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The Importance of Thioredoxin (Trx) and Glutathione-Glutaredoxin (GSH/Grx) Systems in Terms of Aging

Tiyoredoksin (Trx) ve Glutatyon-Glutaredoksin (GSH/Grx) Sistemlerinin Yaşlanma Açısından Önemi

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ABSTRACT

Oxidative stress results from an imbalance between the production of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the body's ability to counteract their harmful effects. This imbalance can lead to cellular damage, contributing to the development of aging and various aging-related diseases, such as cardiovascular disease, neurodegenerative disorders, and cancer. Both endogenous and exogenous sources generate ROS, and enzymatic antioxidant systems including glutathione peroxidase (GPx), thioredoxin (Trx), and glutathione-glutaredoxin (GSH/Grx) systems as well as non-enzymatic antioxidants like GSH, urate, and coenzyme Q10 protect against them. Besides providing antioxidant defense, thiol-based cysteine modifications mediated by redox signals, including S-glutathionylation, S-nitrosylation, and S-sulfhydration, can be reversed by Trx and GSH/Grx systems. These systems may also alter cellular senescence and lifespan by interacting with different signaling pathways and transcription factors. The essential properties of these systems may increase interest in them soon. Understanding the complex interactions between the Trx and GSH/Grx systems might help develop novel anti-aging treatment strategies that increase cellular resilience and longevity. This review's objective is to investigate how thioredoxin (Trx) and glutathione-glutaredoxin (GSH/Grx) systems, which perform roles such redox homeostasis, antioxidant defense, thiol-based signal transduction, and cysteine modification, impact longevity and cellular senescence.

Keywords: Thioredoxin (Trx), glutathione (GSH), glutaredoxin (Grx), antioxidant system, aging.

ÖZ

Oksidatif stres, reaktif oksijen türleri (ROT) ile reaktif nitrojen türleri (RNT) gibi serbest radikallerin üretimi ile vücudun bunların zararlı etkilerine karşı koyma yeteneği arasındaki dengesizlikten kaynaklanır. Bu dengesizlik hücresel hasara yol açarak yaşlanma ve yaşlanmaya bağlı kardiyovasküler hastalıklar, nörodejeneratif bozukluklar ve kanser gibi çeşitli hastalıkların gelişimine katkıda bulunabilir. Endojen ve eksojen kaynaklı üretilen ROT'lara karşı vücutta glutatyon peroksidaz (GPx), tiyoredoksin (Trx) ve glutatyon-glutaredoksin (GSH/Grx) sistemleri gibi enzimatik ve redükte glutatyon (GSH), ürat, koenzim Q10 gibi non-enzimatik antioksidan sistemler savunmaya geçerler. Trx ve GSH/Grx sistemleri, antioksidan koruma haricinde, redoks sinyalleri tarafından aracılık edilen S-glutatyonilasyon, S-nitrozilasyon ve S-sülfhidrasyon gibi tiyol- bazlı sistein modifikasyonlarını tersine dönüştürebilirler. Yine farklı sinyal yolları ve transkripsiyon faktörleriyle etkileşim sonucunda hücresel yaşlanma ve yaşam süresi üzerinde değişiklikler yapabilirler. Böyle önemli özelliklere sahip olmaları yakın gelecekte bu sistemlere olan ilgiyi arttırabilir. Trx ve GSH/Grx sistemleri arasındaki karmaşık ilişkilerin anlaşılması, hücresel dayanıklılığı ve ömrü artıran yeni yaşlanma karşıtı tedavi stratejilerinin geliştirilmesine yardımcı olabilir. Bu derlemenin amacı, redoks homeostazı, antioksidan savunma, tiyol bazlı sinyal iletimi ve sistein modifikasyonu gibi rolleri üstlenen tiyoredoksin (Trx) ve glutatyon-glutaredoksin (GSH/Grx) sistemlerinin uzun ömür ve hücresel yaşlanma üzerindeki etkilerini incelemektir.

Anahtar Kelimeler: Tiyoredoksin (Trx), glutatyon (GSH), glutaredoksin (Grx), antioksidan sistem, yaşlanma.

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Introduction

The gradual reduction in fitness caused by detrimental changes that occur over time at the molecular and cellular levels is known as aging. Its characteristics include dysregulation of cellular activities, the accumulation of toxins and damaged materials, altered gene expression, and insufficient immune and stress responses.[1-3]

Free radicals are very reactive and unstable atoms or molecules that have one or more unpaired electrons. These ROS and RNS are produced from both internal and external sources.[4] Organic waste products of metabolic activities, immunological responses, enzymatic reactions, and mitochondrial electron transport create free radicals endogenously.[5] Exposure to environmental variables such as pollution, tobacco smoke, industrial chemicals, and ultraviolet (UV) radiation causes them to develop exogenously.[6]

Free radicals that include oxygen, or ROS, are essential for both physiological and pathological activities. The hydroxyl radical ($^{\bullet}OH$), peroxyl radical ($RO_2^{\bullet}$), and superoxide radical ($O_2^{\bullet-}$) are important types of ROS.[7] The mitochondria are the primary source of the superoxide radical, which is the precursor of the majority of ROS. Despite its low reactivity, it can dismutate to produce hydrogen peroxide (H_2O_2) either naturally or by the action of the enzyme superoxide dismutase (SOD).[8] Despite not being a radical, H_2O_2 can undergo Fenton or Haber-Weiss reactions to transform into the very reactive hydroxyl radical, especially when transition metals like iron or copper are present.[9] The most reactive ROS is the $^{\bullet}OH$, which may react with and harm practically every kind of biomolecule, including proteins, lipids, and nucleic acids. Its tiny size and absence of charge enable fast diffusion across cellular structures, which accounts for its high reactivity. In contrast to other ROS, it targets biomolecules directly, resulting in widespread cellular damage via mechanisms such as DNA strand breaks and lipid peroxidation.[8]

In contrast, RNS contains radicals that include nitrogen, such as nitrogen dioxide ($NO_2^{\bullet}$) and nitric oxide ($NO^{\bullet}$). Nitric oxide synthases (NOS) produce $NO^{\bullet}$, which is essential for immunological responses, neurotransmission, and vascular control.[8] Even while $NO^{\bullet}$ has many positive uses, too much of it can combine with superoxide to produce peroxynitrite ($ONOO^-$), a strong oxidizing and nitrating agent.[10] The capacity of $ONOO^-$ to nitrate and oxidize tyrosine residues may alter protein function and signaling.[11]

Numerous endogenous and exogenous activities produce ROS and RNS, and antioxidant defenses counteract their negative effects. Oxidative stress (OS) occurs when the formation of ROS and RNS exceeds antioxidant defenses.[12] The process of aging causes tissues and organs to lose their capabilities or perform less effectively. According to the OS hypothesis of aging, damage deposition produced by ROS and RNS is the source of these age-related functional impairments. Concurrently, OS is linked to a number of age-related conditions, such as frailty and sarcopenia, as well as cardiovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, neurodegenerative disorders, and cancer.[12]

OS-induced aging and associated disorders lead to soft tissue deterioration and disturbance of homeostasis.[13,14] Furthermore, OS causes abnormal signaling in the mitochondria, which modifies ROS signaling to change mitochondrial homeostasis and cause age-dependent cellular damage.[12,15] Cell aging results from the progressive formation of ROS, which also reduces the activity of scavenger enzymes and promotes a pro-oxidant state.[12] Depletion of mitochondrial catalase (CAT) and SOD has been shown to increase OS in mice, causing accelerated aging and age-related pathogenic diseases.[16]

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OS-induced increased mitochondrial dysfunction reduces cell life expectancy by impairing the efficiency of proteins, enzymes, and other macromolecules. It also speeds up peroxidative damage to membrane lipids, lowers fatty acid levels, and breaks down proteins.[12,16] ROS cause replication errors, disrupt the mitochondrial DNA repair mechanism, cause lipids and proteins to deteriorate, and reduce DNA's capacity to replicate.[12]

This study examines the thioredoxin (Trx) and glutathione-glutaredoxin (GSH/Grx) systems, which are involved in redox homeostasis, thiol-based signaling, cysteine modification, and cellular senescence. It also investigates how biochemical and genetic research into these systems affects lifetime.

Cellular Sources of Reactive Oxygen Species (ROS)

One of the main cell sources of ROS is mitochondrial respiration. Some of the electrons may leak out as they move between the complexes of the electron transport chain and combine with oxygen directly to generate superoxide.[17,18,19] Most electron leakage is believed to happen when electrons are transferred from Complex I or Complex II to Complex III via ubiquinone.[20]

ROS in the cell can also come from significant non-mitochondrial sources. To fight infections in the body, immune cells adopt a tactic known as the respiratory burst, which involves releasing ROS extracellularly or inside the phagolysosome.[21] Both the granule-localized MPO and the membrane-bound phagocyte NOX produce the ROS used in this assault.[22] MPO transforms H_2O_2 into hypochlorous acid (HOCl), whereas NOX uses the electrons given by NADPH to change molecular oxygen into a superoxide anion (O_2^-).[22] İmportantly, ROS generation for signal transmission in growth, survival, and death pathways is greatly affected by NOX homologs (NOX enzymes) produced in different cell types.[23]

In actuality, a large number of ROS-producing enzymes are vital to numerous physiological processes. Among them are the cytochrome P450 (CYP) family of enzymes, which generate ROS during the detoxification and excretion of xenobiotics[24]; xanthine oxidoreductase (XOR), which generates superoxide anions during the breakdown of purines to uric acid[25]; superoxide dismutase (SOD), which breaks down O_2^- to H_2O_2 and oxygen[26] and monoamine oxidase (MAO), which breaks down the neurotransmitter dopamine after signaling and generates hydrogen peroxide in neurons throughout the process.[27]

Lastly, the peroxisome's β-oxidation of fatty acids produces hydrogen peroxide, which can pass through the peroxisome's plasma membrane and enter the cytoplasm.[21] This is another source of ROS. Peroxisome-generated ROS are believed to help regulate the activity of nuclear factor-KB (NF-κB) and mammalian target of rapamycin complex 1 (mTORC1), two proteins crucial for cell survival in the face of stress, in addition to ROS produced by NOX.[28]

Harmful Effects of Oxidative Damage on the Human Body Due to Aging

According to a several of aging research studies, OS is one of the lead of cellular senescence, and high ROS levels can prevent cell division and hasten cellular senescence. Multiple mechanisms, including mitochondrial dysfunction, DNA damage, telomere length, lipid peroxidation, chronic inflammation, and oxidative protein modification, are mechanisms by which OS causes cellular senescence.[29]

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There are several avenues by which free radicals carry out their actions. Lipid peroxidation, in which polyunsaturated fatty acids (PUFA) in cell membranes are attacked by free radicals, is one of the main processes.[30] A lipid radical is created when a hydrogen atom is abstracted from the fatty acid at the start of this process. By removing hydrogen atoms from nearby fatty acids, the lipid peroxyl radical, which is created when the lipid radical combines with molecular oxygen, can continue the chain reaction and cause a cascade of lipid peroxidation.[30] Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), two extremely reactive byproducts of lipid peroxidation, can interact with proteins and DNA to disrupt their function.[31]

Another important process by which free radicals alter the side chains of amino acids, create cross-links between proteins, and break up peptide chains is protein oxidation. These changes can lead to cellular malfunction and mortality by altering cellular signaling, degrading structural proteins, and decreasing enzyme activity.[32,33] Certain amino acids, including cysteine and methionine, are especially prone to oxidation, which can interfere with the function of proteins and redox-sensitive signaling pathways.[8]

Base changes, strand breakage, and cross-linking are examples of DNA damage brought on by free radicals. The hydroxyl radical is particularly well-known for damaging DNA. It may add to the double bonds of DNA bases to create base alterations like 8-hydroxydeoxyguanosine (8-OHdG) or extract hydrogen atoms from the deoxyribose sugar backbone, causing strand breakage.[34] These alterations, in addition to causing mutations and genomic instability, can lead to carcinogenesis and other genetic illnesses if not properly repaired.[8]

Antioxidant Defense Systems Against Oxidative Damage

Enzymatic Antioxidant System

SOD initiates the detoxification of ROS by dismutating $O_2^{\bullet-}$ and transforming it into H_2O_2. Glutathione peroxidase (GPx) and CAT perform further detoxification of the H_2O_2 to produce H_2O and oxygen. When GPx lowers H_2O_2 to H_2O using two reduced glutathione (GSH) molecules as electron donors, it produces glutathione disulfide (GSSG). The GSH redox cycle occurs when GPx changes GSH to GSSG, which glutathione reductase (GR) may subsequently convert back to GSH utilizing NADPH.[35] The Trx and GSH/Grx systems are other significant antioxidant enzymes that provide protection by repairing damage to thiol-containing proteins exposed to oxidants.[36] The conversion of $NADP^+$ into NADPH is facilitated by several enzymatic antioxidant systems in the cell, such as glucose-6-phosphate dehydrogenase (G-6PD), 6-phosphogluconate dehydrogenase (6-PGD), isocitrate dehydrogenase (IDH) and NADP-malate dehydrogenase (NADP-MDH).[37]

Nonenzymatic Antioxidant System

Vitamins E and C, β-carotene, ubiquinone (coenzyme Q10), lipoic acid, urate, and reduced glutathione (GSH) are examples of nonenzymatic antioxidants. The most significant natural antioxidant is GSH, the primary low-molecular-weight thiol-containing peptide found in the majority of living cells.[38] Given that GSH is a cosubstrate of GPx and facilitates the reduction of peroxides and the generation of GSSG, it scavenges electrophilic and oxidant species directly or through enzymatic catalysis.[39] The other low-molecular-mass antioxidants may serve as vital cofactors for different enzymatic antioxidant systems or directly contribute to free radical scavenging.[40]

The thioredoxin (Trx) and glutathione-glutaredoxin (GSH/Grx) systems

The Trx system includes Trx, thioredoxin reductase (TrxR), and nicotinamide adenine dinucleotide phosphate (NADPH), whereas the GSH/Grx system includes GSH, GR, Grx, and NADPH.[41] These

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systems let target proteins return to their reduced state by catalyzing the transfer of electrons to their disulfide bonds.[42] These are accomplished by a sequence of events, starting with the oxidation of the Grx or Trx active site, which is made up of cysteine residues, and the reduction of the target residue.[43] Next, each enzyme must be reduced back to its active form: Trx is reduced by an enzyme known as TrxR, whereas Grx is reduced by two GSH molecules, which are oxidized to GSSG.[43] After that, TrxR uses electrons from NADPH molecules to return its own thiol-containing active site to its active state, and the GR uses electrons from NADPH to reduce GSSG back to two GSH molecules (Figure 1).[42]

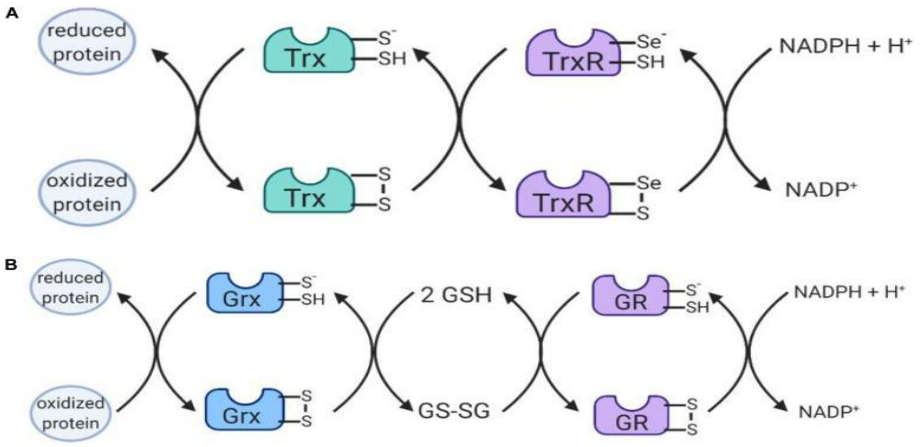

Figure 1. Mechanisms of action of antioxidant redox systems A) Trx system, B) GSH/Grx system[36]

Functions of the thioredoxin (Trx) and glutathione-glutaredoxin (GSH/Grx) systems affecting aging

In antioxidant protection

The GSH/Grx system has a role in removing lipid hydroperoxides, $ONOO^-$, and H_2O_2 through GPx-mediated processes, reducing disulfides, and reducing Grx.[44] Reduced Trx is not only required in the Trx system to decrease cellular oxidized proteins such as oxidized peroxiredoxins, ribonucleotide 5′-diphosphatase, and methionine sulfoxide, but it also serves as a cofactor for numerous enzymes and transcription factors.[44] In other words, Trx is considered a biomarker for age-related illnesses, oxidative stress, inflammation, and cellular senescence.[45] For instance, decreased Trx forms complexes with apoptosis-signal-regulating protein 1 (ASK1) and phosphates and tensin homolog (PTEN), rendering these binding partners inactive.[46]

In redox homeostasis

The main thiol antioxidant in cells is GSH. It functions within a significant biological network of redox couples, which includes GSH/GSSG, NAD^+/NADH, and $NADP^+$/NADPH. These couples cooperate with GSH/GR, Grx/GSH, Trx/oxidized Trx, and TrxR to preserve redox homeostasis.[47] The cellular redox state is often characterized by the ratio of GSH to GSSG, or GSH/GSSG, which is 100/1 in the cytoplasm, 10/1 in the mitochondria, and 3/1 to 1 in the endoplasmic reticulum.[48] Significant alterations in cellular signaling processes result from its disruption, and this ratio fluctuates according to the physiological state of cells, including proliferation, differentiation, or death. GSH/GSSG plays this role in large part because it regulates the functional activity of protein thiols.[49] Retinal cells require the maintenance of appropriate GSH levels, turnover rates, and oxidation states. As people age, their eyes' GSH levels drop, and glaucoma has been linked to lower GSH levels.[47]

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GSH, taurine, and hydrogen sulfide are all precursors of cysteine and have important antioxidant, neuroprotective, and neuromodulatory qualities. As people age, their extracellular cysteine (Cys)/ cystine (CySS) ratio changes to a more oxidized value, which is thought to be a major risk factor for illness.[47] For instance, a higher oxidized Cys/CySS redox potential dramatically raises the activation of extracellular signal-regulated kinase (ERK) in astrocytes by metabotropic glutamate receptor 5 (mGluR5), which enhances the production of the transcription factor, NF-κB and inducible NOS, releases ROS and RNS, and promotes neurotoxicity.[50]

In thiol-based redox signaling and cysteine thiol modification

Increased generation of free radicals and ROS can have an influence on a variety of critical cellular functions, including phosphorylation pathways, gene transcription, cytoskeletal structure, and ion channel activity, which activates thiol-based signaling as part of normal physiological activities.[51,52] H_2O_2 functions as a second messenger in the thiol network, conveying the signal regardless of the oxidant that initiated it.[51] The precise actions of the enzymes that use GSH and other associated antioxidant systems, including Grx and Trx systems, are essential for GSH's impact on thiol signaling.[52]

A significant portion of signal transduction mediated by RNS and ROS depends on changes to cysteine thiol (-SH) in proteins. Protein degradation and irreversible thiol modification (sulfonic acid, $-SO_3H$) are typically the results of this process, which has been identified as a hallmark for a number of pathological conditions. Redox signaling involves reversible thiol modifications, including disulfide formation (-S-S-), S-sulfhydration (-S-SH), sulfinic acid ($-SO_2H$), S-nitrosylation (-SNO), S-sulfenylation (sulfenic acid, -SOH), and S-glutathionylation (-SSG).[41]

The Trx system catalyzes the opposite of sulfhydration, desulfhydration, and the opposite of nitrosylation, denitrosylation, under different circumstances. Although other proteins, including Trxs, show deglutathionylase activity under different conditions, Grxs are considered the principal deglutathionylases due to their high affinity and selectivity for glutathionylated proteins.[41]

In cellular senescence

Cellular senescence is brought on by increased oxidative stress and DNA damage caused by Trx deficiency, which can activate the p53-p21 or p16-Retinoblastoma protein (Rb) pathways. Additionally, Trx controls NF-κB, a crucial transcription factor that regulates the synthesis of inflammatory factors, which in turn controls senescence-associated secretory phenotype (SASP) in senescent cells.[45,53] The link between Trx and cellular senescence is supported by several experimental results. For instance, human fibroblasts that overexpress Trx have longer replication lifetimes and slower senescence. On the other hand, Trx reduces the cell's capacity to fend against oxidative stress when it is knocked down or removed, which can result in aging, apoptosis, cellular damage, and dysfunction.[45]

In altering the lifetime

The intricate relationships between Trx and other redox signaling pathways and Trx's direct engagement in stress response cascades linked to lifetime processes, including the control of the apoptotic pathway, hypoxia response, and mitochondrial unfolded protein response (mitoUPR), may be key components of the Trx system's anti-aging function.[45] TrxR inhibitors dramatically decreased the clearance rate of exogenous H_2O_2 in rat brain mitochondria by 80%, suggesting that cells may choose to upregulate Trx to combat oxidative stress, a known mechanism that controls cellular senescence and individual lifetime.[54]

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The impact of antioxidant genes, such as Trx and TrxR, on lifetime has been the subject of several investigations. While overexpression shortens lifetime, downregulation of the negative regulator cytosolic Trx1, thioredoxin-interacting protein (Txnip), enhances resilience to oxidative stress and prolongs lifetime.[45] While deletion of the mitochondrial thioredoxin gene, trx-2, has no effect on lifetime, disruption of the cytoplasmic thioredoxin gene, trx-1, significantly reduces lifetime in the worm species *Caenorhabditis elegans*, which shares genetic and molecular traits with humans.[55] In contrast to *C. elegans*, mutations that diminish TrxR activity in *Drosophila melanogaster*, a kind of fruit fly, induce a significant reduction in adult lifetime.[56] In mice, a 50% decrease in the expression of the mitochondrial Trx2 gene enhances ROS generation and oxidative damage while decreasing lifetime somewhat.[57]

There are fewer studies looking at how lifetime is affected by the expression of antioxidant genes, such as Grx. When *C. elegans* consumes recombinant buckwheat Grx, their lifetime and resilience to oxidative stress are increased.[36] By increasing ROS buildup, which in turn triggers the RAS/PKA signaling cascade and reduces stress tolerance, the deletion of either grx1 or grx2 in yeast of the species *Saccharomyces cerevisiae* shortens the chronological lifetime.[58] Yeast lifetime is likewise reduced when the mitochondrial glutaredoxin gene, grx5, is disrupted.[59]

Conclusion and Recommendations

In order for crucial redox couples like GSH/GSSG, NAD^+/NADH, and $NADP^+$/NADPH to perform their physiological and biochemical functions, Trx and GSH/Grx systems help reverse thiol-based cysteine modifications, including S-glutathionylation, S-nitrosylation, and S-sulfhydration, that are mediated by redox signals. Trx, TrxR, and Grx interact with signaling pathways and transcription factors to cause changes in cellular senescence and lifetime, according to studies. Further research is required since the genetic studies on this topic are few and inadequate. In addition, ongoing research seeks to uncover the precise mechanisms through which these systems influence cellular processes, potentially leading to new therapeutic strategies for diseases associated with oxidative stress and redox imbalance. Understanding the intricate dynamics of the Trx and GSH/Grx systems could pave the way for innovative interventions aimed at enhancing cellular resilience and longevity.

References

1. Partridge L., & Gems, D. (2002). Mechanisms of ageing: public or private? *Nat. Rev. Genet*., 3, 165–175.
2. Kennedy, B.K., Berger, S.L., Brunet, A, Campisi, J, Cuervo, A.M., Epel, E.S., Franceschi, C, Lithgow, G.J., Morimoto, R.I., Pessin, J.E., Rando, T.A., Richardson, A., Schadt, E.E., Wyss-Coray. T., & Sierra. F. (2014). Geroscience: linking aging to chronic disease. *Cell.,* 159(4), 709-13.
3. DiLoreto, R., & Murphy, C.T. (2015). The cell biology of aging. *Mol. Biol. Cell.,* 26(25), 4524–4531.
4. Mandal, M., Sarkar, M., Khan, A., Biswas, M., Masi, A., Rakwal, R., Agrawal, G.K., Srivastava, A., & Sarkar, A. (2022). Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) in plants–maintenance of structural individuality and functional blend. *Advances in Redox Research*, 5, 100039.
5. Zorov, D.B., Juhaszova, M., & Sollott, S.J. (2014). Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev*., 94(3), 909-50.
6. Phaniendra, A., Jestadi, D.B., & Periyasamy, L. (2015). Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem*., 30(1), 11-26.
7. Martemucci, G., Costagliola, C., Mariano, M., D'andrea, L., Napolitano, P., & D'Alessandro, A. G. (2022). Free Radical Properties, Source and Targets, Antioxidant Consumption and Health. *Oxygen*, 2(2), 48-78.
8. Chandimali, N., Bak, S.G., Park, E.H., Lim, H.J., Won, Y.S., Kim, E.K., Park, S.I., & Lee, S.J. (2025). Free radicals and their impact on health and antioxidant defenses: a review. *Cell Death Discov.*, 11(1), 19.

Sorumlu yazar/Corresponding author
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9. Collin, F. (2019). Chemical Basis of Reactive Oxygen Species Reactivity and Involvement in Neurodegenerative Diseases. *Int J Mol Sci*., 20(10), 2407.
10. Pacher, P., Beckman, J.S., & Liaudet, L. (2007). Nitric oxide and peroxynitrite in health and disease. *Physiol Rev*., 87(1), 315-424.
11. Radi, R. (2004). Nitric oxide, oxidants, and protein tyrosine nitration. *Proc Natl Acad Sci USA*., 101(12), 4003-8.
12. Hajam, Y.A., Rani, R., Ganie, S.Y., Sheikh, T.A., Javaid, D., Qadri, S.S., Pramodh, S., Alsulimani, A., Alkhanani, M.F., Harakeh, S., Hussain, A., Haque, S., & Reshi, M.S. (2022). Oxidative Stress in Human Pathology and Aging: Molecular Mechanisms and Perspectives. *Cells*., 11(3), 552.
13. Biala, A.K., Dhingra, R., & Kirshenbaum, L.A. (2015). Mitochondrial dynamics: Orchestrating the journey to advanced *age. J. Mol. Cell. Cardiol.,* 83, 37–43.
14. Bratic, A., & Larsson, N.G. (2013). The role of mitochondria in aging. *J. Clin. Investig.,* 123, 951–957.
15. Indo, H.P., Yen, H.C., Nakanishi, I., Matsumoto, K.I., Tamura, M., Nagano, Y., Matsui, H., Gusev, O., Cornette, R., Okuda, T., Minamiyama, Y., Ichikawa, H., Suenaga, S., Oki, M., Sato, T., Ozawa, T., Clair, D.K., & Majima, H.J. (2015). A mitochondrial superoxide theory for oxidative stress diseases and aging. *J. Clin. Biochem. Nutr.,* 56, 1–7.
16. Bjelakovic, G., Nikolova, D., Gluud, C. (2014). Antioxidant supplements and mortality. *Curr. Opin. Clin. Nutr. Metab. Care.,* 17, 40–44.
17. Kushnareva, Y., Murphy, A.N., & Andreyev, A. (2002). Complex I-mediated reactive oxygen species generation: modulation by cytochrome c and NAD(P)+ oxidation-reduction state. *Biochem. J.,* 368(Pt 2), 545–553.
18. Chen, Q., Vazquez, E.J., Moghaddas, S., Hoppel, C.L., & Lesnefsky, E.J. (2003). Production of reactive oxygen species by mitochondria: central role of complex III. *J. Biol. Chem.,* 278(38), 36027–36031.
19. Balaban, R.S., Nemoto, S., & Finkel, T. (2005). Mitochondria, oxidants, and aging. *Cell*, 120(4), 483–495.
20. Van Raamsdonk, J.M., & Hekimi, S. (2010). Reactive oxygen species and aging in caenorhabditis elegans: causal or casual relationship? *Antioxid Redox Signal*., 13(12), 1911–1953.
21. Beckman, KB, & Ames, B.N. (1998). The free radical theory of aging matures. *Physiol Rev.,* 78(2), 547-81.
22. Nguyen, G.T., Green, E.R., & Mecsas, J. (2017). Neutrophils to the ROScue: Mechanisms of NADPH Oxidase Activation and Bacterial Resistance. *Front Cell Infect Microbiol*., 7, 373.
23. Lambeth, J.D. (2004). NOX enzymes and the biology of reactive oxygen. *Nat Rev Immunol.,* 4(3), 181-9.
24. McDonnell, A.M., & Dang, C.H. (2013). Basic review of the cytochrome p450 system. *J Adv Pract Oncol*., 4(4), 263-8.
25. Battelli, M.G., Polito, L., Bortolotti, M., & Bolognesi, A. (2016). Xanthine Oxidoreductase in Drug Metabolism: Beyond a Role as a Detoxifying Enzyme. *Curr Med Chem*., 23(35), 4027-4036.
26. McCord, J.M., & Fridovich, I. (1969). Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). *J Biol Chem*., 244(22), 6049-55.
27. Shih, J.C., Chen, K., & Ridd, M.J. (1999). Monoamine oxidase: from genes to behavior. *Annu Rev Neurosci*., 22, 197-217.
28. Lismont, C., Nordgren, M., Van Veldhoven, P.P., & Fransen, M. (2015). Redox interplay between mitochondria and peroxisomes. *Front Cell Dev Biol*., 3, 35.
29. Yang, J., Luo, J., Tian, X., Zhao, Y., Li, Y., & Wu, X. (2024). Progress in Understanding Oxidative Stress, Aging, and Aging-Related Diseases. *Antioxidants (Basel)*., 13(4), 394.
30. Ayala, A., Muñoz, M.F., & Argüelles, S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev.,* 2014, 360438.
31. Barrera, G., Pizzimenti, S., Daga, M., Dianzani, C., Arcaro, A., Cetrangolo, G.P., Giordano, G., Cucci, M.A., Graf, M., & Gentile, F. (2018). Lipid Peroxidation-Derived Aldehydes, 4-Hydroxynonenal and Malondialdehyde in Aging-Related Disorders. *Antioxidants (Basel).,* 7(8), 102.

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32. Domínguez, R., Pateiro, M., Munekata, P.E.S., Zhang, W., Garcia-Oliveira, P., Carpena, M., Prieto, M.A., Bohrer, B., & Lorenzo, J.M. (2021). Protein Oxidation in Muscle Foods: A Comprehensive Review. *Antioxidants (Basel).,* 11(1), 60.
33. Höhn, A., König, J., & Grune, T. (2013). Protein oxidation in aging and the removal of oxidized proteins. *J Proteomics*., 92, 132-59.
34. Juan, C.A., Pérez de la Lastra, J.M., Plou, F.J., & Pérez-Lebeña, E. (2021). The Chemistry of Reactive Oxygen Species (ROS) Revisited: Outlining Their Role in Biological Macromolecules (DNA, Lipids and Proteins) and Induced Pathologies. *Int J Mol Sci*., 22(9), 4642.
35. van der Pol, A., van Gilst, W.H., Voors, A.A., & van der Meer, P. (2019). Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail*., 21(4), 425-435.
36. Shields, H.J., Traa, A., & Van Raamsdonk, J.M. (2021). Beneficial and Detrimental Effects of Reactive Oxygen Species on Lifespan: A Comprehensive Review of Comparative and Experimental Studies. *Front Cell Dev Biol*., 9, 628157.
37. Lushchak, VI. (2014).Classification of oxidative stress based on its intensity.*EXCLI J*., 13, 922-37.
38. D'Oria, R., Schipani, R., Leonardini, A., Natalicchio, A., Perrini, S., Cignarelli, A., Laviola, L., & Giorgino, F. (2020). The Role of Oxidative Stress in Cardiac Disease: From Physiological Response to Injury Factor. Oxid Med Cell Longev., 2020, 5732956.
39. Gaucher, C., Boudier, A., Bonetti, J., Clarot, I., Leroy, P., & Parent. M. (2018). Glutathione: Antioxidant Properties Dedicated to Nanotechnologies. *Antioxidants (Basel).,* 7(5), 62.
40. Aramouni, K., Assaf, R., Shaito, A., Fardoun, M., Al-Asmakh, M., Sahebkar, A., & Eid, A.H. (2023). Biochemical and cellular basis of oxidative stress: Implications for disease onset. *J Cell Physiol*., 238(9), 1951-1963.
41. Ren, X., Zou, L., Zhang, X., Branco, V., Wang, J., Carvalho, C., Holmgren, A, & Lu, J. (2017). Redox Signaling Mediated by Thioredoxin and Glutathione Systems in the Central Nervous System. *Antioxid Redox Signal*., 27(13), 989-1010.
42. Lee, S., Kim, S.M., & Lee, RT. (2013). Thioredoxin and thioredoxin target proteins: from molecular mechanisms to functional significance. *Antioxid Redox Signal*., 18(10), 1165-207.
43. Hanschmann, E.M., Godoy, J.R., Berndt, C., Hudemann, C., & Lillig, CH. (2013). Thioredoxins, glutaredoxins, and peroxiredoxins--molecular mechanisms and health significance: from cofactors to antioxidants to redox signaling. *Antioxid Redox Signal*., 19(13), 1539-605.
44. Arnhold, J. (2020). Cell and Tissue Destruction. Mechanisms, Protection, Disorders. Academic Press; London, UK: San Diego, CA, USA: Cambridge, MA, USA: Oxford, UK. *Oxidation and reduction of biological material*, pp. 55–97.
45. Yang, B., Lin, Y., Huang, Y., Shen, Y.Q., & Chen, Q. (2024). Thioredoxin (Trx): A redox target and modulator of cellular senescence and aging-related diseases. *Redox Biol*., 70, 103032.
46. Lee, S., Kim, S.M., & Lee, RT. (2013). Thioredoxin and thioredoxin target proteins: from molecular mechanisms to functional significance. *Antioxid Redox Signal*., 18(10),1165-207.
47. McBean, G.J., Aslan, M., Griffiths, H.R., & Torrão, R.C. (2015). Thiol redox homeostasis in neurodegenerative disease. *Redox Biol.*, 5, 186-194.
48. Moriarty-Craige, S.E., & Jones, D.P. (2004). Extracellular thiols and thiol/disulfide redox in metabolism. *Annu. Rev. Nutr*., 24, 481-509.
49. Kalinina, E, & Novichkova, M. (2021). Glutathione in Protein Redox Modulation through S-Glutathionylation and S-Nitrosylation. *Molecules*., 26(2), 435.
50. Zhu, J.W., Yuan, J.F., Yang, H.M., Wang, S.T., Zhang, C.G., Sun, L.L., Yang, H., & Zhang, H. (2012). Extracellular cysteine (Cys)/cystine (CySS) redox regulates metabotropic glutamate receptor 5 activity. *Biochimie*., 94(3), 617-27.
51. Winterbourn, CC. (2014). Are free radicals involved in thiol-based redox signaling? *Free Radic Biol Med*., 80, 164-70.
52. Ferguson, G.D., & Bridge, W.J. (2019). The glutathione system and the related thiol network in Caenorhabditis elegans. *Redox Biol*., 24, 101171.

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53. Gorgoulis, V., Adams, P.D., Alimonti, A., Bennett, D.C., Bischof, O., Bishop, C., Campisi, J., Collado, M., Evangelou, K., Ferbeyre, G., Gil, J., Hara, E., Krizhanovsky, V., Jurk, D., Maier, A.B., Narita, M., Niedernhofer, L., Passos, J.F., Robbins, P.D., Schmitt, C.A., Sedivy, J., Vougas., K., von Zglinicki, T., Zhou, D., Serrano, M., & Demaria, M. (2019). Cellular Senescence: Defining a Path Forward. *Cell*., 179(4), 813-827.
54. Drechsel, D.A., & Patel, M. (2010). Respiration-dependent H_2O_2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system. *J Biol Chem*., 285(36), 27850-8.
55. Jee, C., Vanoaica, L., Lee, J., Park, B.J., & Ahnn, J. (2005). Thioredoxin is related to life span regulation and oxidative stress response in Caenorhabditis elegans. *Genes Cells*., 10(12), 1203-10.
56. Missirlis, F., Phillips, J.P., & Jäckle, H. (2001). Cooperative action of antioxidant defense systems in Drosophila. *Curr Biol*., 11(16), 1272-7.
57. Pérez, VI, Lew, C.M., Cortez, L.A., Webb, C.R., Rodriguez, M., Liu, Y., Qi, W., Li, Y., Chaudhuri, A., Van Remmen, H., Richardson, A., & Ikeno, Y. (2008). Thioredoxin 2 haploinsufficiency in mice results in impaired mitochondrial function and increased oxidative stress. *Free Radic Biol Med*., 44(5), 882-92.
58. Liu, Y., Yang, F., Li, S., Dai, J., & Deng, H. (2018). Glutaredoxin Deletion Shortens Chronological Life Span in Saccharomyces cerevisiae via ROS-Mediated Ras/PKA Activation. *J Proteome Res*., 17(7), 2318-2327.
59. Zadrag, R., Bartosz, G., & Bilinski, T. (2008). Is the yeast a relevant model for aging of multicellular organisms? An insight from the total lifespan of Saccharomyces cerevisiae. *Curr Aging Sci.,* 1(3), 159-65.

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