Review Article

A REVIEW ON MITOCHONDRIA AND REACTIVE OXYGEN SPECIES: THE BETTER SIDE
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ABSTRACT

Ever since the reactive oxygen species (ROS) were discovered in biology, the researchers have tried to understand the impact of these molecules in physiological pathways. They are known to be toxic since they are involved in plethora of diseases that include metabolic disorders, genetic diseases, neurodegenerative diseases, diabetes, cancer and premature aging. No doubt, at high concentrations, they are harmful for living organisms, but at moderate and optimum levels, ROS play an important role as regulatory and signaling molecules and regulate various biological pathways and are critical for healthy cell function. At the cellular level, ROS regulate growth, apoptosis, autophagy, memory, blood pressure, cognitive function, immune function; enable the response to growth factor stimulation and the generation of the inflammatory response. They are involved in the cross-linking of the extracellular matrix and regulate many cellular processes, including differentiation, proliferation, growth, cytoskeletal regulation, migration and contraction. They are involved in gene activation and modulation of chemical reactions in the cell. They also act as mediators in the biosynthesis of prostaglandins, act as signaling molecules within the individual cell and among cells. They also influence contractility of vascular smooth muscle cells, control vascular endothelial cell proliferation, migration and mediate platelet activation. Thus, ROS, originally envisioned as a necessary evil of oxidative metabolism & a product of an imperfect system are involved in regulation of normal physiological functions and this review tries to unlock the conception about their involvement in normal physiology.

Keywords: Autophagy, cognition, mitochondria, reactive oxygen species

INTRODUCTION

Mitochondria, identified over a century ago were termed as “bioblasts” by Richard Altman who described them as “elementary organisms” living inside cells. The term mitochondrion, was later coined by Carl Benda and literally means “mitos-thread” and “chondrion-granule”1 and theory of endosymbiosis is still one of the most widely accepted theories of mitochondrial evolution.2 The role of mitochondria in the cell was thought to be only to generate energy in the form of adenosine triphosphate (ATP) which is called ”powerhouse of the cell”. Beside ATP generation, mitochondria are actively involved in a multitude of cellular activities including cell signalling, proliferation and death. In fact, while most eukaryotic cells contain mitochondria, the size, number and location of mitochondria in a cell vary significantly based on the cellular needs.3 Given the role of mitochondria in a variety of cellular processes, it is not surprising that damage to the mitochondria has been implicated in the pathogenesis of end-organ injury in a variety of diseases.4 How does a single organelle decide the fate of cell? This question has captivated scientists and studies have revealed fascinating mechanisms which relies on the generation of free radical species that determine the outcome of the cellular processes involved. This review will mainly focus on the role of these reactive oxygen species in the modulation of cellular activities.5

Structurally, mitochondria are composed of a smooth outer membrane followed by an inner membrane having larger surface area that, in turn, surrounds the matrix which is a protein-rich core. Most likely, mitochondria are derived from aerobic prokaryotes integrated into nucleated cells. Mitochondria are ubiquitous in eukaryotes. Their number per cell ranges from zero in erythrocytes to ten thousands in striated muscle cells. Their main function is to support aerobic respiration and to provide energy as ATP, by means of the electron transport chain (ETC). The ETC consist of four multimeric protein complexes located in the inner mitochondrial membrane and it provides the cell with the most efficient energetic outcome in terms of ATP production. The ETC also requires cytochrome c (cyt c) and a small electron carrier, coenzyme Q10 (CoQ10, or ubiquinone). Electrons are transported along the complexes to molecular oxygen (O2), finally producing water. At the same time, protons are pumped across the mitochondrial inner membrane, from the matrix to the inter membrane space, by complexes I, III, and IV. This process creates an electrochemical proton gradient. ATP is produced by the influx of these protons back through the complex V, or ATP synthase (the “rotary motor”). This metabolic pathway is under control of both nuclear (nDNA) and mitochondrial genomes.6,8

The outer membrane of the organelle is identical to the plasma membrane in its content (equal ratio of protein to phospholipid content by weight). It contains porins that allow molecules that are less than 5 KDa to freely diffuse through. However, larger proteins require the presence of a mitochondria targeted sequence that will enable binding to specific transporters on the membrane for entry into the organelle.9,10

The outer membrane therefore mainly serves as a permeability barrier to the cytosolic components. The inter membrane space which was thought to have no specific function, but emerging studies have suggested an important role for this space in maintaining mitochondrial homeostasis, including protein sorting and lipid homeostasis.11

The better side
Physiology of oxidative phosphorylation

The respiratory chain is localized in cristae, structures formed by the inner mitochondrial membrane and extending to the surface. ETC consists of complexes with supramolecular organization, where mitochondrial proton pumps (complexes I, III and IV) transport protons and generate a proton gradient. Continuously, electrons are transported to complex III and finally complex IV enables the conversion of O₂ to H₂O. Most of the ATP synthesis comes from the electrochemical gradient across the inner membranes of mitochondria by ATP synthase (complex V). The CoQ cofactor is responsible for transferring electrons from complexes I and II to complex III; the second important cofactor is cytochrome c (cyt c), which transfers electrons from complex III to complex IV. 

The main mechanisms responsible for mitochondrial ROS production are the respiratory chain, in particular its complexes I and III, in the inner mitochondrial membrane, and monoamine oxidase in the outer membrane. ROS and their peroxidation metabolites are neutralized by inbuilt protective mechanisms mainly consisting of mitochondrial and cytosolic superoxide dismutases, glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase. However, under conditions of increased ROS generation, e.g., in ischemia-reperfusion, use of xenobiotics, inflammation, aging and ultraviolet or ionizing irradiation, or conditions of impaired antioxidant defense system, ROS may accumulate, exerting a potent damaging effect on the cell and the whole organism.

The biological importance of ROS has attracted an enormous interest during recent years due to their major role, both beneficial and noxious, in numerous vital processes. Mitochondria are the main source of the superoxide radical and other reactive oxygen species that may generate from them.

Physiological role of ROS

Many systems (enzymatic and non enzymatic) can be considered as sources of ROS in the living organism. Exogenously, ROS are produced from exposure to environmental agents such as ultraviolet (UV) radiation and redox-cycling agents. Endogenously, ROS are derived mostly from the incomplete reaction of oxygen during aerobic metabolism in vivo. They are produced from mitochondrial electron transport chain, NADH/NAPDH oxidases, arachidonic acid pathway enzymes, cyclooxygenase and lipoxygenase, NO synthase, peroxidases, xanthine oxidases, phagocytes - derived myeloperoxidase. Reactive oxygen species present a paradox in their biological function as on one hand they prevent disease by assisting the immune system, mediating cell signalling and playing an essential role in several other processes.

At the cellular level, ROS regulate growth, apoptosis and other signalling. At the systems level they contribute to complex functions such as blood pressure regulation, cognitive function and immune function. ROS enable the response to growth factor stimulation and the generation of the inflammatory response, as well as having vital roles in the immune system where they directly kill pathogens. Other examples of a biochemical role of ROS are found in primitive organisms, where ROS are involved in the cross-linking of the extracellular matrix and in the hardening of the fertilization envelope after egg-sperm fusion. They participate in the regulation of many cellular processes, including differentiation, proliferation, growth, apoptosis, cytoskeletal regulation, migration and contraction. ROS play crucial roles in gene activation, cellular growth, and modulation of chemical reactions in the cell. They also participate in blood pressure control, are mediators in the biosynthesis of prostaglandins, function in embryonic development, and act as signaling molecules within the individual cell and among cells during their lifespan. The brief description and involvement of ROS is described in the present review.

ROS and Memory

ROS play important role in normal cognitive attributes at cellular and behavioral domain and they are required for a form of synaptic plasticity called long-term potentiation (LTP), learning and memory, and for biochemical signal transduction cascades that are believed to underlie LTP and memory formation. ROS have a role in the function of brain cells or in CNS cell-to-cell communication. For example, there is evidence for regulation of neuronal ion channels, kinases, and transcription factors by ROS.

Synaptic plasticity describes the ability of synapses to adjust their strength, connectivity and structure in response to previously experienced activity. The inherent plasticity of neurons is key to neuronal network development and in networks allows for adaptation, memory and learning. Synaptic strength may be enhanced or reduced depending upon the neuronal context and the nature of stimulation, the best-studied examples being LTP and long-term depression (LTD). Synaptic plasticity is the physiological process that is thought to underlie learning and memory at the cellular level. One form of plasticity that has been commonly studied is LTP. Many of the molecular processes underlying LTP also are required for learning and memory.

LTP studies in the rodent hippocampus have revealed that scavenging superoxide blocks LTP induced with high-frequency stimulation (HFS–LTP), suggesting that superoxide is required for HFS-LTP high concentrations of superoxide or H2O2 resulted in the depression of excitatory postsynaptic field potentials (fEPSPs) measured in hippocampal area CA1, whereas lower concentrations resulted in a potentiation of the fEPSP.

The high-frequency stimulation (HFS) used for induction of LTP results in opening of NMDA receptors and thus elevates intracellular Ca²⁺, leading to adjustment of synaptic strength via direct and transcriptionally regulated modification of synaptic proteins, and changes in the composition of synaptic protein complexes.

ROS production is elevated in hippocampal slice preparations following increased neuronal activity, NMDA receptor activation and subsequent LTP. In mouse hippocampus NMDA receptor activation triggers ROS generation through the NOX2 NAPDH oxidase, regulated by PKC. Importantly, acute application of cell
Mitochondrial ROS Regulate Autophagy

Autophagy is the process by which cells engulf and break down intracellular proteins and organelles in the lysosome and repurpose the constituents for new biosynthesis. It occurs continuously under normal conditions to remove and recycle damaged proteins and organelles as a method of quality control. In addition to its role in maintenance of homeostasis, autophagy is also an important response to cellular stress, including starvation, ischemia/reperfusion and pathogen infection. Under starvation, it is thought that autophagy functions to recycle intracellular molecules when external nutrients are limiting. Mitochondrial ROS are required for induction of autophagy under starvation. The starvation induced PI3K activation, which induced mROS, which subsequently oxidized and inactivated the cysteine protease Atg4 to promote Autophagy. As such, mROS and mitophagy can form a feedback loop, where by mROS induce mitophagy, which limits further production of ROS by reducing mitochondria quantity.

Apoptosis

Apoptosis or programmed cellular death is an utmost criteria and requirement for regularized/generated and sustainable cell development and also for destruction of cells that represent a threat to the integrity and survival of the organism. The decision of a cell to commit suicide is based on the balance between the withdrawal of positive signals (those needed for continued survival, e.g. growth factors for neurons, interleukin-2, etc.) and the receipt of negative signals (e.g. increased levels of oxidants within the cell, damage to DNA by oxidants, or other harmful effects such as high-energy irradiation, chemotherapeutics, etc.). Generally, there are three different mechanisms by which a cell commits suicide by apoptosis: one triggered by internal signals: the intrinsic or mitochondrial pathway; another triggered by external signals: the extrinsic or death receptor pathway; and a third triggered by apoptosis inducing factor (AIF).

The internal signals initiate an mechanism that is identified as intracellular damage to the cell (e.g. from ROS, irradiation, etc.) which initialize Bcl-2 (a protein located in the outer membranes of mitochondria) activation to further promote initiation of a protein, Bax, which makes pores in the outer mitochondrial membrane so that cytochrome c can be released from mitochondria. The released cytochrome c with help of ATP, binds to the protein—apoptotic protease activating factor-1 (Apaf-1), followed by aggregation of these complexes to form apoptosomes which bind to and caspase-9. The cleaved caspase-9 activates other executioner caspases (3 and 7) leads to digestion of structural proteins in the cytoplasm, degradation of DNA and phagocytosis of the cell and cellular debris.

Immunological functions of ROS

Normal immune function requires specific oxidative states. ROS are necessary for microbial killing, for limiting the specific immune response, and for inflammation termination. The studies on patients suffering from chronic granulomatous disease (CGD) has shown strong evidence for involvement of ROS in immune function and this disease has helped to unleash various mechanisms of involvement of ROS in immune functions. CGD is caused by a lack of the ROS-generating phagocyte NADPH oxidase NOX2. Notably, CGD and the associated lack of ROS leads to immunodeficiency associated with recurrent infections, including pneumonia, abscesses, and osteomyelitis. In response to stimulation, phagocytes of CGD patients do not generate ROS. This is problematic for host defence because macrophages and neutrophils must generate ROS to efficiently kill the bacteria through phagocytosis. Hypochlorous acid is approximately 50 times more potent in microbial killing than hydrogen peroxide; myeloperoxidase catalyses the conversion of hydrogen peroxide and chloride ions into hypochlorous acid. ROS have a vital role in bacterial, fungal, and microbial killing.

The more subtle changes in intracellular redox state mediated by mROS appear to be essential for a wide range of innate immune function, including antiviral, antibacterial, and antiparasitic responses. ROS have also been observed to have important roles in proper functioning of the innate immune response, activation of the adaptive immune response, as well as downregulation of inflammation and immune system activity. Disruption of dysregulation of immune system functions can lead to diseases characterized by inflammation, including atherosclerosis and cancer. During the initial response to an invading pathogen, activation of the innate immune response, characterized by generation of ROS within phagocytic cells such as macrophages and neutrophils, is a critical event in the initiation of phagocytosis and subsequent destruction of these microorganisms.

The generation of ROS promotes activation of signal transduction pathways responsible for the production of inflammatory cytokines and chemokines, apparently by ROS-mediated inactivation of intracellular tyrosine phosphatases. This allows increased phosphorylation and activity of signal transducer and activator of transcription (STAT) 1 and 3, transcription factors that regulate expression of interferon regulatory factors 1 and 7. These regulatory factors, in turn, promote up-regulation of genes necessary for an effective antiviral response. In addition ROS also have a role in influenza, HIV, hepatitis B and hepatitis C infections.

The generation of ROS during the innate immune response also modulates apoptosis of neutrophils at the site of inflammation. Failure to down-regulate these processes can lead to pathologically chronic inflammation. Several groups have shown that a sustained and robust oxidative burst is required for neutrophil apoptosis.

Role of ROS against cancer

Production of free radicals in cancer cells seems a defence mechanism by which body tries to fight against cancer cells. Free radicals especially oxygen species provide a supply for hydrogen peroxide which eventually decomposes to water and oxygen. Oxygen, in turn, reduces neovascularisation and metastasis. Thus, cancer is a condition which is accompanied with decrease in intracellular oxygen. It look likes that every drug or plant extract which can increase intracellular hydrogen peroxide and further decomposition to water and oxygen may be effective in treatment of cancer.

Thyroid functions

Another example of the importance of ROS in health has been revealed by patients with a rare form of hypothyroidism. Hydrogen peroxide is a necessary cofactor for thyroperoxidase, the enzyme participating in a final step of hormone production. For years, thyroid researchers had been actively looking for an enzyme that produces hydrogen peroxide in an NADPH-dependent manner. Notably, this is another example where the
ROS-generating function was described long before the responsible NOX protein and its structure were discovered. It is now clear that DUOX2 (and probably also DUOX1) is the enzyme that generates the hydrogen peroxide required for thyroid peroxidise function; this theory is well supported by the existence of congenital hypothyroid patients with mutations in the DUOX2 gene.44,51

**Aging**

Aging is a physiological process, defined as a series of time-dependent physiological changes that reduce physiological reserve and functional capacity.52 In eukaryotic cells, this process is regulated by several factors such as the "target of rapamycin" (TOR), a nutrient-sensing protein kinase 53, and the "AMP-activated kinase" (AMPK), a conserved sensor of increased levels of AMP and ADP originating from ATP depletion.54 Expression and activation of these two factors are finely modulated by ROS, both in physiological and pathological processes.55 Also, the mitochondrial free radical theory of aging proposes that aging is caused by damage to macromolecules by ROS. However, recent findings suggest that ROS generation is not the primary or initial cause of aging. Thus, it has been proposed that ROS modulate the aging process mediating the stress response to age-dependent damage.56 Further investigations are required to understand better the mechanisms and the specific targets underlying the positive effects of ROS on the aging process further recent data suggest that low levels of ROS activate stress responses that are beneficial to the organism and extend life span.57 Further, ROS have been suggested as prevalent regulators of several nuclear factors, including erythroid 2-related factor 2 (Nrf2), nuclear factor kappa-B (NFkB) cells, mitogen-activated protein kinase (MAPK) and p53, which are further associated with several signaling cascades.57

**CONCLUSION**

Reactive oxygen species (ROS) are extremely chemically reactive moieties that have origin from normal physiological functions. They are naturally produced within biological systems and thus they must have important role in regulation of normal physiological system. Efforts to reveal the multi-faceted and complex roles of ROS has explored the better side of ROS that shows their involvement in variety of physiological processes including cell signaling, immune response, synaptic plasticity, hormonal functions, stress response and many others.

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