Introduction of COST B35 Homeostasis, Stress & Aging

COST B35 Takdim Homeostaz, Stres ve Yaşlanma

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ABSTRACT Homeostasis is the property of a living organism to regulate its internal environment tending to maintain a stable, constant condition denoted also as a steady state. Opposite to that stress implies misbalance of dynamic equilibrium which often causes acute or chronic, pronounced or latent damage to the organism. On molecular level, undesirable stress is often manifested as excess in free radical production, known as oxidative stress. However, stress does not necessarily imply pathology. So, if oxidative stress and stress in general are not only pathological but also physiological processes, we should raise the question can (oxidative) stress also expand the quality of life and the life endurance? If so, the term oxidative homeostasis should reflect positive aspects of oxidative stress.

Key Words: Oxidative stress, homeostasis, lipid peroxidation, aging

ÖZET Homeostaz, canlı bir organizmanın aynı zamanda dengeli hal olarak bilinen stabil, sabit durumu sürdürme eğiliminde olan iç ortamını düzenleme özelliğidir. Bunun tersi durum ise organizmada genelde akut ya da kronik, bariz ya da gizli hasara neden olan dinamik ekilibriyum dengesizliğini belirtir. Moleküler seviyede, istenmeyen stres genelde serbest radikal üretiminde aşırılık olarak kendisini gösterir, bu duruma da oksidatif stres adı verilir. Ancak, stres illa da patolojiyi ifade etmez. Bu nedenle, oksidatif stres ve genel olarak stres yalnızca patolojik değil aynı zamanda fizyolojik süreçlerse, (oksidatif) stres ayı zamanda yaşam kalitesini ve yaşam direncini arttırabilir mi şeklinde bir soru sormalıyız. Eğer doğruysa, oksidatif homeostaz oksidatif stresin olumlu yanlarını yansıtmalıdır.

Anahtar Kelimeler: Oksidatif stres, homeostaz, lipid peroksidasyon, yaşlanma

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OXIDATIVE HOMEOSTASIS AND AGING

Homeostasis is the property of a living organism to regulate its internal environment tending to maintain a stable, constant condition denoted also as a steady state. When homeostasis is disrupted, stress occurs. Aging is an extremely complex, multifactorial process and represents the gradual deterioration in function that occurs after maturity and leads to disability and death. Since stress is inevitable part of aging, this definition of aging is extended and identifies aging with the inability of the organism to respond to stress and to maintain homeostatic regulation when given a challenge, thereby decreasing the capacity of organism to survive detrimental changes occurring with time.[1] Oxidative stress arises from a

significant increase in concentrations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) to the levels that are toxic to biomolecules, including DNA, proteins and lipids. Therefore, only excessive ROS or RNS production and/or decrease in detoxification mechanisms leads to oxidative stress and lipid peroxidation and plays important role in aging and pathology of different diseases (cardiovascular and neurodegenerative diseases, malignant tumors, osteoporosis, diabetes and others).[2,3]

Lipid peroxidation is an autocatalytic and degenerative process affecting cell membranes and other lipid-containing structures and is therefore associated with numerous pathological implications, some of which are previously mentioned.[4] It is initiated by ROS generated under conditions of oxidative stress and ends in the formation of reactive aldehydes which are more stable than ROS, so they can diffuse from their site of origin and affect targets distant from the initial free radical attack, because of which they are also known as second messangers of free radicals.[5] The end products of lipid peroxidation, in particular aldehydes such as 4-hydroxynonenal (HNE) are the effectors which act in parallel with ROS to cause molecular damage, and ultimately aging. However, low, physiological levels of HNE might be considered also as growth stimulating.[7]

Oxidative homeostasis might therefore be result of a biological balance between toxic ROS and reactive aldehydes on one side and their physiological detoxification to benefical levels by antioxidant mechanisms. It is becoming increasingly clear that an optimal ROS level is essential for the cell survival. Too much ROS and their second messengers (HNE) may cause impaired physiological function due to either random cellular damage causing necrosis or activating programmed cell death (apoptosis), whereas lowered ROS and/or HNE may lead to proliferative response and enhance antioxidant defense capacity.[6] Hence, disruption of such homeostasis either by enhancing oxidative stress or modulating capacity of antioxidants could have important physiological consequences.

RADICALS AS SIGNALS THAT INCREASE ORGANISM LONGEVITY

While some argue that ROS and lipid peroxidation products are produced in rather uncontrolled reactions and therefore cannot be candidates for physiological signal transduction, others emphasize their presence in physiological state. Especially presence of HNE which is, similar to ROS, present under physiological conditions, even in the relatively stable forms of protein adducts and is thereby considered as biomarker.[7]

Moreover, HNE binds to cysteine residues which were shown to participate in physiological signal transduction.[8] On the other hand, HNE bound to cysteine could be detoxified through binding to glutathione5, in reaction catalyzed by glutathione-S-transferase (GST).[9] Reaction of specific GST regulates intracellular HNE concentration which has further impact of signal transduction by HNE.[10] This suggests involvement of HNE in physiological signaling resulting in homeostatic control of balance between ROS production and lipid peroxidation and antioxidant capacity of the cells.[11] Thus, radicals can be considered as signals and stimulators that increase cellular defense and organism longevity.

There is growing evidence that the continued presence of a small stimulus such as low concentrations of reactive oxygen species is in fact able to induce the expression of antioxidant enzymes and other defense mechanisms. The basis for this phenomenon may be encompassed by the concept of hormesis, which can be characterized as a particular dose–response relationship in which a low dose of a substance is stimulatory and a high dose is inhibitory.[12,13] In this context radicals seems to be beneficial, by acting as signal that enhances defense, rather than being deleterious as they are when cells are exposed to high levels of these radicals.[14] It is also becoming clear that animals and humans engaged in long-term heavy exercise are more resistant to oxidative stress, mainly due to the adaptation of their antioxidant defense systems.[15–18] The key to understanding exercise-induced hormetic response lies in the fact that mammalian cells are endowed with signaling pathways that are sensitive to intracellular redox environment and can be activated by oxidative stress. Those include NF-κB, heat-shock transcriptional factor 1 (HSF-1), and p53 pathways, as well as mitogen-activated protein kinase (MAPK) and PI(3)K/Akt that regulate the first three pathways through phosphorylation.[19] If hormetic response can indeed be beneficial to the oxidative-antioxidant homeostasis in the cell, then the suppression of the ROS source is expected to attenuate not only oxidative damage, but also the cellular ability to adapt under oxidative stress and consequently lead cell to senescence and death.[20] On the other hand, physiologically low levels of ROS and in particular HNE acting as signaling molecules could support the physiological growth and function (proliferation and differentiation) of some cells,

in particular those of mesenchymal origin such as bone and connective tissue.[21,22]

CONCLUSION

Oxidative stress does not necessarily have deleterious consequences that lead to pathology. There is more evidence every day about physiology of oxidative stress and its beneficial influence on organism. According to this point of view, on a timescale of years, modest but ongoing oxidative stress may play an important role in aging. Hence, if we could move boundaries of oxidative homeostasis to a higher level i.e. adopt organism to a higher amount of ROS and consequently enhance its antioxidative capacity, we would be able to prolong lifespan, while controlling oxidative homeostasis would help us to delay aging and attenuate the age associated disorders.

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