# Reactive oxygen species

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**Reactive oxygen species** (ROS) are ions or very small molecules that include oxygen ions, free radicals, and peroxides, both inorganic and organic. They are highly reactive due to the presence of unpaired valence shell electrons. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress (such as for example, UV or heat exposure) ROS levels can increase dramatically, which can result in significant damage to cell structures. This cumulates into a situation known as oxidative stress. They are also generated by exogenous sources such as ionizing radiation.

## Contents



## Damaging effects

Cells are normally able to defend themselves against ROS damage through the use of enzymes such as superoxide dismutases, catalases, glutathione peroxidases and peroxiredoxins. Small molecule antioxidants such as ascorbic acid (vitamin C), tocopherol (vitamin E), uric acid, and glutathione also play important roles as cellular antioxidants. Similarly, polyphenol antioxidants assist in preventing ROS damage by scavenging free radicals. In contrast, the antioxidant ability of the extracellular space is relatively less--e.g., the most important plasma antioxidant in humans is probably uric acid.

Effects of ROS on cell metabolism have been well documented in a variety of species. These include not only roles in apoptosis (programmed cell death), but also positive effects such as the induction of host defence genes and mobilisation of ion transport systems. This is implicating them more frequently with roles in redox signaling or oxidative signaling. In particular, platelets involved in wound repair and blood homeostasis release ROS to recruit additional platelets to sites of injury. These also provide a link to the adaptive immune system via the recruitment of leukocytes.

Reactive oxygen species are implicated in cellular activity to a variety of inflammatory responses

including cardiovascular disease. They may also be involved in hearing impairment via cochlear damage induced by elevated sound levels, ototoxicity of drugs such as cisplatin, and in congenital deafness in both animals and humans. Redox signaling is also implicated in mediation of apoptosis or programmed cell death and ischaemic injury. Specific examples include stroke and heart attack.

Generally, harmful effects of reactive oxygen species on the cell are most often:

1. damage of DNA
2. oxidations of polydesaturated fatty acids in lipids
3. oxidations of amino acids in proteins
4. Oxidatively inactivate specific enzymes by oxidation of co-factors

## Oxidative damage

In aerobic organisms the energy needed to fuel biological functions is produced in the mitochondria via the electron transport chain. In addition to energy, reactive oxygen species (ROS) are produced which have the potential to cause cellular damage. ROS can damage DNA, RNA, and proteins which theoretically contributes to the physiology of ageing.

ROS are produced as a normal product of cellular metabolism. In particular, one major contributor to oxidative damage is hydrogen peroxide ($H_2O_2$) which is converted from superoxide that leaks from the mitochondria. Within the cell there is catalase and superoxide dismutase that help to minimize the damaging effects of hydrogen peroxide by converting it into oxygen and water, benign molecules, however this conversion is not 100% efficient, and residual peroxides persist in the cell. While ROS are produced as a product of normal cellular functioning, excessive amounts can cause deleterious effects.[1]

Memory capabilities decline with age, evident in human degenerative diseases such as Alzheimer's disease which is accompanied by an accumulation of oxidative damage. Current studies demonstrate that the accumulation of ROS can decrease an organism's fitness because oxidative damage is a contributor to senescence. In particular, the accumulation of oxidative damage may lead to cognitive dysfunction as demonstrated in a study where old rats were given mitochondrial metabolites and then given cognitive tests, results showed that the rats performed better after receiving the metabolites, suggesting that the metabolites reduced oxidative damage and improved mitochondrial function.[2] Accumulating oxidative damage can then affect the efficiency of mitochondria and further increase the rate of ROS production.[3]

The accumulation of oxidative damage and its implications for aging depends on the particular tissue type where the damage is occurring. Additional experimental results suggest that oxidative damage is responsible for age related decline in brain functioning. Older gerbils were found to have higher levels of oxidized protein in comparison to younger gerbils. When old and young mice were treated with a spin trapping compound the level of oxidized proteins decreased in older gerbils but did not have an effect on younger gerbils. Additionally, older gerbils performed cognitive tasks better during treatment but ceased functional capacity when treatment was discontinued causing oxidized protein levels to increase. This lead researchers to conclude that oxidation of cellular proteins is potentially important for brain function (Carney, 1991).

# Internal production

Free radicals are also produced inside (and also released towards the cytosol [4][5]) organelles, such as the mitochondrion. Mitochondria convert energy for the cell into a usable form, adenosine triphosphate (ATP). The process in which ATP is produced, called oxidative phosphorylation, involves the transport of protons (hydrogen ions) across the inner mitochondrial membrane by means of the electron transport chain. In the electron transport chain, electrons are passed through a series of proteins via oxidation-reduction reactions, with each acceptor protein along the chain having a greater reduction potential than the last. The last destination for an electron along this chain is an oxygen molecule. Normally the oxygen is reduced to produce water; however, in about 0.1-2% of electrons passing through the chain(this number derives from studies in isolated mitochondria, though the exact rate in live organisms is yet to be fully agreed upon), oxygen is instead prematurely and incompletely reduced to give the superoxide radical, $\cdot O_2^-$, most well documented for Complex I and Complex III. Superoxide is not particularly reactive in and of itself, but can inactivate specific enzymes or initiate lipid peroxidation in its $HO_2\cdot$ form. If too much damage is caused to its mitochondria, a cell undergoes apoptosis or programmed cell death.

Bcl-2 proteins are layered on the surface of the mitochondria, detect damage, and activate a class of proteins called Bax, which punch holes in the mitochondrial membrane, causing cytochrome C to leak out. This cytochrome C binds to Apaf-1, or apoptotic protease activating factor-1, which is free-floating in the cell's cytoplasm. Using energy from the ATPs in the mitochondrion, the Apaf-1 and cytochrome C bind together to form apoptosomes. The apoptosomes binds to and activates caspase-9, another free-floating protein. The caspase-9 then cleaves the proteins of the mitochondrial membrane, causing it to break down and start a chain reaction of protein denaturation and eventually phagocytosis of the cell.

# Cause of aging

According to the Free-radical theory, oxidative damage initiated by reactive oxygen species is a major contributor to the functional decline that is characteristic of aging. While studies in invertebrate models indicate that animals genetically engineered to lack specific antioxidant enzymes (such as SOD) generally show a shortened lifespan (as one would expect from the theory), the converse, increasing the levels of antioxidant enzymes, has yielded inconsistent effects on lifespan (though some well-performed studies in Drosophila do show that lifespan can be increased by the overexpression of MnSOD or glutathione biosynthesizing enzymes). In mice, the story is somewhat similar. Deleting antioxidant enzymes generally yields shorter lifespan, though overexpression studies have not (with some recent exceptions), consistently extended lifespan [6].

# Superoxide dismutase

Superoxide dismutase (SOD) is present in two places naturally in the cell. SOD that is present in the mitochondria contains manganese (MnSod). This SOD is transcribed in the nucleus and has a mitochondrial targeting sequence, thereby localizing it to the mitochondrial matrix. SOD that is present in the cytoplasm of the cell contains copper and zinc (CuZnSod). The genes that control the formation of

SOD are located on chromosomes 21, 6, and 4. When superoxide dismutase comes in contact with superoxide, it catalyzes the formation of hydrogen peroxide. Hydrogen peroxide is dangerous in the cell because it can easily be converted into hydroxyl radicals, one of the most destructive free radicals, by interacting with $Fe^{2+}$ (this process is known as a Fenton reaction).

$2\ O_2^-\ (aq) \rightarrow H_2O_2\ (aq)$ *(superoxide dismutase)*

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$ *(spontaneous reaction)*

Catalase, which is concentrated in peroxisomes located next to mitochondria, reacts with the hydrogen peroxide to catalyze the formation of water and oxygen. Glutathione peroxidase reduces hydrogen peroxide by transferring the energy of the reactive peroxides to a very small sulfur containing protein called glutathione. The selenium contained in these enzymes acts as the reactive center, carrying reactive electrons from the peroxide to the glutathione. Peroxiredoxins also degrade $H_2O_2$, within the mitochondria, cytosol and nucleus.

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$ *(catalase)*

$2GSH + H_2O_2 \rightarrow GS–SG + 2H_2O$ *(glutathione peroxidase)*

# See also

- Antioxidant
- Melanin
- Mitohormesis
- Oxidative stress
- Oxygen toxicity
- Polyphenol antioxidants
- Pro-oxidant
- Redox signaling
- Evolution of dietary antioxidants
- Iodide

# Footnotes

1. **^** Patel RP, T Cornwell, and VM Darley-USMAR: The biochemistry of nitric oxide and peroxynitrite: implications for mitochondrial function. In: Understanding the process of ageing: The roles of mitochondria, free radicals, and antioxidants. (1999) Eds: E Cadenas and L Packer, Marcel Dekker, Inc. NY. Basel 39-40
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6. **^** 1 Muller, F. L., Lustgarten, M. S., Jang, Y., Richardson, A. and Van Remmen, H. (2007) Trends in oxidative aging theories. Free Radic. Biol. Med. 43, 477-503

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