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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 mileu 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^+ 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:

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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 quinnones or cytochromes. Flavins have been isolated and measured in isolated PM vesicles (23) Exogenous FMN stimulated redox activity of a purifies 27 kDa maize PM reductase upon reconstitution (24) suggesting that the enzyme was a flavoprotien. 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 is 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+ which in turn donates to O^2 or any other acceptor with the help of PM bound oxido-reductases (34-36). There is some information on other natural electron donars such as GSH, ascorbate and semi-dehydroascorbate. The involvement of –SH groups in TPMET has been discussed by various workers (37) Acorbate 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, Ferricynide 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 ferricynide 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 the oxygen radicals act as intermediate in the electron transfer between these acceptors and NAD(P)H dehydrogenases on the membrane surface or directly.

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4) Reduction of extracellular Ferricynide and other $Fe3^{+}$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 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 the 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 (CoQH2 /CoQ) redox pair and a-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 a-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 hydroquinine form.(9)Thus an internal NADH:CoQ oxidoreductase acts as an electro doanr 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 (H_2O_2) and water.

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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 a-subunit and a larger b- 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 is 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 desinfectants 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.

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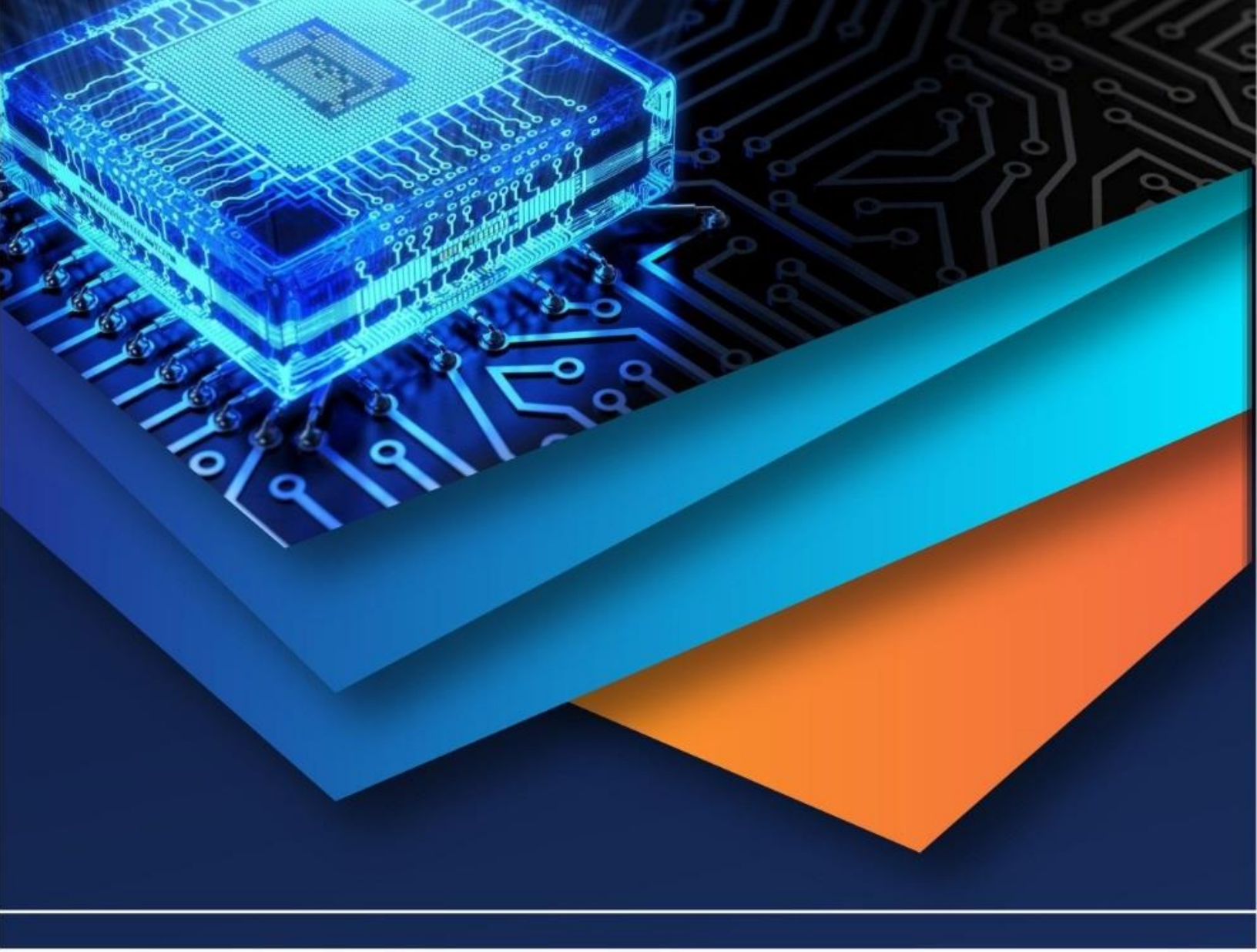
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