

**MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION, REACTIVE OXYGEN
SPECIES, AND CELLULAR ENERGY HOMEOSTASIS: MOLECULAR
MECHANISMS AND BIOLOGICAL SIGNIFICANCE**

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Mitochondria play a central role in cellular ATP production, redox balance maintenance, calcium signaling regulation, and stress response management. The mitochondrial electron transport chain and oxidative phosphorylation constitute the primary molecular basis of these processes. Electrons carried by NADH₂ and FADH₂ enter the respiratory chain, and their transfer to oxygen drives the formation of a proton electrochemical gradient. This gradient drives ATP synthesis via ATP synthase.

However, the flow of electrons through the mitochondrial respiratory chain is also associated with the generation of reactive oxygen species (ROS). At low levels, ROS can act as signaling molecules, whereas high levels lead to oxidative stress and cellular damage.

This review examines the molecular mechanisms of mitochondrial biological oxidation, the electron transport chain, oxidative phosphorylation, ROS generation, and reverse electron transport. Additionally, the biological and clinical significance of mitochondrial oxidation along with current research directions in this field are discussed.

Introduction

Mitochondria are one of the main organelles that provide the energetic and metabolic activity of eukaryotic cells. One of their main functions is ATP synthesis through oxidative phosphorylation. In addition, mitochondria also participate in redox signaling, calcium homeostasis, apoptosis, and cellular stress response reactions.

The mitochondrial electron transport chain consists of complexes I, II, III, and IV located in the inner mitochondrial membrane. Electrons are transferred from NADH_2 and FADH_2 to oxygen. The energy released in this process is used to pump protons into the intermembrane space, and a proton electrochemical gradient is formed.

This gradient is used for ATP synthesis via ATP synthase. In addition, incomplete transfer of electrons can lead to the formation of reactive oxygen species.

Therefore, it is important to view mitochondrial respiration not only as an ATP-producing process, but as a system that integrates energy metabolism, redox signaling, and cellular homeostasis.

Molecular Mechanisms of Biological Oxidation

Biological oxidation is a set of reactions involving the release of electrons from organic substrates and their ultimate transfer to oxygen.

The metabolism of glucose, fatty acids, and amino acids produces NADH_2 and FADH_2 . They deliver high-energy electrons to the mitochondrial electron transport chain.

The electrons of NADH_2 enter the electron chain mainly through complex I, while the electrons associated with FADH_2 enter the chain via complex II.

Complex I — “ NADH_2 - CoQ Reductase”

Contains FMN and NAD^+ as a free coenzyme. It has iron-sulfur centers (Fe-S) for electron transport. It takes hydrogen from the NADH_2 formed in mitochondrial reactions, first transfers it to FMN to form FMNH_2 , and then transfers it to CoQ to form CoQH_2 (dihydroubiquinone).

Complex II — “Succinate dehydrogenase”.

Contains FAD^+ . It takes hydrogen from the succinate formed in mitochondrial reactions and converts it to fumarate, while converting its own FAD to FADH_2 . This complex also transfers the “hydrogen” to CoQ, and CoQH_2 is formed.

Complex III — “ CoQH_2 -reductase” .

Contains cytochromes b and c_1 . It takes electrons from CoQH_2 and releases protons into the intermembrane space. It transfers the electrons to cytochrome C, the intermediate carrier.

Complex IV — “Cytochrome oxidase”.

Contains cytochromes a_1 and a_3 . It takes electrons from cytochrome C and transfers them to O_2 , and O_2 becomes activated. Then it combines with H (protons) to form H_2O .

Mitochondrial Oxidative Phosphorylation and Energy Homeostasis



As a result of electron transport chain activity, a proton gradient is formed across the inner mitochondrial membrane. This gradient is called the proton motive force.

It is mainly defined by:

- membrane potential;
 - pH gradient
- together.

The return of protons from the intermembrane space to the matrix occurs through ATP synthase. ATP synthase uses the energy of the proton flow to synthesize ATP from ADP and inorganic phosphate.

Thus:

Substrate oxidation $\rightarrow$ NADH/FADH₂ $\rightarrow$ electron transport $\rightarrow$ proton gradient $\rightarrow$ ATP synthesis this sequence forms the main energy system of the cell.

Reactive Oxygen Species and Mitochondrial Redox Signaling

During mitochondrial electron transport, partial transfer of electrons to oxygen can lead to the formation of the superoxide anion radical.

Complexes I and III are important sources of ROS formation. However, mitochondrial ROS are not limited to these complexes. Other enzymes involved in mitochondrial metabolism may also contribute to ROS formation.

Superoxide is converted to hydrogen peroxide by the action of superoxide dismutase.

ROS are not always harmful. At low and controlled levels, they can participate in cellular signaling.

ROS participate in:

- metabolic adaptation;
- stress response;
- gene expression;
- mitochondrial biogenesis;
- cell survival

and similar processes.

Oxidative stress can occur when ROS formation exceeds the capacity of antioxidant defenses.

In this case:

- oxidation of proteins;
- peroxidation of lipids;
- damage to mitochondrial DNA;
- impairment of membrane function;
- altered enzyme activity

may be observed.

Mitochondrial antioxidant systems include SOD₂/MnSOD, glutathione, thioredoxin, and peroxiredoxin systems.

Reverse Electron Transport and Mitochondrial ROS

Reverse electron transport (RET) is an important mechanism in mitochondrial redox biology.

Under certain metabolic conditions, especially when succinate levels rise and the mitochondrial membrane potential is high, electrons can move in the direction opposite to the usual one.

Under RET conditions, ROS formation at complex I can increase significantly.

This mechanism may be important in processes associated with ischemia-reperfusion, inflammation, metabolic stress, and mitochondrial dysfunction.

Biological and Clinical Significance of Mitochondrial Oxidation

Mitochondrial energetic and redox disturbances are associated with various pathological conditions.

Among them:

- metabolic diseases;
- cardiovascular diseases;
- neurodegenerative diseases;
- inherited mitochondrial diseases;
- aging-related changes

are included.

However, mitochondrial dysfunction is not always the sole cause of disease. In many cases, it interacts with metabolic changes, inflammation, and signaling processes.

Therefore, when studying the mitochondrion as a therapeutic target, it is important to take into account the cell type, disease stage, metabolic state, and ROS level.

Modern Research Directions and Future Prospects

In current research, the difference between physiological and pathological ROS levels, mitochondrial supercomplexes, reverse electron transport, and the role of membrane potential in signaling are among the important directions.

The effect of ROS depends not only on their amount but also on the site of formation, duration, and cellular context.

In the future, mitochondrial therapeutic strategies may be aimed not only at eliminating ROS, but also at normalizing redox signaling, controlling electron flow, and optimizing mitochondrial function.

Conclusion



The mitochondrial electron transport chain and oxidative phosphorylation are central mechanisms ensuring the energetic homeostasis of the cell. At the same time, these processes are closely linked to mitochondrial ROS formation and redox signaling.

Under physiological conditions, ROS participate in the adaptation and signaling mechanisms of the cell. When the amount of ROS is excessive, however, oxidative stress can lead to mitochondrial and cellular damage.

An in-depth study of the mechanisms of reverse electron transport, mitochondrial membrane potential, and the electron transport chain helps to better understand mitochondrial physiology and the pathogenesis of disease.

Overall, viewing the mitochondrion as a dynamic system that integrates ATP production, redox signaling, and cellular energy homeostasis is one of the important concepts of modern mitochondrial biology.

REFERENCES

1. Nolfi-Donagan D, Braganza A, Shiva S. Mitochondrial electron transport chain: oxidative phosphorylation, oxidant production, and methods of measurement. *Redox Biology*. 2020;37:101674.
2. Palma FR, Gantner BN, Sakiyama MJ, et al. ROS production by mitochondria: function or dysfunction? *Oncogene*. 2024;43(5):295–303.
3. Ježek P, Dlasková A, Engstová H, et al. Mitochondrial Physiology of Cellular Redox Regulations. *Physiological Research*. 2024;73(S1):S217–S242.
4. Müller-Eigner A, Wojtovich AP. Mitochondrial metabolism and redox signaling. *Redox Biology*. 2025;79:103448.
5. Selim NA, Wojtovich AP. Mitochondrial membrane potential and compartmentalized signaling: Calcium, ROS, and beyond. *Redox Biology*. 2025;86:103859.
6. Mitochondrial Reverse Electron Transport: Mechanisms, Pathophysiological Roles, and Therapeutic Potential. *Biology*. 2025;14(9):1140.