Physicians* 1999; 111: 383–389. 43. Dang PM-C, Cross AR, Babior BM. Assembly of the neutrophil respiratory oxidase: A direct interaction between p67phox and cytochrome b558. *Proc Natl Acad Sci USA* 2001; 98: 3001–3005.
- [56] Fu X, Beer DG, Behar J, Wands J, Lambeth D, Cao W. cAMP-response element-binding protein mediates acid-induced NADPH oxidase NOX5-S expression in Barrett esophageal adenocarcinoma cells. *J Biol Chem* 2006; **281**: 20368–20382.
- [57] Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiol Rev* 2007; **87**: 245–313.
- [58] Hyun DH and Lee GH (2015) Cytochrome b5 reductase, a plasma membrane redox enzyme, protects neuronal cells against metabolic and oxidative stress through maintaining redox state and bioenergetics *Age Dordr* 2015 Dec; 37(6): 122. PMID: PMC5005863
- [59] Bewley MC, Marohnic CC, Barber MJ. The structure and biochemistry of NADH-dependent cytochrome b5 reductase are now consistent. *Biochemistry*. 2001; 40:13574–13582. doi: 10.1021/bi0106336.
- [60] Siendones E, SantaCruz-Calvo S, Martin-Montalvo A, Cascajo MV, Ariza J, Lopez-Lluch G, Villalba JM, Acquaviva-Bourdain C, Roze E, Bernier M, de Cabo R, Navas P. Membrane-bound CYB5R3 is a common effector of nutritional and oxidative stress response through FOXO3a and Nrf2. *Antioxid Redox Signal*. 2014;21:1708–1725. doi: 10.1089/ars.2013.5479.
- [61] David A Wink, H B Hines, RYS Cheng, C H Switzer, W F Santana, M P Vitek, LA Ridnour and C A Colton. (2011). Nitric oxide and redox mechanisms in the immune response. *J Leukoc Biol*. 2011 Jun; 89(6): 873–891.
- [62] Forman H. J., Fukuto J. M., Torres M. (2004) Redox signaling: thiol chemistry defines which reactive oxygen and nitrogen species can act as second messengers. *Am. J. Physiol. Cell Physiol*. 287, C246–C256
- [63] Linzner, Nico, Loi, Vu Van Fritssh, V Nadin and Antelmann Haiké. "Thiol-based redox switched in the major pathogen *Staphylococcus aureus*," *Biological Chemistry*, Vol. 402, no 3, 2021, pp 333-361.
- [64] Van Laer, K., Hamilton, C.J., and Messens, J. (2013). Low-molecular-weight thiols in thiol-disulfide exchange. *Antioxid. Redox. Signal* 18: 1642–1653.
- [65] Loi, V.V., Rossius, M., and Antelmann, H. (2015). Redox regulation by reversible protein S-thiolation in bacteria. *Front. Microbiol*. 6: 187.
- [66] Walsh, B.J.C. and Giedroc, D.P. (2020). H2S and reactive sulfur signaling at the host-bacterial pathogen interface. *J. Biol. Chem*. 295: 13150–13168.
- [67] Halliwell B., Gutteridge J. M. C. (1999) *Free Radicals in Biology and Medicine*, Oxford, UK, Oxford University Press.
- [68] Colton C., Gilbert D. (1999) *Reactive Oxygen Species in Biological Systems*, New York, NY, USA, Springer [[Google Scholar](#)]
- [69] Panday, A., Sahoo, M., Osorio, D. et al. (2015). NADPH oxidases: an overview from structure to innate immunity-associated pathologies. *Cell Mol Immunol* **12**, 5–23 (2015).
- [70] Steven J F, Daniel S K, Marina S H, Qian Xu, K K Griendling: Reactive Oxygen species in metabolic and inflammatory signaling. *Circulation research* 2018; 122, 877-902.



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