Intracellular redox homeostasis

Intracellular redox homeostasis refers to the delicate balance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) within the cell, maintained in equilibrium with antioxidants. This balance is critical for various cellular processes, including metabolism, signaling, and protection against oxidative damage.

Key Components

Reactive Oxygen Species (ROS):

Produced during normal cellular metabolism, especially in the mitochondria. Common ROS include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH\cdot$).

Antioxidant Systems:

Enzymatic Antioxidants:

Superoxide dismutase (SOD): Converts superoxide into H_2O_2.

Catalase: Decomposes H_2O_2 into water and oxygen.

Glutathione peroxidase (GPx): Reduces H_2O_2 and lipid peroxides using reduced glutathione (GSH).

Non-enzymatic Antioxidants:

Glutathione (GSH): A tripeptide that directly scavenges ROS and regenerates other antioxidants.

Vitamin C and E: Protect cellular membranes and aqueous compartments.

Oxidative Stress:

Occurs when ROS production exceeds the cell's antioxidant capacity.

Can lead to damage of DNA, proteins, and lipids, contributing to aging, cancer, and neurodegenerative diseases.

Redox Signaling:

Low levels of ROS act as signaling molecules regulating cellular processes like apoptosis, cell proliferation, and immune responses.

Key pathways involve redox-sensitive transcription factors, such as:

NF-κB

Nrf2 (Nuclear factor erythroid 2–related factor 2)

Redox Buffers:

Glutathione (GSH/GSSG system): Maintains the reduced environment within cells.

Thioredoxin system: Regulates protein disulfide bonds and protects against oxidative stress.

Mechanisms Maintaining Redox Homeostasis

ROS Generation and Scavenging:

Mitochondrial electron transport chain (ETC) is a major source of ROS.

NADPH oxidases (NOX enzymes) contribute to ROS production in specific signaling contexts.

Antioxidant enzymes counterbalance ROS production.

Glutathione Pathway:

GSH is synthesized from cysteine, glutamate, and glycine.

The GSH/GSSG ratio is a key indicator of redox status.

Glutathione reductase regenerates GSH from GSSG using NADPH.

Adaptation to Stress:

Upregulation of antioxidant genes via transcription factors like Nrf2 in response to oxidative stress.

Activation of repair mechanisms for damaged macromolecules.

Implications of Disrupted Redox Homeostasis

Pathological States:

Chronic oxidative stress contributes to diseases like:

Cancer: Due to mutations and genomic instability.

Neurodegenerative diseases: From damage to neurons (e.g., Parkinson's, Alzheimer's).

Cardiovascular diseases: Through lipid peroxidation and endothelial dysfunction.

Therapeutic Strategies:

Antioxidants as supplements or drugs to restore redox balance.

Targeting redox-sensitive pathways for diseases involving oxidative stress.

Redox in Therapy Resistance:

In cancer, altered redox homeostasis can lead to resistance against chemotherapy and radiotherapy.

Conclusion

Maintaining intracellular redox homeostasis is essential for cellular function and survival. Understanding the balance between ROS and antioxidant systems helps elucidate the mechanisms underlying various diseases and the development of therapeutic strategies targeting oxidative stress.