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CELL BIOPHYSICS

Free Radicals and Signal Transduction in Cells

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Abstract—This review provides an overview of molecular mechanisms of intracellular signal transduction involving free radicals. The structure and functions of enzymes that can produce superoxide anion-radical and hydrogen peroxide are considered in detail. The mechanisms of regulation of cell properties with the participation of specialized redox chains formed by a group of proteins interacting through electron transport processes are discussed. Genetically mediated mechanisms of regulation of cellular redox homeostasis are analyzed. Particular attention is paid to the issue concerning quantitative characterization of the network of interactions of oxidizing and reducing agents, which determines the species-specific and individual characteristics of redox homeostasis and the stress response of cells.

Keywords: free radicals, reactive oxygen species, redox regulation, oxidative stress, reductive stress, transcription factor Nrf2

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Intense research of free-radical processes in living systems began in the middle of the 20th century, when it was found that oxidant formation in the body was associated with the development of chronic and degenerative diseases. In 1954, R. Gerschman et al. suggested that the known toxic effects of oxygen were due to the formation of its reactive radical intermediates [1]. In the same year, B.N. Tarusov hypothesized that the leading role in the development of radiation-induced cell damage belonged to free-radical reactions of lipid peroxidation [2]. Further works by N.M. Emanuel and numerous other authors helped elucidate the mechanisms underlying free radical oxidation of lipids, as well as antioxidant defense and repair processes in cells [3, 4]. Subsequently, it was found that free radical products of oxygen metabolism, or reactive oxygen species (ROS), as they were later called, are formed not only after irradiation, but are also produced metabolically, causing damage to cellular structures in pathological states of the organism [5, 6].

Abbreviations: ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; Nox, NADPH oxidase; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; NADH, nicotinamide adenine dinucleotide; SOD, superoxide dismutase; ARE, antioxidant respons(iv)e element; Duox, Dual oxidase; Nrf2, NF-E2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; Klf9, Kruppel-like factor 9; Prx6, peroxiredoxin 6.

In 1956, D. Harman proposed the free-radical theory of aging, according to which the weakening of physiological functions with age occurs as the organism, including its genetic material, accumulates various damages induced by free radicals formed during cell respiration [7]. This theory became the basis of aging biology, a whole research field that investigates the role of ROS in aging processes and the development of age-related pathology, as well as the ways to regulate aging processes using antioxidant agents [8, 9]. This research has given rise to the notion of "free radical-induced conditions" and significantly expanded the list of diseases and pathological processes under this umbrella term.

The discovery of the regulatory role of nitrogen monoxide ($^{\cdot}$NO), which was previously considered a cytotoxic compound, initiated research into the physiological functions of free-radical processes. The first evidence that $^{\cdot}$NO can be produced during metabolic processes in living systems, leading to the formation of iron dinitrosyl complexes, was obtained by A.F. Vanin [10, 11]. Further study of the regulatory properties of this free radical led to the discovery of its physiological function consisting in the regulation of vascular tone, for which R.F. Furchgott, L. Ignarro, and F. Murad were awarded the Nobel Prize in Physiology and Medicine in 1998 [12].