Hypercholesterolemia-Induced Oxidative Stress & Its Link to Age Related Diseases

Hiperkolesteroleminin İndüklediği Oksidatif Stres ve Yaşlanmayla İlişkili Hastalıklarla Bağlantısı

Betül ÇATALGÖL,[a]
Tilman GRUNE,[b]
Nesrin KARTAL ÖZER[a]

[a]Department of Biochemistry,
Faculty of Medicine,
Marmara University,
34668 Haydarpasa,
Istanbul, TURKEY
[b]Institute of Biological Chemistry and Nutrition,
University Hohenheim,
Stuttgart, GERMANY

Yazışma Adresi/*Correspondence:*
Nesrin KARTAL ÖZER
Department of Biochemistry,
Faculty of Medicine,
Marmara University,
34668 Haydarpasa, Istanbul, TURKEY
nkozer@marmara.edu.tr

ABSTRACT Free radicals and oxidants, cause potential danger for cellular molecules during the lifetime. Oxidative stress is the imbalance between free radical formation and antioxidant defense towards free radicals. Oxidative stress plays role in aging and pathogenesis of several diseases. In this process, age related diseases such as Alzheimer and atherosclerosis are crucial. Since protein mechanisms play important role in these diseases, protein oxidation parameters are preferred as indicator of oxidative stress. Protein aggregates as advanced protein oxidation products especially accumulate with aging are widespread used in studies and investigation of their production and determination of these products are thought to bring benefit for the prevention and treatment of the diseases.

Key Words: Oxidative stress, protein oxidation, aging, disease

ÖZET Serbest radikaller ve oksidanlar, yaşam boyunca hücre yapısındaki moleküller için hasar oluşturan yapılardır. Oksidatif stres, serbest radikal oluşumu ile antioksidan savunma arasındaki dengenin serbest radikaller yönünde değişmesi sonucu ortaya çıkmaktadır. Oksidatif stres, yaşlılık ve birçok hastalık patojenezinde rol oynamaktadır. Başlıca Alzheimer ve ateroskleroz gibi genellikle yaşlılık sonucu ortaya çıkan hastalıklar, bu açıdan önem taşımaktadır. Bu hastalıklarda çeşitli protein mekanizmalarının önemli rol oynaması nedeniyle oksidatif stresin göstergesi olarak protein oksidasyonu parametreleri öncelikli tercih edilmektedir. Özellikle yaşla birikimi artan, ileri protein oksidasyonu ürünü olan protein agregatları son zamanlarda araştırmalarda geniş yer tutmakta ve bu ürünlerin olusum mekanizmalarının aydınlatılması ve tayini ile hastalıkların önlenmesi ve tedavisinde klinikte fayda sağlanacağı düşünülmektedir.

Anahtar Kelimeler: Oksidatif stres, protein oksidasyonu, yaşlılık, hastalık

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Free radicals are atoms or molecules that contain unpaired electrons in their outer orbitals and this feature makes them to take place in oxidation reactions easily. Free radicals include several reactive species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Reactive species (RS), generated by diverse mechanisms, cause oxidative modifications of cellular components. The most prominent feature of RS is their high reactivity with biomolecules, causing their denaturation and inactivation. Several cellular systems exist to minimize oxidizing effects of RS are called antioxidant systems. Oxidative stress is referred to as an imbalance between the RS generation and the corresponding antioxidant defenses. Oxidative stress can produce injury by multiple pathways that

overlap and interact in complex ways.[1-3] Consequences of oxidative stress include increased proliferation, adaptation by up-regulating of defense systems, cell injury with increased burden of oxidatively damaged macromolecules like lipids, DNA, proteins and carbohydrates, or senescence and cell death.[4] Following the interactions of RS with cellular components as DNA, lipids and proteins, several products are known to be formed. The main investigated products are malondialdehyde (MDA) and 4-hydroxynonenal (HNE) for lipid peroxidation, 8-hydroxydeoxyguanosine for DNA oxidation and protein carbonyls for RS interaction with proteins.[5]

Protein oxidation is an important damage since proteins are the most abundant molecules in the organism and take place in the structures of receptors, antibodies, transport proteins and enzymes. For the determination of protein oxidation, several methods are used according to the side chain or backbone oxidation of the amino acids. Direct oxidation of lysine, arginine, proline and threonine residues may produce carbonyl derivatives. Since carbonyl groups are formed early and stabil, they are the most commonly used markers of protein oxidation.[6-8] As another late product, insoluble protein aggregates can be formed following cross-link formation, hydrophobic and electrostatic interactions.[9,10] The accumulation of the large aggregates are known to be often toxic to cells and poor substrates for proteases.[11] This aggregate accumulation has been reported for many experimental models especially age related diseases, as measured by several markers for protein oxidation.[9,12]

Protein damage may be caused by direct attack of reactive species or by secondary damage involving attack by products of lipid peroxidation, such as isoketals, MDA and HNE. Proteins can also be damaged by glycation/glyoxidation.[13]

The degradation of proteins is a physiological process required to maintain normal cellular function. Therefore, cells have developed highly regulated intracellular proteolytic systems responsible for the removal of such non-functional proteins before they start to aggregate. Mammalian cells contain several pathways for general protein breakdown, comprising membrane proteases, lysosomal cathepsins, calcium-activated calpains, caspases, mitochondrial proteases and the proteasomal system.[14-16] Besides all proteolytic systems, the major proteolytic system responsible for the removal of oxidized cytosolic and nuclear proteins is the proteasomal system.[17] The proteasome, known to be localized in the cytosol and in the nuclei of mammalian cells and furthermore attached to the endoplasmic reticulum and the cell membrane, is mainly composed of 20S core proteasome. This core complex degrades the oxidized proteins as a ubiquitin and ATP independent manner.[12,18,19]

Experimantal evidence from several studies shows that many of the alterations during aging and the progression of certain diseases are the result of the occurence of protein oxidation products and decrease in the degradation of oxidized proteins.[8]

OXIDATIVE STRESS IN AGING AND AGE RELATED DISEASES

Biological aging is a process, results in the loss of cellular functions that leads to development of related neurodegenerative and cardiovascular diseases and cancer. Therefore understanding the mechanisms underlying aging is necessary to develop therapeutic interventions against age related diseases.[20] The biomedical literature is full of claims that reactive species are involved in age related diseases. Denham Harman introduced the free radical theory of aging in 1956 and proposed that aging results from random deleterious damage to tissues by free radicals.[21]

Several in vivo and in vitro studies in this field revealed that oxidative stress biomarkers are increased and antioxidative defense is effected in several ways with age. Protein carbonyl content was found to increase in rat hepatocytes,16 human brain,[22] human red blood cells[23] and eye lens as age related.[24] The results from Gil et al. showed an increase in oxidative stress during aging process as measured by MDA, HNE, protein carbonyls and GSSG.[25]

Age pigments such as lipofuscin, ceroid or AGE-pigment like fluorophores are highlights those support the free radical theory of aging. Lipofuscin is thought to be conjugates of MDA and protein thiol groups deduced from the fluorescence character[26] and it was recently shown by several groups that the presence of such material influences the proteasomal activity.[27,28] These aggregated cross-linked material will be autophagozytosed resulting in a major accumulation of this material in lysosomes. The observed age-related accumulation of oxidized cross-linked material may be the result of both increased protein oxidation followed by aggregation and/or decline in protein breakdown and a malfunction of the proteasomal system.[29]

Amyloid formation also underlie a range of age-related disease that results when protein aggregates form

ordered filaments. Amyloid fibrils are resistant to proteolytic degradation and may act as nucleation sites for further aggregation.[20]

Alzheimer is an important age-related disease, most common form of adult onset dementia. The major alterations in this disease are senile plaques (SP) and neurofibrillary tangles (NFT) represent an accumulation of intraneuronal and extracellular filamentous protein aggregates. Major proteins in these formations are hyperphosphorylated tau in NFT and amyloid beta (Aβ) peptide, derived from amyloid precursor protein for SP.[30] These protein aggregate formations in Alzheimer disease (AD) cause the researchers to focus on the role of oxidative stress mainly protein oxidation in the process. The oxidative damage found in AD includes advanced glycation end products,[31,32] nitration,[33] lipid peroxidation adduction products,[34,35] carbonyl modified neurofilament protein and free carbonyls.[36,37] Oxidized proteins (protein carbonyls) were found to be increased in frontal pole and occipital pole in AD patients compared with controls.[36] Mishto et al. found a decrease in trypsin-like activity of proteasome emerged in hippocampus and cerebullum of AD patients.[38] In a study of AD subjects compared with control groups, there was a significant increase in mitochondrial DNA oxidation in parietal cortex.[39] Lovell et al. found elevated levels of free and protein-bound HNE in ventricular fluids of AD patients.40 Iron in a redox-active state, thought to play an important role in free radical production in AD, was shown to be increased in NFT as well as Aβ deposits.[41,42] Iron catalyzes the formation of hydroxyl radical from H_2O_2 and also the formation of advanced glycation end products. Aβ itself, has been directly implicated in ROS formation through peptidyl radicals.[43-45] Additionally, advanced glycation end products and Aβ, activate specific receptors, such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor, to increase reactive oxygen production.[46,47]

Hypercholesterolemia is a major risk for coronary artey diseases.[48,49] Hypercholesterolemia was reported to increase the levels of ROS through stimulation of polymorphonuclear leukocytes and ROS have been implicated in the development of hypercholesterolemic atherosclerosis.[50] In the development of atherosclerosis, ROS are produced by endothelial cells, smooth muscle cells and macrophages oxidize LDL in the subendothelial space, at the sites of endothelial damage, initiating events that culminate in the formation of a fibrous plaque. Rupture of fibrous plaque leads to thrombus formation and occlusion of the vessel.[51] Prasad et al. showed that cholesterol feeding of rabbits caused an increase in MDA levels and glutathione peroxidase activities and a decrease in superoxide dismutase activity in the myocardium.[52] High cholesterol is suggested to play role in the Alzheimer disease.[53] Patients with elevated cholesterol may have increased susceptibility to AD in addition to coronary artery disease and hypertension.[54] Cholesterol may initiate Aβ formation, that mentioned as a potent source of oxidative stress and irreversible protein aggregation. In a colloborative study of our groups, to show the possible role of high cholesterol in AD, rabbits were fed with high cholesterol and following the increase in the serum cholesterol levels, MDA levels were shown to be increased consistent with the previous results.[55-57] Additionally, slight increase in HNE-proteins, 3-nitrotyrosinated proteins and protein carbonyls was observed in hippocampus area of the rabbits.

CONCLUSION

Oxidative stress has been implicated as one of the earliest events in the pathogenesis of age-related diseases. Inhibitors of oxidative stress and glycation may be effective in reduction of the clinical manifestations of age related diseases. Additionally, micronutrients may be effective to protect the targets from oxidative damage in aging.

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