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How do viruses use oxidative stress?

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ABSTRACT

Oxygen is a vital element for all living beings to continue their life activities and is the main component of oxidant–antioxidant metabolism, which should be in balance. The free radicals formed as a result of this metabolic process in the organism constitute a source of oxidants; external factors (radiation, exposure to sunlight, environmental pollution, cigarettes, etc.), inflammation and microbial agents also cause the formation of oxidants. Oxidative stress occurs when the balance between free radicals and antioxidants (which have an eliminating effect against them) shifts in favour of free radicals. Many studies have reported that oxidative stress may affect the virulence of pathogens during infection. Viruses use a pathological pathway that causes the production of reactive oxygen species (ROS) and the consumption of antioxidants. Thus, after viral infections, higher levels of ROS are often formed. Not only DNA-containing but also RNA-containing viruses were found to be associated with severe oxidative stress supporting DNA damage, high mutagenicity, initiation and/or progression of neoplasia. This review focuses on the relationship between oxidative stress and viruses.

Keywords: oxidative stress, viruses, virus infections, oxidative stress in infections

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Introduction

All living things need oxygen and, as such, it is an essential element to sustain vital activities. However, antioxidants are also needed for the organism to maintain a sensitive balance for neutralizing oxygen and oxygen-containing products. Any deterioration of this balance in favour of oxidants leads to “oxidative stress”; in other words, insufficient antioxidant metabolism initiates a chain of events resulting in tissue damage.

Free radicals are a primary source of oxidants and they initiate the oxidation of many structural components of cells. This abnormal event leads to pathological changes and initiates a process leading to collapse of the organism.

This review focuses on the oxidative stress caused by oxidation reactions of reactive oxygen species (ROS) in structural components, the damage that results from this process, the antioxidant system that effectively defends against this damage and also how viruses make use of this event.

History: In the 19th century, Paul Bert proposed that high oxygen concentrations are harmful to many organs, especially brain and lungs, therefore it became important to examine the damage caused by excess oxygen in organisms (Donald, 1947; Kliszczewska et al., 2018). The curiosity rised about free radicals, which are toxic agents caused by x-radiation , pollution, alcohol, etc. (Phaniendra et al., 2015), brought along an increase in studies on this matter to understand the role of viruses on oxidants release (Peterhans, 1979).

Peterhans (1979) published the first evidence that viruses can cause oxidative stress by increasing the

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number of ROS (Peterhans, 1979). He showed that a relationship exists between cell activation and ROS formation as a result of the virucidal effects of viruses (Peterhans, 1997).

Other studies have shown that influenza and paramyxoviruses cause an increase in phagocytic cells by infecting respiratory system cells and activating monocytes and polymorphonuclear leukocytes in vitro to form ROS (Schwarz et al., 1996; He et al., 2013).

Reactive species in oxidative stress: ROS, as a term, describes free radicals and moleculess, containing one or more unpaired electrons in the outer electronic shell (Turrens,2003; Lobo, 2010). They are essential products for physiological functions of cell but have also been proven by researchers to contribute to the pathogenesis of many diseases (Phaniendra et al., 2015). In amounts beyond physiological limits, it is possible that they can damage many structural components. There are three types of oxygen in the atmosphere: atomic oxygen (O), molecular oxygen (O2) and ozone (O3) (Donald, 1947). In physiological conditions, it is reported that every cell in the human body is exposed to 1010 O2 molecules per day (Donald, 1947; Phaniendra et al, 2015) and oxygen-derived free radicals (ROS) are a series of metabolites derived from O2 (Phaniendra et al., 2015). It has been known that mitochondria produce ROS (Zorov et al., 2014). Mitochondria consume 90% of the oxygen in as cell and only 3–5% of oxygen taken into the body is converted to products expressed as ROS (Phaniendra et al., 1979).

Although the majority of free radicals are formed in the respiratory tract, ROS are also produced during phagocytosis, redox reactions of xenobiotics and enzymatic reactions catalyzed by lipoxygenases, cyclooxygenases, oxidases and dehydrogenases (Di Meo et al., 2016; Kliszczewska et al., 2018). They are also secreted from dendritic cells, neutrophils and macrophages in response to inflammatory agents (Di Meo et al., 2016).

The role of ROS in physiological cell function was investigated by lots of researchers (Dröge, 2002), so it has been proven that reactive species contribute to many positive events, such as regulation of cytokines, growth factors, transcription, immunomodulation and apoptosis (Di Meo et al., 2016). Loss of enzyme activity, inhibition of protein synthesis, DNA damage as well as tissue damage are examples of negative events caused by excessive ROS production that can lead to disorders of cell integrity, functional losses and also cell death (Camini et al., 2017).

Levels of ROS are also affected by physical factors such as ionizing radiation, ultraviolet radiation, high or low temperature and environmental pollution (Phaniendra et al., 2015). Mitochondria, cytochrome P450 mechanism, peroxisomes and activation of inflammatory cells are examples of endogenous sources of ROS whereas environmental factors such as non-genotoxic carcinogens, xenobiotics, ultrasound and microwave radiation, air pollution and drug toxicities such as carbon tetrachloride and paracetamol are exogenous sources (Kliszczewska et al., 2018; Żukowski et al., 2018). It has been proven that besides stress, forest fires, using alcohol and smoking can also trigger oxidative stress by contributing to free radical formation (Phaniendra et al., 2015; Sebastiano et al., 2016). Hydroxyl radicals are the most reactive products known and their lifetime is concise (10-9 seconds) or the peroxyl radical (ROO-) has a long lifetime of 7 seconds, this knowledge proves that the lifetimes of ROS are variable (Camini et al., 2017).

Oxidative stress: There is a delicate balance between free radicals and antioxidants that has a sweeping effect in the biological system. The deterioration of this balance in favour of free radicals is called ‘oxidative stress’ (Özcan et al., 2015) and because it occurs in multiple systems such as redox signaling pathways it is known as a disorder of redox control and signaling (Camini et al., 2017). In tissues, the continuous flow of single electrons into oxygen causes endogenous oxidative stress (Phaniendra et al., 2015; Özcan et al., 2015).

Excessive increase in the number of free radicals causes damage to many structural components of cells, especially membrane, proteins and nucleic acids. Cytoplasm can be released by rupture of cell membranes, resulting in cell damage or even cell death (Özcan et al., 2015). Migraine triggers also seem to have the capacity to increase oxidative stress (Borkum et al., 2016).

Antioxidant defence: Antioxidants are substances that prevent or delay the damage of substances prone to oxidation, such as proteins, lipids, carbohydrates and DNA in living cells (Lobo et al., 2010). The process that uses these substances is called ‘antioxidant defence’ (Surai et al., 2019).

Antioxidants can also be classified as endogenous (enzymatic and non-enzymatic) and exogenous (Roehrs et al., 2011; Sen et al., 2011). Enzymatic antioxidants are enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) (Camini et al., 2017). SOD is an important enzymes because it forms the first line of defence against ROS

and also plays a role in killing phagocytosed bacteria in the intracellular environment (Ihara et al., 2005). It catalyzes the superoxide radical (O2.-) to hydrogen peroxide (H2O2) and O2 with H2O2 being removed by CAT or GPx (Lushchak et al., 2006). GPx is one of the most important antioxidants found in the cytoplasm and is responsible for protecting cells against oxidative damage caused by H2O2 (Sen et al., 2011). The majority of non-enzymatic antioxidants are present in food: glutathione, melatonin, uric acid, bilirubin, albumin, coenzyme Q10, selenium, α-lipoic acid, ceruloplasmin and transferrin (Sen et al., 2011; Camini et al., 2017). Glutathione plays a vital role in effectively sustaining the antioxidant defence system and removing ROS (Sen et al., 2011).

Exogenous antioxidants can be classified as vitamins and also some chemical substances taken from foods. Butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), sodium benzoate, ethoxyquin, propylgalate and Fe-SOD are examples of antioxidants taken from foods (Shahidi et al., 2000). Vitamin E (α-tocopherol) is one of the critical exogenous antioxidants and is a fat-soluble vitamin (Shahidi et al., 2000; Sen et al., 2011). Vitamin C is a member of anti-oxidant species capable of reducing ROS formation (Shahidi et al., 2000), it plays role as electron donor (Padayatty et al., 2003). In vitro experiments have shown that , as well as protection, vitamin Ccan damage different components of the cell (Padayatty et al., 2003). Antioxidants seems as a potential therapeutic option in the fight against influenza and many other viral infections and it is important to develop new compounds that block oxidative stress (Fulda et al., 2010).

While antioxidant defense network, existed inside the host cell, reduce the oxidative damage; at the same time they control ROS levels to allow beneficial functions (Sgarbanti et al., 2014).

Relationship between apoptosis and oxidative stress: The cell behaviors that occur in stressful medium is variable from survival to eliminate damaged cells (Fulda et al., 2010). When the cell choices the death, different pathways activate and process begin. There are different criteria used in the classification of cell death. For example; morphological appearance, enzymological criteria, functional aspects or immunological characteristics are some of them (Kroemer et al., 2009). Apoptosis, autophagy, necrosis, cornification, paraptosis, ferroptosis, methuosis and pyroptosis are among the examples of this (Yan et al., 2020). In maintaining physiological cellular homeostasis, a successful apoptosis process is a essential step (Fulda et al., 2010). In this context, it has been known that cell signaling and the regulation of the main pathways of apoptosis is depend on ROS (Di Meo et al., 2016). Apoptosis, which is one of cell death types, is defined as programmed cell death, where tissues surrounding the cells are not damaged, whereas necrosis is characterized by spillage of intracellular components and lysis of the plasma membrane (Schweizer et al., 1999; Liu et al., 2017). Apoptosis is triggered by various signaling pathways: receptors activated by stimulation of exogenous signaling molecules control the extracellular pathway; intracellular pathways are regulated by mitochondrial-mediated signaling pathways (Liu et al., 2017). Some research have revealed that ROS, such as O2•−and H2O2, can induce autophagy also (Yun et al., 2020).

One of the defence mechanisms used against virus infections is the destruction of infected cells by apoptosis; however, numerous viruses have developed strategies to prevent apoptosis (Schweizer et al., 1999). Oxidative stress is a mediator with an essential role in the induction of apoptosis (Liu et al., 2017) It is believed that oxidants contribute to the loss of CD4 T cells by way of apoptosis (Peterhan, 1979) and that intracellular levels of ROS, an indicator of oxidative stress, increase in the early part of apoptosis (Schweizer & Peterhans, 1999).

DNA mutations caused by oxidation: Oxidative DNA damage is one of the significant event observed as a result of oxidation (Cadet et al., 2017). Lots of damage occur and repaired by some mechanism, about 105 lesions per cell each day (Mehta et al., 2014). It is known that lesions caused by various mechanisms, such as base and sugar modifications, single- and double-chain fractures, non-basic regions and DNA–protein crosslinking, can all cause damage (Cooke et al., 2003). This damage is the starting point of a series of processes leading to mutagenicity (Lee et al., 2006), carcinogenicity (Klaunig et al., 2010) and aging (Junqueira et al., 2004). Guanine is the base that is most susceptible to oxidation and DNA damage caused by ROS was most frequently encountered on this base (Mc Dorman et al., 2005). Unlike other DNA damage, when guanine is oxidized its response will be a mutation but not a stop in development. It is one of the best-described mutations and can lead to more significant problems because the 8-oxoG level is important as a biomarker for measuring oxidative stress in cells. In physiological conditions 103 8-oxoG is produced in a cell, but this increases to 105 in cancer cells (Phaniendra et al., 2015; Markkanen, 2017). The reaction of nucleic acids with free radicals and also mutations in DNA are shown to be the main causes of cell death (Süleyman et al., 2018).

Determination of increased level of 8-hydroxydeoxyguanosine (8-OH-dG) is indicator of oxidative damage in DNA so it has important role as a biochemical marker in tissue, plasma and urine (Markkanen et al., 2017; Rehman et al., 2018).

Relationship between viral infections and oxidative stress: Plant and animal immune systems rapidly begin to secrete ROS in the presence of pathogens (Novaes et al., 2019). This is defined as the first line of defence and is called 'oxidative explosion' (Gambino et al., 2015; Di Meo et al., 2016). Examples of reactive species are: superoxide radical (O2.-), hydroxyl radical (OH), nitric oxide (NO), hydrogen peroxide (H2O2) and peroxynitrite (ONOO-).The most important mediators of reactives species that are induced by inflammatory processes, particularly microbial infections, are oxygen and nitric oxide (Borkum et al., 2016). The electrical charges of the reactive species can be positive, negative and also neutral (He et al., 2013; Phaniendra et al., 2015; Di Meo et al., 2016). Hydroxyl and superoxide radicals are examples of the most active species (Kliszczewska et al., 2018), with hydroxyl being the most reactive to attack biological molecules. Although this radical is synthesized from H2O2 via Fenton and Haber–Weiss reactions (in the presence of Fe2+ and Cu+), it also occurs when water is exposed to high-energy radiation. However, H2O2 does not have toxic effects unless converted to other free radicals (Kliszczewska et al., 2018). It should be noted that not all ROS are free radicals. For example, O2 and H2O2 are not radicals (Süleyman et al., 2018).

After viral infections, the formation of reactive species is frequently observed. Viruses are known to alter the balance between the host cell and the antioxidant system by causing an increase in the number of cellular pro-oxidants, such as iron and nitric acid, or by inhibiting the synthesis of important products for the antioxidant system, such as SOD (Durgur et al., 2013; Phaniendra et al., 2015). This situation contributes to viral evolution and facilitates viral replication. Viruses have also been shown to promote the synthesis of oxidants, such as superoxide and nitric acid (Camini et al., 2017). It is known that some DNA viruses have proteins that may show an antioxidant effect that depends on the oncogenic potential of the virus (Panda et al., 2008; Durgut et al., 2013). Regarding the role of cells in activation, it is showed that reactive species facilitates or promote viral replication, but this situation is depending on the cell type and the virus (Camini et al.,2017).

The following are examples of virus infections that use oxidative stress:

RNA viruses: Oxidative stress is one of the important factors that causes some disabilities associated with metabolic and physiological, also various diseases (Novaes et al., 2019). Many studies have revealed the relationship between oxidative stress and RNA viruses (Camini et al.,2017).

In addition to respiratory symptoms such as fever and pneumonia; the pandemic infection caused by Sars-CoV-2 (Severe acute respiratory syndrome coronavirus-2), which binds to the ACE receptors (Yang et al., 2020), is a big health problem nowadays due to high ratio of death (Delgado-Roche et al., 2020).

Infections of Sars-CoVs seems also one of the infections associated with oxidative stress (Delgado-Roche et al., 2020). The ''cytokine storm'' that is a result of overreaction of immune system causes severe tissue damage (Huang et al., 2020). The connection between inflammation and oxidative stress has been determined (Sies, 2015). Some researchers found that excessive production of ROS and a insufficient antioxidant system can play a major role in the pathogenesis of SARS-CoV infections (Delgado-Roche et al., 2020).

It has been showed that SARS-CoV 3CLpro (a viral protease) caused a significant increase in ROS production in HL-CZ cells and plays important role in 3CLpro-induced cell apoptosis (Lin et al., 2006).

Bovine viral diarrhoea virus (BVDV) infection has been reported frequently in Turkey (Oguzoglu et al., 2010; Oguzoglu et al., 2012). There are two different biotypes, cytopathic and non-cytopathic, but it is the cytopathic biotype that induces apoptosis. Early in the process of apoptosis the cells show a rise in intracellular ROS, indicative of oxidative stress (Schweizer & Peterhans, 1999).

Research to determine the effects of Bluetongue virus infection on oxidative stress parameters has detected an increase in some parameters related to oxidative stress and a decrease in antioxidant system parameters. However, the serum albumin, cholesterol, creatinine, total protein and GGT (γ-glutamyltransferase) values did not differ significantly between the two groups (Aytekin et al., 2015).

Distemper virus has been shown to have a pathology associated with ROS accumulation. Research has reported that plasma concentrations of methylenedioxyamphetamine (MDA), nitrate and nitrite were significantly increased in the infected group compared to the control group. Also, a significant decrease in plasma concentrations of antioxidants such as glutathione, ascorbic acid, retinol and β-carotene was found in the infected group (Karadeniz et al., 2008).

Levels of NO and MDA, which are indicative of lipid peroxidation and oxidative stress, were found to be high in animals with foot-and-mouth disease. As a result of the study, compared to healthy animals there was a significant decrease in total protein, albumin, globulin, calcium and cholesterol in infected animals (Mousa & Galal, 2013).

Studies on Chandipura infection have demonstrated that this can cause neuronal apoptosis by stimulating oxidative stress. ROS induced by oxidative stress are a critical factor for apoptosis following Chandipura infection. Calcium release or an increase in calcium in cells is one of the agents that causes oxidative stress and consequently ROS production (Verma et al., 2018).

In influenza infection, the signaling pathways associated with oxidative stress have been investigated in more detail. After infection of the respiratory epithelium, ROS levels have been found to be above threshold values (Liu et al., 2017). In H5N1 infected mice, it was observed that the SOD level was lower and the ROS concentration and lung destruction were higher than the control group. Superoxide anion (O2-) detected in the lungs of influenza-infected mice was considered to be a potential pathogenic agent for this infection (He et al., 2013).

In oxidative stress associated with influenza infection, three signaling pathways have been described. As a result of these three signaling pathways being triggered by oxidative stress, the immune response to influenza infection is suppressed. The mechanisms for these pathways are outlined as follows (Liu et al., 2017).

NF-E2-related factor 2 (Nrf2) is a highly sensitive transcription factor that regulates the cellular antioxidant response. Inactive Nrf2 needs cytosolic protein Keap1 in order to enter the cell. Phosphorylated Nrf2 enters the cell, where oxidative stress leads to the dissociation of Keap1 and NrF2, suppressing antioxidant formation (Liu et al., 2017).

The p38 MAPK signaling pathway participates in cellular responses due to its wide stimulus range, both in vivo and in vitro, and mediates a variety of processes: growth, development, differentiation and death of cells. Phosphorylated p38 enters the nucleus of host cells and plays a role in the expression of cytokine genes under oxidative stress stimuli (Liu et al., 2017).

NF-kB is a transcription factor that has a critical regulatory role in the immune response. The activity of NF-kB is induced by various stimuli, such as tumour necrosis factor alpha (TNF-α), para-methoxyamphetamine (PMA), cigarette smoke stress, lipopolysaccharides (LPS), antioxidants and viral infections. In general, the detection of NF-kB is considered to be a biomarker of oxidative stress (Liu et al., 2017).

Retroviruses: The observation of multiple pathogenetic interactions between ROS and the retrovirus HIV (human immunodeficiency virus) infers that such interactions may also play a role in the pathogenesis of other virus infections (Schwarz, 1999; Wang et al., 2018). The HIV infection process contributes to the disruption of the balance between the formation of free radicals and antioxidant defence. Oxidative stress contributes to the pathogenesis of HIV infection by stimulating the proliferation of the virus, decreasing the proliferation of immune cells and increasing the susceptibility to drug toxicity (Wang et al., 2018).

DNA viruses: Researchers have shown that oxidative stress, known as one of the suggested mechanisms to facilitate the replication of herpesviruses, changes the oxidative balance by increasing the formation of free radicals or inhibiting the enzymes involved in oxidative defence in the host cell (Kavouras et al., 2007) The biomarkers of oxidative stress may vary between tissues. When the effect sizes of infections are evaluated, it is known that virus strains cause significant changes (Sebastiano et al., 2016).

The latent membrane protein of Epstein-Barr virus and adenovirus 19K E1B transforming protein can inhibit apoptosis and thus increase oncogenic transformation. All of these viral proteins can inhibit apoptosis by using antioxidant pathways (Schwarz, 1996).

Ecthyma contagiosum is a zoonotic disease (Karakas et al., 2013). In animals diagnosed with this disease, elevated PON1 activity, TSA (total sialic acid), HDL (high-density lipoprotein), NO and glutathione levels have been measured in blood samples (Deveci et al., 2017). Besides playing an essential role in antioxidant defence against lipid peroxidation in the cell membrane, PON1 is believed to play a role in the anti-inflammatory process and in the protection of LDL (low-density lipoprotein) and HDL from oxidation (Çakırca, 2013).

In one study, oxidative stress parameters have been evaluated by taking blood and cerebrospinal fluid from animals infected with coryza gangrenosa bovum. Significant changes in the blood samples were found due to the inflammatory process associated with oxidative stress (Erkiliç et al., 2017).

Reductions in MDA level and SOD and CAT activities have been seen in dogs infected with

parvovirus in oxidative stress. In the haemogram obtained from the infected dogs, zinc levels also were decreased (Panda et al., 2008; Süleyman et al., 2018).

Conclusions

Although ROS are the basic products for cell function under physiological conditions (Chawla et al., 2001), they have been shown to play important roles at different stages of many diseases. ROS also cause or contribute to the development of head and neck cancer (Qian et al., 2018). DNA-containing and RNA-containing viruses have been reported to increase the production of oxidants such as superoxide and nitric oxide, affecting the cellular redox balance and inhibiting the synthesis of antioxidant enzymes. Thus, given the discussions so far, it is concluded that oxidative stress is associated with several aspects of the pathogenesis of various viral aetiological agents. Oxidative stress can both help and also inhibit viral replication (Camini et al., 2017). As a treatment approach, the use of antioxidants is an option. However, further studies on the use of antioxidants for the treatment of viral infections are needed. The extent to which the, as yet, unknown mechanisms may affect viral evolution should also be investigated further.

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