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INVITED EDITORIAL

Antioxidants as future medicines: redox homeostasis concept

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Antioxidants are agents that counteract harmful reactive oxygen species (ROS) molecules. Reactive oxygen species are widely recognized as playing a role in various pathological processes in the human body, including aging, metabolic disease, cardiovascular disease, neurodegenerative disease, inflammation, and even cancer. In these conditions, it has been proven that there is a change in the redox state, where the endogenous antioxidant defense cannot eliminate ROS production, and a condition of oxidative stress occurs.[1–3] This editorial highlights the possible role of antioxidant therapy as an effective therapeutic strategy from the perspective of the physiological redox homeostasis concept.

The concept of homeostasis is the main pillar of human physiology. Homeostasis is defined as the system where various variables are regulated by the body such that internal conditions remain stable and relatively constant. The concept of homeostasis was first conceived by Claude Bernard using the term milieu intérieur to describe the physiologic control processes of the body. Subsequently the term homeostasis was first used by Walter Bradford Cannon in his book "The Wisdom of the Body" in accordance with Bernard's concept.[4,5] Unlike the literal meaning of the term, homeostasis is a dynamic process that works at the cellular, tissue, and organ levels and at the level of the organisms as a whole, as an important element of the health status of an individual. Therefore maintaining homeostasis is a relevant universal concept in the prevention and treatment of past, present, and future diseases.

In the human body a series of continuous catabolic and anabolic reactions maintain the body's physiological functions. This process involves the oxidation and reduction of substrates, producing reactive oxygen species and subsequently causing the body to maintain the redox balance. The balance between reducing and oxidizing reactions, also known as redox homeostasis, is maintained by comparatively recent molecular mechanisms, allowing not only life to continue in an oxidizing environment but also contributing to biodiversity.[6]

Apart from the internal metabolic processes, oxidative reactions also occur in nature as a result of photosynthesis that accumulates atmospheric oxygen, which mainly binds to other elements, producing oxides. The evolutionary recent molecular mechanisms are directed to cellular biological redox approaches, namely the regulation of electron donors and acceptors, such that redox adaptation and equilibrium is achieved in the body.[7]

Redox interaction is closely associated with the regulation of various biological processes, including the cell cycle (cell development, differentiation, and death), immune responses, metabolism, degenerative processes, circadian rhythms etc. In healthy humans, reactive oxygen species (ROS) are messengers that are regulated and have a highly specific action, that involves exogenous factors.[2] The term ROS collectively

refers to oxygen-containing reactive species, including superoxide anions, hydrogen peroxides, hydroxyl radicals, singlet molecular oxygen, peroxyl radicals, alkoxyl radicals, lipid hydroperoxides, peroxynitrites, hypochlorous acid, ozone etc.[8]

Failure of the body to adapt and regulate ROS can damage biomolecules of the body, including proteins, lipids, and nucleic acids, leading to cellular damage and tissue injury. The reaction between ROS and these biomolecules also produces secondary reactive products called electrophiles. The term electrophiles refers to electron-deficient chemical species that react covalently by accepting donor electron pairs from electron-rich biomolecular compounds. [9] Currently, insufficient human body responses to oxidative stress are associated with various diseases, including inflammatory, metabolic, degenerative, autoimmune, and malignant diseases. The biomolecular damage caused by oxidative stress may result in cell death through necrosis, apoptosis, aging, and autophagy.[10]

The human body possesses defense systems in the form of antioxidants to protect its biomolecular components against ROS and other reactive species, through enzymatic as well as non-enzymatic processes. An antioxidant is defined as any substance that can prevent, reduce, or repair ROS-induced damage in the biomolecules of the body. Antioxidants in the human body are grouped into endogenous and exogenous. Endogenous antioxidants can be enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), or non-enzymatic such as glutathione, L-arginine, lipoic acid, etc. Exogenous antioxidants cannot be produced by the human body, for example vitamin E, vitamin C, phytochemicals (flavonoids, polyphenols, isoflavones), as well as trace elements (Se, Cu, Zn, Mn).[11] The antioxidant components act through several chemical mechanisms: hydrogen atom transfer (HAT), single electron transfer (SET), and the capacity of forming transitional metal chelates.[12] The redox environment in the cellular compartment is assumed to be proportional to the reducing potential of all available redox pairs. Therefore, the frequently applied estimation procedure is through the GSSG/GSH, NAD/NADH, or NADP/NADPH ratios.[6]

The role of antioxidants as part of future medicine is being increasingly explored. In general, the reason for using antioxidants is based on the application of three strategies: (i) removing radical species, (ii) preventing inflammation, and (iii) accelerating tissue repair.[10] Several studies have been developed to determine the regulatory mechanisms of antioxidant enzymes, particularly their implications in disease and their role as potential inducers for therapeutic purposes. The development of several antioxidant enzyme mimics is one of the therapeutic methods currently employed, such as the use of SOD mimics, SOD-catalase mimics, and glutathione peroxidase mimics. Currently there is an ongoing phase II clinical trial for ebselen, a glutathione peroxidase mimic, for the treatment of Menière's disease. Menière's disease is a condition when fluid buildup in the chamber of the inner ear affects balance and hearing. One SOD mimic is also under test in a phase I clinical trial for the treatment of squamous cell carcinoma. Another study is testing sulforaphane, an activator of the NRF2 transcription factor, in a phase II trial for the treatment of chronic obstructive pulmonary disease.[13]

The translational medicine concept leads to a better understanding of the process of disease initiation and development. New approaches should be developed to address emerging problems, including homeostatic redox imbalance as a component of disease progression. Precision medicine as the future direction of "next medicine" should also include redox precision as part of its make-up.

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