

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,500

Open access books available

135,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Modulations in Oxidative Stress of Erythrocytes during Bacterial and Viral Infections

Vani Rajashekaraiyah, Carl Hsieh and Masannagari Pallavi

Abstract

Oxidative stress (OS) occurs when the generation of free radicals and reactive oxygen species (ROS) overwhelms the antioxidant capacity. OS causes storage lesions which can be defined as a series of biochemical and biomechanical changes. Erythrocytes are constantly exposed to OS due to the presence of ROS, which are countered by the endogenous antioxidant system. Various irreversible changes that occur include fragmentation and aggregation of proteins and lipids. The changes in proteins, lipids and antioxidant capacity are used as OS biomarkers to assess the efficacy of the erythrocytes, post oxidative insult. Aging of erythrocytes is also associated with the changes in its physical, biochemical and physiological properties and OS causes its rapid aging. Bacterial and viral infections also cause OS which alters the erythrocytes' antioxidant capacity. These modulations in its microenvironment are both beneficial in terms of protection against invading microorganisms as well as harmful to the erythrocytes, causing damage to surrounding cells and tissues. Thus, OS biomarkers can be used to gain insights into the effects of bacterial and viral infections on the erythrocyte microenvironment.

Keywords: Erythrocytes, Young and Old Erythrocytes, Oxidative stress, Antioxidant capacity

1. Introduction

Oxidative stress is defined as an imbalance between oxidants and antioxidants leading to excessive levels of reactive oxygen species (ROS). Oxidative damage includes oxidative modification of cellular macromolecules, cell death by apoptosis or necrosis, as well as structural tissue damage. DNA, proteins and lipids, are the natural targets of oxidation [1].

In recent years, ROS have gained more attention, because of their central role in the progression of many inflammatory diseases [2]. The radical groups include hydroxyl radical ($\text{OH}\cdot$), nitric oxide ($\text{NO}\cdot$) and superoxide ($\text{O}_2\cdot^-$). Non-radical compounds can also be highly reactive, which includes peroxynitrite (ONOO^-), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) [3]. ROS can be described as oxygen free radicals and other non-radical oxygen derivatives involved in oxygen radical production [4], which are generated by the cells in most tissues and involved in normal cellular metabolism [5].

ROS can react with DNA and cause damage to purines and pyrimidines [6], resulting in the formation of 8-Hydroxy-deoxyguanosine (8-OHdG) [7]. ROS also cause polypeptide chain fragmentation and covalent crosslinking that results in changes in its protein functional activity [8]. The covalent modifications of proteins induced by ROS or by reacting with secondary products of oxidative stress is termed as protein oxidation. These changes lead to many consequences such as, inhibition of enzyme activity, binding activity, aggregation, proteolysis, increased or decreased cell uptake, altered immunogenicity.

Protein oxidation serves as marker for determination of the levels of OS *in vitro*. There are many mechanisms that can induce protein oxidation as all the amino acyl side chains can be oxidatively modified. Cysteine and Methionine are the two amino acids that are most susceptible to oxidative attack due to the presence of sulfur atoms. Oxidation of cysteine leads to the formation of disulfide bonds, mixed disulfides and thiyl radicals, whereas modification of Methionine produces Methionine sulfoxide [8].

Lipids are important constituents of the lipid bilayer of the cellular membrane. Unsaturated fatty acids, which are easily oxidized, initiate the chain reactions, resulting in further oxidative damage. Lipids are susceptible to oxidation and reacts with molecular oxygen to form lipid peroxy radicals which further oxidizes the neighboring lipids and propagates the oxidative damage [3]. Lipid peroxidation results in the changes of structural integrity and functioning of cell membranes. Lipid peroxidation markers such as malondialdehyde (MDA), 4-hydroxyl-2-nonenal (HNE), and isoprostane are used to evaluate oxidative damage.

Another category of substances called antioxidants exist in the cells and can effectively delay or inhibit ROS-induced oxidation. Antioxidants present in erythrocytes can be broadly classified into enzymatic and non-enzymatic antioxidants. There are three main groups of enzymatic antioxidants that play a significant role in protecting the cells from OS. Superoxide Dismutase (SOD) catalyzes the conversion of superoxides into hydrogen peroxide (H_2O_2) & oxygen (O_2). H_2O_2 is less toxic than compared to superoxides. SOD are metal containing enzymes that depend on a bound Mg, Cu or Zn for their antioxidant activity. There are 3 major families of SOD: Cu/Zn SOD, Fe/Mn SOD and Ni SOD [9–11]. Catalase (CAT) is the most common enzyme that is found in nearly all living organisms. It is found in the peroxisome of eukaryotic cells. It degrades H_2O_2 to H_2O & O_2 . Hence it finishes the detoxification reaction started by SOD [12]. Glutathione peroxidase (GPx) contain Selenium, with peroxidase activity whose main activity is to protect the organism against OS. These enzymes like catalase degrade H_2O_2 to H_2O . They also reduce organic peroxides to their corresponding alcohol, thus provides another route for detoxification [13].

The extracellular endogenous antioxidants generally include the transition metal binding proteins i.e. ceruloplasmin, transferrin, hepatoglobin and albumin [14] and Vitamin C, α -tocopherol and Glutathione [15].

- a. Glutathione (GSH), a major thiol antioxidant is a multifunctional intracellular antioxidant. It is one of the most important cellular antioxidants due to its high concentration and its role in maintaining the redox state of the cell. GSH is a cysteine containing peptide and possesses antioxidant property due to the thiol group that serves as a reducing agent which can be reversibly oxidized and reduced. [16, 17].
- b. Vitamin C, also known as L-ascorbic acid or ascorbate, is present naturally in the body and interconverts between each other depending on the pH. Ascorbic acid is well known reducing agent, thus serves as a good antioxidant [18]. Vit C is a water-soluble electron donor vitamin as it donates two of its electrons from

the C-2 and C-3 double bond to act as antioxidants that result in the formation of semi dehydroascorbic acid, an intermediate free radical. This then reduces to a neutral ascorbate molecule [14]. In cells, ascorbic acid is maintained in its reduced form by reacting with glutathione, catalyzed by protein disulfide isomerase and glutaredoxins [17].

- c. Vitamin E is a collective name that is given for a set of eight related tocopherols and tocotrienols that are fat soluble. α -tocopherol is the most commonly occurring natural antioxidant and has a phytyl chain that is attached to its chromanol nucleus [14]. It is a lipid soluble antioxidant and acts in the glutathione peroxidase pathway [19]. It protects the cell membranes against lipid peroxidation chain reaction by reacting with the lipid radicals produced due to OS. It removes the free radical intermediates, thus preventing the cascade and further damage [20].

1.1 Bacterial and viral and infections cause OS

Bacterial infections cause OS, which trigger ROS production leading to organ damage by altering the metabolic pathway [21].

1.1.1 Periodontitis-*Fusobacterium nucleatum*

Periodontitis is a common bacterial infection, caused *Fusobacterium nucleatum*, resulting in the destruction of teeth supporting tissues. Periodontitis is associated with overproduction of ROS by neutrophils. It is characterized by increased metabolites of lipid peroxidation, DNA damage and protein damage.

After pathogen stimulation, neutrophils produce $O_2^{\cdot-}$ via the metabolic pathway called “respiratory burst” catalyzed by NADPH oxidase during phagocytosis [22]. $O_2^{\cdot-}$ can be released into phagosome and gets converted to different radical and non-radical derivatives, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hydroxyl radical (OH^{\cdot}) and singlet oxygen (1O_2). *In vitro* studies have shown that not only neutrophils, but also other phagocytes and cells of periodontal tissues such as monocytes, gingival fibroblast and periodontal ligament cells exhibit enhanced ROS production upon stimulation by periodontal pathogens and their components [23–25]. This was evident in the results of lipid peroxidation and protein oxidation products. Higher levels of TBARS, MDA and 8-isoprostanes were found in blood plasma, erythrocytes, gingival crevicular fluid (GCF) [26], saliva, GCF [27–30] respectively in periodontitis patients compared to healthy controls. Higher levels of protein carbonyl groups (PC) were found in GCF, saliva and serum of periodontitis patients [31–34] and 8-Hydroxy-deoxyguanosine (8-OHdG) in GCF and saliva of periodontitis patients [35–44].

Variations in antioxidant enzymes were also observed in many studies. SOD, CAT, GPx and glutathione reductase activities decreased in saliva of periodontitis patients [36, 45]. However, SOD and CAT in plasma, erythrocytes and gingival tissues were elevated, whereas activities of non-enzymatic antioxidants (vitamins E, vitamin C, and reduced glutathione) decreased in periodontitis [26]. Periodontitis is associated with decreased Total antioxidant capacity (TAC) [46–52].

1.1.2 Tuberculosis-*mycobacterium tuberculosis*

Mycobacteria initiate infection at oxygen rich lung microenvironments, generating oxidative radicals. These toxic radicals kill the pathogens by causing

disintegration of bacterial cell membrane, DNA damage, deactivation of metabolic enzymes or proteins [53–56]. After invasion into the host, mycobacteria induce NADPH oxidase 2 (NOX2) expression to generate superoxide radicals ($O_2^{\cdot-}$), which are then converted to more toxic hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and subsequently reduced to water and molecular oxygen by catalase [57, 58]. NADPH oxidase 2 (NOX2) is the key enzyme responsible for the cellular ROS production by using superoxide radicals ($O_2^{\cdot-}$) as precursor molecule [59]. Alterations in regulatory components of NOX2 results in generation of phagocytic oxidative stress and phagocytic burst to eliminate enclosed pathogen [58].

However, pathogenic mycobacteria can inhibit oxidative stress mechanisms by modulation of cell signaling mechanisms, up-regulation of antioxidant enzymes and redox buffering systems [59–62].

1.1.3 *Pneumococcal meningitis- streptococcus pneumoniae*

Pneumococcal meningitis is a life-threatening disease characterized by acute infection affecting the pia mater, arachnoid, and subarachnoid spaces [63]. *Streptococcus pneumoniae* crosses the blood–brain barrier (BBB) and disrupts the intraepithelial tight junctions. Host polymorphonuclear leukocytes produce nitric oxide, superoxide radicals, and hydrogen peroxide in response to bacterial infection. $O_2 - \cdot$ and $NO\cdot$ can lead to the formation of peroxynitrite (ONOO), a strong oxidant [64–66]. ONOO⁻ can damage neurons and glial cells by lipid peroxidation and cell membrane destabilization, resulting in DNA disintegration and subsequent poly (ADP-ribose) polymerase (PARP) activation. Elevated 4-HNE and MDA levels are found in bacterial meningitis patients [67]. Thus, ROS/ RNS can be considered key players of immune activation, blood–brain barrier disruption, vascular failure, neuronal injury, and cochlear damage during pneumococcal meningitis.

1.1.4 *Gastritis/gastric cancer- Helicobacter pylori*

Helicobacter pylori is the causative pathogen for human gastritis or gastric cancer, which is characterized with inflammation and ulceration of the stomach and duodenum. Gastric cancer arises from oxidative stress and environmental toxins, which increase DNA mutation rates [68]. The possible sources of ROS/ RNS in *H. pylori* infected stomach, include neutrophils, vascular endothelial cells and gastric mucosal cells. Neutrophils are believed to be the main source of ROS/ RNS [69] and their production is catalyzed by NADPH oxidase on the cell membrane [59]. These highly reactive ROS ($HOCl$ and $\cdot OH$) are used by the phagocyte to kill pathogenic bacteria. *H. pylori* infected gastric mucosal phagocytes produce greater amounts of ROS, which is believed to be the major cause of gastric mucosal damage.

1.1.5 *HIV and Hepatitis*

Oxidative Stress has always played a major pathogenic role in HIV and hepatitis infections. HIV causes decrements in glutathione (GSH), cystine, vitamin C and SOD levels, and increments in lipid peroxidation [70–73]. A decline in the antioxidant capacity represents a weakened immune system, thus requiring more antioxidants to maintain normal functionality [74]. Hepatitis, similar to HIV, also increases the lipid peroxidation (malondialdehyde (MDA) and 4-hydroxynonenal (HNE)) and activity of caspases, whereas reduces zinc [75–77] (**Table 1**).

OS Markers	Bacterial diseases	Viral diseases	References
TBARS	Periodontitis- Increased		[26]
	Tuberculosis- Increased		[78]
	Sepsis- Increased		[79]
MDA	Periodontitis- Increased	HBV- Increased	[26]
	Meningitis- Increased	HCV- Increased	[80]
		HIV- Increased	[81]
		JEV- Increased RSV- Increased	
8-IP	Periodontitis- Increased		[26]
4-HNE	Meningitis- Increased		[80]
PC	Periodontitis- Increased		[31]
	Sepsis- Increased		[79]
8-OHdG	Periodontitis- Increased	HCV- Increased	[35]
			[81]
NO	Tuberculosis- Decreased	RSV- Increased	[78]
	Sepsis- Increased		[82]
			[81]
NT	Meningitis- Increased		[80]
	Sepsis- Increased		[82]
SOD	Periodontitis- Decreased	HBV- Decreased	[36, 45]
	Gastritis- Decreased	HIV- Decreased	[83]
		JEV- Increased	[81]
		DENV- Decreased RSV- Decreased	
CAT	Periodontitis- Decreased	Paramyxovirus- Decreased	[36, 45]
	Tuberculosis- Decreased	DENV- Decreased	[78]
		RSV- Decreased	[81]
GPx	Periodontitis- Decreased	HBV- Decreased	[36, 45]
	Gastritis- Decreased	Paramyxovirus- Decreased	[83]
		DENV- Decreased	[81]
		RSV- Decreased	
GSH	Sepsis- Decreased	HIV- Decreased	[82]
		JEV- Increased	[81]
		Influenza virus- Decreased	
GR	Periodontitis- Decreased		[36, 45]
GST		Paramyxovirus- Decreased	[81]
		RSV- Decreased	
Vit-C	Sepsis- Increased	Influenza virus- Decreased	[79]
	Meningitis- Decreased	HIV- Decreased	[80]
		Covid-19- Decreased	[81]
			[84]
Vit-E		Covid-19- Decreased	[81]
		Influenza virus- Decreased	[84]
β -Carotene		Covid-19- Decreased	[84]
Bilirubin, UA, FRAP, TRAP	Sepsis- Increased		[79]

HBV- Hepatitis B virus; HCV- Hepatitis C virus; HIV- Human immunodeficiency virus; JEV- Japanese encephalitis virus; DENV- Dengue virus; RSV- Respiratory syncytial virus; Covid-19- Coronavirus Disease 2019.
 TBARS- Thiobarbituric acid reactive substances; MDA- Malondialdehyde; 8-IP- 8-isoprostanes; 4-HNE- 4-hydroxynonenal; PC- Protein Carbonyls; 8-OHdG- 8-Hydroxy-deoxyguanosine; NO- nitric oxide; NT- Nitrotyrosine; SOD- Superoxide dismutase; CAT- Catalase; GPx- Glutathione Peroxidase; GSH- Glutathione; GR- Glutathione Reductase, GST- Glutathione S-Transferase; UA- Uric acid; Vit-C- Vitamin C; Vit-E- Vitamin E; FRAP- ferric reducing antioxidant power; TRAP- Total-trapping radical antioxidant potential.

Table 1.
 Oxidative stress (OS) in bacterial and viral diseases.

2. OS has dual role in diseases

OS offers protection against invading microorganisms, and on the other hand can cause damage to cells/tissues.

Erythrocytes being heme rich, provides the invading bacteria a rich source of iron for its metabolism. Bacteria have evolved mechanisms to scavenge the iron through hemolytic toxins and heme scavenging systems [85–87]. Erythrocytes counteract the bacteria through the production of ROS. The α and β sub units of hemoglobin possess high affinity binding sites for lipopolysaccharides (LPS), and leads to macrophage cytokine production and enhances the macrophage binding to LPS. Hemoglobin in μM concentrations have shown to inhibit yeast and bacterial growth through the production of ROS [88–90].

The protection conferred by hemoglobin against invading organisms have a detrimental effect in case of pathological states. Elevations in free hemoglobin is associated with increased mortality. Globin is associated with the protective properties, whereas heme triggers the proinflammatory response. During endotoxemia, the protective effects of hemoglobin is attributed to globin scavenging free heme, which has the property of activating a host of proinflammatory proteins and ROS generation. It has also been shown to increase the transcription of proinflammatory genes by 100-fold [91–93].

3. Modulations in erythrocytes due to OS

3.1 ROS cascade

The ROS cascade in erythrocytes begins with the autooxidation of hemoglobin (Hb) into methemoglobin (MetHb). Oxidation of MetHb results in the formation of sulfhemoglobin (SulfHb) along with superoxide anion (O_2^-). Erythrocytes have an innate antioxidant system that detoxifies the cells. The superoxide generated is detoxified by superoxide dismutase into H_2O and H_2O_2 , which is further detoxified by catalase and glutathione peroxidase (with the help of glutathione) into H_2O and O_2 . Erythrocytes also contain non-enzymatic antioxidants such as glutathione, ascorbic acid (Vit C), and α -tocopherol (Vit E). This antioxidant mechanism helps the erythrocyte's survival in an oxygen-rich environment. Glutathione redox system: reduced glutathione (GSH), glutathione disulfide (GSSG), glutathione reductase (GR), glutathione peroxidase plays an important role in inactivating the ROS [94, 95].

3.2 Erythrocyte aging

The lifespan of erythrocytes *in vivo* is around 120 days. About 1% of the erythrocytes are cleared or phagocytized from circulation every day in humans. The membrane of erythrocytes comprises of proteins (50%), lipids (40%), and carbohydrates (10%). Hb comprises about 95% of the total cytoplasmic proteins. The membrane-associated proteins include band 3 (anion exchanger), band 4.1, spectrin, ankyrin, and glycophorin C which are responsible for maintaining the structure of the cell [94].

As the reticulocyte ages and transforms into erythrocyte, various changes occur in its membrane, composition, appearance and catalytic functions [96]. Aging of erythrocytes is associated with the changes in physical, biochemical and physiological properties. Thus, aged cells are more prone to be trapped and ultimately

destroyed during microcirculation [97]. During aging, a decrease in the cell volume and hemoglobin is observed. The old erythrocytes also increase in density as they bind to autologous IgG (immunoglobulin G), that serves as an initiator for the removal of senescent erythrocytes. The binding of antibodies is also associated and triggered by changes to the anion exchanger, Band 3. There is a decline in sulphate transport with age, thus hampering the binding of ankyrin to Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis [98]. The N- and C- terminal regions of Band 3 are conformationally changed during aging that results in the formation of neoantigens, which serve as a senesce marker. It is also observed that damaged hemoglobin (Hb) bind to band 3 resulting in cluster formations [99–102]. There is also an increase in the amount of glycated Hb.

Aging erythrocytes also lose water, 2,3-BPG, ATP, proteins, Hb and vesicles that cause the cell volume and surface charge to decrease. There is also loss of some of the surface materials such as sialic acids that alter the structure and function of the membrane. These sialic acids are 90% *N*-acetylneuraminic acid (NANA) which accords the electrical charge to the cells [103]. These senescent RBCs also expose membrane phosphatidylserine. An increase in erythrocyte OS causes accelerated aging, resulting in decreased function and survival [97].

The study of Igbokwe *et al.*, 1994 reported the effects of *Trypanosoma brucei* infection in mice. They concluded that a lowered ability to prevent lipid peroxidation in infected mice may increase aging of erythrocytes [104].

4. Bacterial and viral infections causing variations in erythrocytes

Erythrocytes were assumed to only function as innate oxygen carriers. However, recent studies have shown them to be important in modulating the innate immune response [105–107]. Mammalian erythrocytes, unlike the erythrocytes of birds, amphibians and fishes, are enucleate and lack major cell organelles. The organelles of the latter modulate the immune response through production of cytokine like factors, upregulating viral response genes and pathogen sequestering through phagocytosis. Mammalian erythrocytes on the other hand modulate the innate immune response through generation of reactive oxygen species (ROS) to promote inflammatory and autoimmune response against invading microorganisms [108].

Minasyan, 2014 highlighted the role of erythrocytes in conferring bacterial immunity, which is comparable to phagocytic leukocytes as: (i) they are more numerous in number; (ii) fend off microorganisms repeatedly without injury; and (iii) resistant to infection. Erythrocytes have a longer lifespan when compared with leukocytes as well as being produced at a faster rate. The cytosol of erythrocytes is unfavorable to parasitic organisms such as chlamidiae, mycoplasmas, rickettsiae, viruses, etc. Erythrocytes elevate to the primary line of defense against bacterial infections when: (i) there is a presence of massive microbial load; (ii) ineffective recruitment of phagocytes; (iii) faster proliferation and spread of the microorganisms than the phagocytes' capacity; and (iv) ineffectiveness of the phagocytes against the invading microorganisms [109].

4.1 Bacterial infections

Sepsis is one of the most recognized life-threatening dysfunctions that is caused due to infections and is the leading cause for mortality in non-cardiac ICUs (intensive care units) around the world. Sepsis may be caused by gram-positive,

gram-negative and poly microbial infection. It results in elevated OS caused due to inflammatory response, which alters erythrocytes leading to phagocytosis by macrophages and polymorphonuclear leukocytes (PMN). This activation of the macrophages and PMN results in a positive feedback mechanism, as the modified erythrocytes trigger its continuous activation with the generation of ROS. This mechanism may further lead to septic shock, even if the blood-derived bacteria have been cleared off the system [110].

Sepsis develops when bacteria in the bloodstream survive oxidation on the surface of erythrocytes [109]. The changes in erythrocytes can be caused due to several reasons, one of them being OS, and these interactions seem to be interconnected. The levels of antioxidants and oxidants are inversely proportional in septic patients. Decrements in Vitamin E, ascorbate, β -carotene and retinol, while increments in lipid peroxidation were observed. Antioxidant supplementation improved the outcome of patients. Thus, erythrocytes can be model cells for the management of sepsis/septic shock to improve the outcome of patients [111]. Larsen *et al.*, 2010, have reported that one of the major causes for sepsis is the increasing levels of free heme released due to hemolysis. It can be sequestered and cleared off using hemopexin, as its administration reduced tissue damage and lethality [112].

4.2 Viral infections

Studies have shown that viruses cause cell death by generating OS within infected cells [113–115]. The influenza virus and parvovirus activates monocytes to generate ROS *in vitro* [113]. The influenza virus also possesses hemagglutinin glycoprotein on its surface, which helps the virus in binding to cells rich in sialic acids like erythrocytes. Influenza carries hemagglutinin in its inactive form (HOA), which is activated by proteases by cleaving HOA into hemagglutinin 1 and hemagglutinin 2 (HA1 and HA2). HOA can be activated by ROS resulting in a non-infectious virus getting converted into an infectious one [116, 117]. Thus, an increase in ROS levels is beneficial for the invading influenza virus.

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was believed to interact with Hb, facilitating the removal of heme, which was proposed by Liu and Li as likely pathway for the loss of function of hemoglobin (Hb) and the accumulation of free heme resulting in elevated OS. De Martino *et al.*, 2020, reported that COVID-19 did not exhibit any hemolytic anemia. The levels of Hb, bilirubin, lactate dehydrogenase, iron, ferritin and haptoglobin in COVID-19 patients were similar to those with acute respiratory distress syndrome (ARDS) not infected with COVID-19, suggesting that the oxygen delivery impairment was not due to red cell hemolysis and removal of iron from heme. [118].

4.3 Bacterial v/s viral infections

Trefler *et al.*, 2014 compared the patterns of OS in bacterial origin community acquired pneumonia [BCAP] and 2009 A/H1N1 virus community acquired pneumonia [VCAP], revealing the distinct responses between bacterial and viral infections. Erythrocyte GR activity was significantly higher in patients with VCAP in respect of BCAP patients. Lower TBARS levels were observed in VCAP patients in comparison to BCAP, suggesting an increase of antioxidant activity related to the redox glutathione system. GR, GSSG, GSSG/GSH and GPx levels were more elevated in patients with viral pneumonia. A higher antioxidant activity in patients with 2009 A/H1N1 viral pneumonia was observed (**Figure 1**) [119].

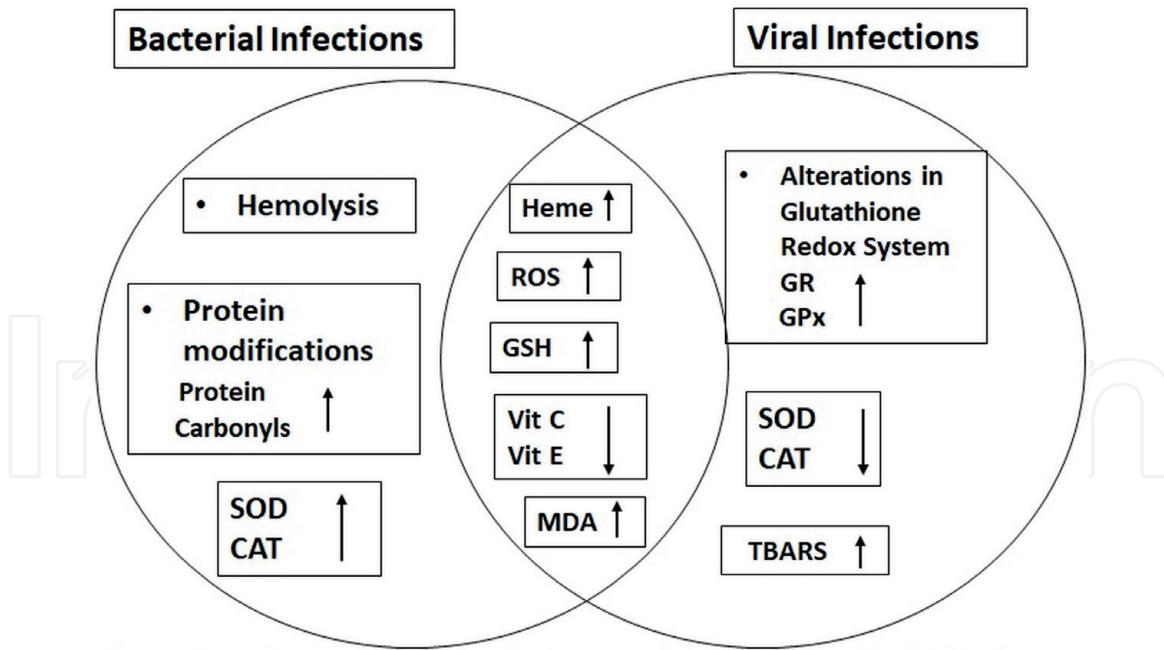


Figure 1. Oxidative modifications in Erythrocytes during Bacterial and Viral infections [109, 112, 118–120]. SOD – Superoxide dismutase; CAT – Catalase; ROS – Reactive oxygen species; GSH – Glutathione; Vit C – Vitamin C; Vit E – Vitamin E; MDA – Malondialdehyde; GR – Glutathione reductase; GPx – Glutathione peroxidase; TBARS – Thiobarbituric acid reactive substances.

5. Conclusion

ROS levels increase rapidly leading to lipid peroxidation and protein oxidation in erythrocytes during infections. Generally, there is a decline in the antioxidant capacity of erythrocytes. Nevertheless, some microbes evade their destruction by altering the antioxidant enzymes of erythrocytes. Thus, OS biomarkers can be used to gain insights into the effects of bacterial and viral infections on the erythrocyte microenvironment. Therefore, erythrocytes act as good indicators and can be promising candidates as peripheral biomarkers during bacterial and viral infections.

Acknowledgements

The authors acknowledge Dr. Leela Iyengar, and JAIN (Deemed-to-be University) for their support.

Conflict of interest

The authors have no conflict of interest to disclose.

IntechOpen

IntechOpen

Author details

Vani Rajashekaraiiah*, Carl Hsieh and Masannagari Pallavi
Department of Biotechnology, School of Sciences, JAIN (Deemed-to-be
University), Bengaluru, India

*Address all correspondence to: tiwari.vani@gmail.com;
vani.rs@jainuniversity.ac.in

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Poulsen HE. Oxidative DNA modifications. *Experimental and Toxicologic Pathology*. 2005;57:161-169.
- [2] Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. *Antioxidants and Redox Signalling*. 2014;20:1126-1167.
- [3] Lykkesfeldt J, Svendsen O. Oxidants and antioxidants in disease: Oxidative stress in farm animals, *The Veterinary Journal*. 2007;173:502-511.
- [4] Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. *Chemico-Biological Interactions*. 2014;224:164-175.
- [5] Sies H. Oxidative stress: Oxidants and antioxidants. *Experimental Physiology*. 1997;82:291-295.
- [6] Halliwell, B. Why and how should we measure oxidative DNA damage in nutritional studies? How far have we come? *American Journal of Clinical Nutrition*. 2000;72:1082-1087.
- [7] Chapple IL, Matthews JB. (2007). The role of reactive oxygen and antioxidant species in periodontal tissue destruction. *Periodontology* 2007;43:160-232.
- [8] Shacter E. (2000). Quantification and significance of protein oxidation in biological samples. *Drug Metabolism Reviews*. 2000;32:307-326.
- [9] Tainer JA, Getzoff ED, Beem KM, Richardson JS, Richardson DC. Determination and analysis of the 2 A-structure of copper, zinc superoxide dismutase. *Journal of Molecular Biology*. 1982;160:181-217.
- [10] Borgstahl GE, Parge HE, Hickey MJ, Beyer WF, Hallewell RA, Tainer JA. The structure of human mitochondria manganese superoxide dismutase reveals a novel tetrameric interface of two 4-helix bundles. *Cell*. 1992;71:107-118.
- [11] Barondeau DP, Kassmann CJ, Bruns CK, Tainer JA, Getzoff ED. Nickel superoxide dismutase structure and mechanism. *Biochemistry*. 2004;43:8038-8047.
- [12] Chelikani P, Fita L, Loewen PC. Diversity of structures and properties among catalases. *Cellular and Molecular Life Sciences*. 2004;61:192-208.
- [13] Otto EPP, Ladenstein R, Wendel A. The refined structure of the selenoenzyme Glutathione Peroxidase at 0.2-nm resolution. *European Journal of Biochemistry*. 1983;133:51-69.
- [14] Chakraborty P, Kumar S, Dutta D, Gupta V. Role of antioxidants in common health diseases. *Research Journal of Pharmacy and Technology*. 2009;2:238-244.
- [15] Machefer G, Groussard C, Rannou-Bekono F, Zouhal H, Faure H, Vincent S, Cillard J, Gratas-Delamarche A. Extreme running competition decreases blood antioxidant defense capacity. *Journal of the American College of Nutrition*. 2004;23:358-364.
- [16] Rahman K. Studies on free radicals, antioxidants, and co-factors. *Clinical Interventions in Aging*. 2007;2:219-236.
- [17] Hamid AA, Aiyelaagbe OO, Usman LA, Ameen OM, Lawal A. Antioxidants: Its medicinal and pharmacological applications. *African Journal of Pure and Applied Chemistry*. 2010;4:142-151.
- [18] McGregor G P, Biesalski H K. Rationale and impact of vitamin C in clinical nutrition. *Current Opinion in*

Clinical Nutrition & Metabolic Care. 2006;9:697-703.

[19] Wefers H, Sies H. The protection by ascorbate and glutathione against microsomal lipid peroxidation is dependent on vitamin E. *European Journal of Biochemistry*. 1988;174:2:353-357.

[20] Herrera E, Barbas C. Vitamin E: Action, metabolism and perspectives. *Journal of Physiology and Biochemistry*. 2001;57:43-56.

[21] Ivanov AV, Bartosch B, Isagulians MG. Oxidative stress in infection and consequent disease. *Oxidative Medicine and Cellular Longevity*. 2017;3496043:1-3.

[22] Chapple IL, Matthews JB. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. *Periodontology* 2007;43:160-232

[23] Bullon P, Cordero MD, Quiles JL, Morillo JM, del Carmen Ramirez-Tortosa M, Battino M. Mitochondrial dysfunction promoted by *Porphyromonas gingivalis* lipopolysaccharide as a possible link between cardiovascular disease and periodontitis. *Free Radical Biology and Medicine*. 2011;50:1336-1343.

[24] Chang MC, Tsai YL, Chen YW, Chan CP, Huang CF, Lan WC, Lin CC, Lan WH, Jeng JH. Butyrate induces reactive oxygen species production and affects cell cycle progression in human gingival fibroblasts. *Journal of Periodontal Research*. 2013;48:66-73.

[25] Gözl L, Memmert S, Rath-Deschner B, Jäger A, Appel T, Baumgarten G, Götz W, Frede S. LPS from *P. gingivalis* and hypoxia increases oxidative stress in periodontal ligament fibroblasts and contributes to periodontitis. *Mediators of Inflammation*. 2014;2014.

[26] Panjamurthy K, Manoharan S, Ramachandran CR. Lipid peroxidation and antioxidant status in patients with periodontitis. *Cellular and Molecular Biology Letters*. 2005;10: 255-264.

[27] Tsai CC, Chen HS, Chen SL, Ho YP, Ho KY, Wu YM, Hung CC. Lipid peroxidation: A possible role in the induction and progression of chronic periodontitis. *Journal of Periodontal Research*. 2005;40:378-384.

[28] Wei D, Zhang XL, Wang YZ, Yang CX, Chen G. Lipid peroxidation levels, total oxidant status and superoxide dismutase in serum, saliva and gingival crevicular fluid in chronic periodontitis patients before and after periodontal therapy. *Australian Dental Journal*. 2010;55:70-78.

[29] Tonguç MÖ, Öztürk Ö, Sütçü R, Ceyhan BM, Kılınc G, Sönmez Y, Yetkin Ay Z, Şahin Ü, Baltacıoğlu E, Kırzioğlu FY. The impact of smoking status on antioxidant enzyme activity and malondialdehyde levels in chronic periodontitis. *Journal of Periodontology*. 2011;82:1320-1328.

[30] Pradeep AR, Rao NS, Bajaj P, Agarwal E. 8-Isoprostane: A lipid peroxidation product in gingival crevicular fluid in healthy, gingivitis and chronic periodontitis subjects. *Archives of Oral Biology*. 2013;58:500-504.

[31] Sculley DV, Langley-Evans SC. Periodontal disease is associated with lower antioxidant capacity in whole saliva and evidence of increased protein oxidation. *Clinical Science*. 2003;105:167-172.

[32] Baltacıoğlu E, Akalin FA, Alver A, Deger O, Karabulut E. Protein carbonyl levels in serum and gingival crevicular fluid in patients with chronic periodontitis. *Archives of Oral Biology*. 2008;53:716-722.

- [33] Pradeep AR, Ramchandra prasad MV, Bajaj P, Rao NS, Agarwal E. Protein carbonyl: An oxidative stress marker in gingival crevicular fluid in healthy, gingivitis, and chronic periodontitis subjects. *Contemporary Clinical Dentistry*. 2013;4:27-31.
- [34] Nguyen TT, Ngo LQ, Promsudthi A, Surarit R. Salivary oxidative stress biomarkers in chronic periodontitis and acute coronary syndrome. *Clinical Oral Investigations*. 2017;21:2345-2353.
- [35] Takane M, Sugano N, Iwasaki H, Iwano Y, Shimizu N, Ito K. New biomarker evidence of oxidative DNA damage in whole saliva from clinically healthy and periodontally diseased individuals. *Journal of Periodontology*. 2002;73:551-554.
- [36] Canakci CF, Cicek Y., Yildirim A, Sezer U, Canakci V. (2009). Increased levels of 8-hydroxydeoxyguanosine and malondialdehyde and its relationship with antioxidant enzymes in saliva of periodontitis patients. *European journal of dentistry*. 2009;3:100-106.
- [37] Su H, Gornitsky M, Velly AM, Yu H, Benarroch M, Schipper HM. Salivary DNA, lipid, and protein oxidation in nonsmokers with periodontal disease. *Free Radical Biology and Medicine*. 2009; 46:914-921.
- [38] Sezer U, Erciyas K, Üstün K, Pehlivan Y, Ziya Şenyurt S, Aksoy N, Tarakçıoğlu M, Taysı S, Onat AM. Effect of chronic periodontitis on oxidative status in patients with rheumatoid arthritis. *Journal of Periodontology*. 2013;84:785-792.
- [39] Dede FO, Ozden FO, Avci B. 8-hydroxy-deoxyguanosine levels in gingival crevicular fluid and saliva in patients with chronic periodontitis after initial periodontal treatment. *Journal of Periodontology*. 2013;84:821-828.
- [40] Hendek MK, Erdemir EO, Kisa U, Ozcan G. Effect of initial periodontal therapy on oxidative stress markers in gingival crevicular fluid, saliva, and serum in smokers and non-smokers with chronic periodontitis. *Journal of Periodontology*. 2015;86:273-282.
- [41] Kurgan Ş, Önder C, Altıngöz SM, Bağış N, Uyanık M, Serdar MA, Kantarcı A. High sensitivity detection of salivary 8-hydroxy deoxyguanosine levels in patients with chronic periodontitis. *Journal of Periodontal Research*. 2015;50:766-774.
- [42] Zamora-Perez AL, Ortiz-García YM, Lazalde-Ramos BP, Guerrero-Velázquez C, Gómez-Meda BC, Ramírez-Aguilar MÁ, Zúñiga-González GM. Increased micronuclei and nuclear abnormalities in buccal mucosa and oxidative damage in saliva from patients with chronic and aggressive periodontal diseases. *Journal of Periodontal Research*. 2015;50:28-36.
- [43] Shin MS, Shin HS, Ahn YB, Kim HD. Association between periodontitis and salivary 8-hydroxydeoxyguanosine among Korean rural adults. *Community Dentistry Oral Epidemiology*. 2016;44:381-389.
- [44] Önder C, Kurgan Ş, Altıngöz SM, Bağış N, Uyanık M, Serdar MA, Kantarcı A, Günhan M. Impact of non-surgical periodontal therapy on saliva and serum levels of markers of oxidative stress. *Clinical Oral Investigations*. 2017;21:1961-1969.
- [45] Trivedi S, Lal N, Mahdi AA, Mittal M, Singh B, Pandey S. Evaluation of antioxidant enzymes activity and malondialdehyde levels in patients with chronic periodontitis and diabetes mellitus. *Journal of Periodontology*. 2014;85:713-720.
- [46] Brock GR, Butterworth CJ, Matthews JB, Chapple IL. Local and systemic total antioxidant capacity in

periodontitis and health. *Journal of Clinical Periodontology*. 2004;31:515-521.

[47] Chapple IL, Brock GR, Milward MR, Ling N, Matthews JB. Compromised GCF total antioxidant capacity in periodontitis: Cause or effect? *Journal of Clinical Periodontology*. 2007;34:103-110.

[48] Guentsch A, Preshaw PM, Bremer-Streck S, Klinger G, Glockmann E, Sigusch BW. Lipid peroxidation and antioxidant activity in saliva of periodontitis patients: Effect of smoking and periodontal treatment. *Clinical Oral Investigations*. 2008;12:345-352.

[49] Baltacıoğlu E, Yuva P, Aydın G, Alver A, Kahraman C, Karabulut E, Akalın FA. Lipid peroxidation levels and total oxidant/antioxidant status in serum and saliva from patients with chronic and aggressive periodontitis. Oxidative stress index: A new biomarker for periodontal disease?. *Journal of Periodontology*. 2014;85:1432-1441.

[50] Baser U, Gamsiz-Isik H, Cifcibasi E, Ademoglu E, Yalcin F. Plasma and salivary total antioxidant capacity in healthy controls compared with aggressive and chronic periodontitis patients. *Saudi Medical Journal*. 2015;36:856-861.

[51] Zhang T, Andrukhov O, Haririan H, Müller-Kern M, Liu S, Liu Z, Rausch-Fan X. Total antioxidant capacity and total oxidant status in saliva of periodontitis patients in relation to bacterial load. *Frontiers in Cellular and Infection Microbiology*. 2016;5:97.

[52] Ahmadi-Motamayel F, Goodarzi MT, Jamshidi Z, Kebriaei R. Evaluation of salivary and serum antioxidant and oxidative stress statuses in patients with chronic periodontitis: A

case-control study. *Frontiers in Physiology*. 2017;8:189.

[53] Gupta S, Chatterji D. Stress responses in mycobacteria. *IUBMB Life* 2005;57:149-159.

[54] Dos Vultos T, Mestre O, Tonjum T, Gicquel B. DNA repair in mycobacterium tuberculosis revisited. *FEMS Microbiology Reviews*. 2009;33:471-487.

[55] Nambi S, Long JE, Mishra BB, Baker R, Murphy KC, Olive AJ, Nguyen HP, Shaffer SA, Sassetti CM. The oxidative stress network of mycobacterium tuberculosis reveals coordination between radical detoxification systems. *Cell Host and Microbe*. 2015;17:829-837.

[56] Tyagi P, Dharmaraja AT, Bhaskar A, Chakrapani H, Singh A. Mycobacterium tuberculosis has diminished capacity to counteract redox stress induced by elevated levels of endogenous superoxide. *Free Radical Biology and Medicine*. 2015;84:344-354.

[57] Voskuil MI, Bartek IL, Visconti K, Schoolnik GK. The response of mycobacterium tuberculosis to reactive oxygen and nitrogen species. *Frontiers in Microbiology*. 2011;2:105.

[58] Dan Dunn J, Alvarez LA, Zhang X, Soldati T. Reactive oxygen species and mitochondria: A nexus of cellular homeostasis. *Redox Biology*. 2015;6:472-485.

[59] Lambeth JD. NOX enzymes and the biology of reactive oxygen. *Nature Reviews Immunology*. 2004;4:181-189

[60] Mohanty S, Jagannathan L, Ganguli G, Padhi A, Roy D, Alaridah N, Saha P, Nongthomba U, Godaly G, Gopal RK, Banerjee S. A mycobacterial phosphoribosyltransferase promotes bacillary survival by inhibiting oxidative stress and autophagy pathways in

macrophages and zebrafish. *Journal of Biological Chemistry*. 2015;290:13321-13343.

[61] Mohanty S, Dal Molin M, Ganguli G, Padhi A, Jena P, Selchow P, Sengupta S, Meuli M, Sander P, Sonawane A. Mycobacterium tuberculosis EsxO (Rv2346c) promotes bacillary survival by inducing oxidative stress mediated genomic instability in macrophages. *Tuberculosis*. 2016;96:44-57.

[62] Chao WC, Yen CL, Hsieh CY, Huang YF, Tseng YL, Nigrovic PA, Shieh CC. Mycobacterial infection induces higher interleukin-1 β and dysregulated lung inflammation in mice with defective leukocyte NADPH oxidase. *PloS One*. 2017;12:e0189453.

[63] Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clinical Microbiology Reviews*. 2011;24:557-591.

[64] Klein M, Koedel U, Pfister HW. Oxidative stress in pneumococcal meningitis: A future target for adjunctive therapy?. *Progress in Neurobiology*. 2006;80:269-280.

[65] Mitchell TJ. Virulence factors and the pathogenesis of disease caused by *Streptococcus pneumoniae*. *Research in Microbiology*. 2000;151:413-419.

[66] Braun JS, Sublett JE, Freyer D, Mitchell TJ, Cleveland JL, Tuomanen EI, Weber JR. Pneumococcal pneumolysin and H₂O₂ mediate brain cell apoptosis during meningitis. *The Journal of clinical investigation*. 2002;109:19-27.

[67] Kastenbauer S, Koedel U, Becker BF, Pfister HW. Oxidative stress in bacterial meningitis in humans. *Neurology*. 2002;58:186-191.

[68] Correa P, Cuello C, Duque E, Burbano LC, Garcia FT, Bolanos O,

Brown C, Haenszel W. Gastric cancer in Colombia. III. Natural history of precursor lesions. *Journal of the National Cancer Institute*. 1976;57:1027-1035.

[69] Naito Y, Yoshikawa T. Molecular and cellular mechanisms involved in helicobacter pylori-induced inflammation and oxidative stress. *Free Radical Biology and Medicine*. 2002;33:323-336.

[70] Reshi ML, Su YC, Hong JR. RNA viruses: ROS-mediated cell death. *International journal of cell biology*. 2014;2014.

[71] Malvy DJ, Richard MJ, Arnaud J, Favier A, Amédée-Manesme O. Relationship of plasma malondialdehyde, vitamin E and antioxidant micronutrients to human immunodeficiency virus-1 seropositivity. *Clinica Chimica Acta*. 1994;224:89-94.

[72] Fuchs J, Emerit I, Levy A, Cernajvski L, Schöfer H, Milbradt R. Clastogenic factors in plasma of HIV-1 infected patients. *Free Radical Biology and Medicine*. 1995;19:843-848.

[73] Peterhans E. Reactive oxygen species and nitric oxide in viral diseases. *Biological Trace Element Research*. 1997;56:107-116.

[74] Sprietsma JE. Zinc-controlled Th1/Th2 switch significantly determines development of diseases. *Medical Hypotheses*. 1997;49:1-14.

[75] Boya P, de la Peña A, Belouqui O, Larrea E, Conchillo M, Castelruiz Y, Civeira MP, Prieto J. Antioxidant status and glutathione metabolism in peripheral blood mononuclear cells from patients with chronic hepatitis C. *Journal of Hepatology*. 1999;31:808-814.

[76] De Maria N, Colantonl A, Fagioli S, Liu GJ, Rogers BK, Farinati F,

- Van Thiel DH, Floyd RA. Association between reactive oxygen species and disease activity in chronic hepatitis C. *Free Radical Biology and Medicine*. 1996;21:291-295.
- [77] Bianchi GP, Marchesini G, Brizi M, Rossi B, Forlani G, Boni P, Melchionda N, Thomaseth K, Pacini G. Nutritional effects of oral zinc supplementation in cirrhosis. *Nutrition Research*. 2000;20:1079-1089.
- [78] Rajopadhye HS, Mukherjee RS, Chowdhary SA, Dandekar PS. Oxidative stress markers in tuberculosis and HIV/TB co-infection. *Journal of Clinical and Diagnostic Research*. 2017;11:24-28.
- [79] Andresen M, Regueira T, Bruhn A, Perez D, Strobel P, Dougnac A, Marshall G, Leighton F. Lipo peroxidation and protein oxidative damage exhibit different kinetics during septic shock. *Mediators of Inflammation*. 2008;2008:168652.
- [80] Kastenbauer S, Koedel U, Becker BF, Pfister HW. Oxidative stress in bacterial meningitis in humans. *American Academy of Neurology* 2002;58: 186-191.
- [81] Camini CF, da Silva Caetano CC, Almeida TL, de Brito Magalhaes LC. Implications of oxidative stress on viral pathogenesis. *Archives of Virology*. 2017;162:907-917.
- [82] Bavunoglu I, Genc H, Konukoglu D, Cicekci H, Sozer V, Gelisgen R, Uzun H oxidative stress parameters and inflammatory and immune mediators as markers of the severity of sepsis. *Journal of Infection in Developing Countries*. 2016;10:1045-1052.
- [83] Augusto AC, Miguel F, Mendonça S, Pedrazzoli Jr J, Gurgueir SA. Oxidative stress expression status associated to helicobacter pylori virulence in gastric diseases. *Clinical Biochemistry*. 2007;40:615-622.
- [84] Pincemai J, Cavalier E, Charlier C, Cheramy-Bien J P, Brevers E, Courtois A, Fadeur M, Meziane S, Goff C L, Misset B, Albert A, Defraigne J O, Rousseau A F. Oxidative Stress status in COVID-19 patients hospitalized in Intensive Care Unit for Severe Pneumonia. A Pilot Study. *Antioxidants* 2021;10:257.
- [85] Diaz-Ochoa V, Jellbauer S, Klaus S, Raffatellu M. Transition metal ions at the crossroads of mucosal immunity and microbial pathogenesis. *Frontiers in Cellular and Infection Microbiology*. 2014;4:2.
- [86] Deriu E, Liu JZ, Pezeshki M, Edwards RA, Ochoa RJ, Contreras H, Libby SJ, Fang FC, Raffatellu M. Probiotic bacteria reduce salmonella typhimurium intestinal colonization by competing for iron. *Cell Host and Microbe*. 2013;14:26-37.
- [87] Skaar EP, Humayun M, Bae T, DeBord KL, Schneewind O. Iron-source preference of *Staphylococcus aureus* infections. *Science*. 2004;305:1626-1628.
- [88] Bahl N, Du R, Winarsih I, Ho B, Tucker-Kellogg L, Tidor B, Ding JL. Delineation of lipopolysaccharide (LPS)-binding sites on hemoglobin: From in silico predictions to biophysical characterization. *Journal of Biological Chemistry*. 2011;286:37793-37803.
- [89] Bodet C, Chandad F, Grenier D. Hemoglobin and LPS act in synergy to amplify the inflammatory response. *Journal of Dental Research*. 2007;86:878-882.
- [90] Liepke C, Baxmann S, Heine C, Breithaupt N, Ständker L, Forssmann WG. Human hemoglobin-derived peptides exhibit antimicrobial activity: A class of host defense

peptides. *Journal of Chromatography B*. 2003;791:345-356.

[91] Hao K, Hanawa H, Ding L, Ota Y, Yoshida K, Toba K, Ogura M, Ito H, Kodama M, Aizawa Y. Free heme is a danger signal inducing expression of proinflammatory proteins in cultured cells derived from normal rat hearts. *Molecular Immunology*. 2011;48:1191-1202.

[92] Yang H, Wang H, Bernik TR, Ivanova S, Wang H, Ulloa L, Roth J, Eaton JW, Tracey KJ. Globin attenuates the innate immune response to endotoxin. *Shock*. 2002;17:485-490.

[93] Su D, Roth RI, Yoshida M, Levin J. Hemoglobin increases mortality from bacterial endotoxin. *Infection and Immunity*. 1997;65:1258-1266.

[94] Çimen MB. Free radical metabolism in human erythrocytes. *Clinica Chimica Acta*. 2008;390:1-11.

[95] Tatsuro Y, Prudent M, D'Alessandro A. Red blood cell storage lesion: Causes and potential clinical consequences. *Blood Transfusion*. 2019;17:27-52.

[96] Ahn J, Johnstone RM. Synthesis of the transferrin receptor in peripheral sheep reticulocytes: evidence for incomplete oligosaccharide processing. *Red Blood Cell Aging*. Springer, Boston, MA. 1991:3-13

[97] Nash GB, Wyard SJ. Changes in surface area and volume measured by micropipette aspiration for erythrocytes ageing in vivo. *Biorheology*. 1980;17:479-484

[98] Bosman GJCGM, Werre JM, Willekens FLA, Novotný VMJ. Erythrocyte ageing in vivo and in vitro: Structural aspects and implications for transfusion. *Transfusion Medicine*. 2008;18:335-347.

[99] Bosman GJCGM, Willekens FLA, Werre JM. Erythrocyte aging: A more than superficial resemblance to apoptosis?. *Cellular and Physiological Biochemistry*. 2005;16:1-8.

[100] Belo L, Rebelo I, Castro EM, Catarino C, Pereira-Leite L, Quintanilha A, Santos-Silva A. Band 3 as a marker of erythrocyte changes in pregnancy. *European Journal of Haematology*. 2002;69:145-151.

[101] Ciccoli L, Rossi V, Leoncini S, Signorini C, Blanco-Garcia J, Aldinucci C, Buonocore G, Comporti M. Iron release, superoxide production and binding of autologous IgG to band 3 dimers in newborn and adult erythrocytes exposed to hypoxia and hypoxia-reoxygenation. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 2004;1672:203-213.

[102] Rossi V, Leoncini S, Signorini C, Buonocore G, Paffetti P, Tanganelli D, Ciccoli L, Comporti M. Oxidative stress and autologous immunoglobulin G binding to band 3 dimers in newborn erythrocytes. *Free Radical Biology and Medicine*. 2006;40:907-915.

[103] Huang YX, Wu ZJ, Mehrishi J, Huang BT, Chen XY, Zheng XJ, Liu WJ, Luo M. Human red blood cell aging: Correlative changes in surface charge and cell properties. *Journal of Cellular and Molecular Medicine*. 2011;15:2634-2642.

[104] Igbokwe IO, Esievo KA, Saror DI, Obagaiye OK. Increased susceptibility of erythrocytes to in vitro peroxidation in acute *Trypanosoma brucei* infection of mice. *Veterinary Parasitology*. 1994;55:279-286.

[105] Hotz MJ, Qing D, Shashaty MG, Zhang P, Faust H, Sondheimer N, Rivella S, Worthen GS, Mangalmurti NS. Red blood cells homeostatically bind mitochondrial

DNA through TLR9 to maintain quiescence and to prevent lung injury. *American Journal of Respiratory and Critical Care Medicine*. 2018;197:470-480.

[106] Neote K, Darbonne W, Ogez J, Horuk R, Schall TJ. Identification of a promiscuous inflammatory peptide receptor on the surface of red blood cells. *Journal of Biological Chemistry*. 1993;268:12247-12249.

[107] Darbonne WC, Rice GC, Mohler MA, Apple T, Hébert CA, Valente AJ, Baker J. Red blood cells are a sink for interleukin 8, a leukocyte chemotaxin. *The Journal of clinical investigation*. 1991;88:1362-1369.

[108] Anderson HL, Brodsky IE, Mangalmurti NS. The evolving erythrocyte: Red blood cells as modulators of innate immunity. *The Journal of Immunology*. 2018;201:1343-1351.

[109] Minasyan H. Erythrocyte and blood antibacterial defense. *European Journal of Microbiology and Immunology*. 2014;4:138-143.

[110] de Oliveira YPA, Pontes-de-Carvalho LC, Couto RD, Noronha-Dutra AA. Oxidative stress in sepsis. Possible production of free radicals through an erythrocyte-mediated positive feedback mechanism. *The Brazilian Journal of Infectious Diseases*. 2017;21:19-26.

[111] Moisă E, Negoită S, Corneci D. Understanding red blood cell rheology in sepsis and its role in clinical practice. From biomolecular aspects to possible therapeutic interventions. *Central European Journal of Clinical Research*. 2018;1:40-58.

[112] Larsen R, Gozzelino R, Jeney V, Tokaji L, Bozza FA, Japiassú AM, Bonaparte D, Cavalcante MM, Chora Â,

Ferreira A, Marguti I. A central role for free heme in the pathogenesis of severe sepsis. *Science Translational Medicine*. 2010;2:51ra71.

[113] Peterhans E, Grob M, Burge TH, Zanoni R. Virus-induced formation of reactive oxygen intermediates in phagocytic cells. *Free radical research communications*. 1987 Jan 1;3(1-5):39-46.

[114] Vierucci A, De Martino M, Graziani E, Rossi ME, London WT, Blumberg BS. A mechanism for liver cell injury in viral hepatitis: Effects of hepatitis B virus on neutrophil function in vitro and in children with chronic active hepatitis. *Pediatric Research*. 1983;17:814-820.

[115] Müller F. Reactive oxygen intermediates and human immunodeficiency virus (HIV) infection. *Free Radical Biology and Medicine*. 1992;13:651-657.

[116] Belding ME, Klebanoff SJ, Ray CG. Peroxidase-mediated virucidal systems. *Science*. 1970;167:195-196.

[117] Russell RJ, Kerry PS, Stevens DJ, Steinhauer DA, Martin SR, Gamblin SJ, Skehel JJ. Structure of influenza hemagglutinin in complex with an inhibitor of membrane fusion. *Proceedings of the National Academy of Sciences*. 2008;105:17736-17741.

[118] DeMartino AW, Rose JJ, Amdahl MB, Dent MR, Shah FA, Bain W, McVerry BJ, Kitsios GD, Tejero J, Gladwin MT. No evidence of hemoglobin damage by SARS-CoV-2 infection. *Haematologica*. 2020;105:2769-2773.

[119] Trefler S, Rodriguez A, Martin-Loeches I, Sanchez V, Marina J, Llauro M, Romeu M, Diaze E, Nogues R, Giralt M. Oxidative stress in

immunocompetent patients with severe community-acquired pneumonia. A pilot study. *Medicina Intensiva*. 2014;38:73-82.

[120] Minasyan H. Sepsis and septic shock: Pathogenesis and treatment perspectives. *Journal of Critical Care*. 2017;40:229-242.

IntechOpen

IntechOpen