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Oxidative Stress in Immunotoxicity: A Biochemical Foe or a Friend?

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Abstract:-The interplay between free radicals and antioxidant has gained a greater research momentum owing to their implication in the pathophysiology of several pathologies. Even though these chemical species have high reactivity and cause damage, they are still essential components of certain biological processes that occur at molecular level including immune function. The functions of such chemical species in immunotoxicity; the beneficial and detrimental effects in immune response remain the central focus of this review. Nature has put in place a system for defense which if compromised will increase the susceptibility of the body to disease-causing agents. The mechanisms of selected free radicals that mediate immune function in a myriad of medical conditions is the subtheme in this short review.

Keywords:- *Oxidative Stress, Immunotoxicity, Immune Response.*

I. INTRODUCTION

The interplay between free radicals and antioxidant has gained a greater research momentum recently. Probably owing to their implication in the pathophysiology of several pathologies [48, 93, 13, 16, 42, 87, 62, 67, 65, 84]. Even with the growing interest on studies relating to oxidative stress and their implications in certain pathologies, it is worthy of note that free radical-induced damage may not necessarily be the primary cause of such diseases. Some believe also that free radicals are beneficial despite their implications in various metabolic dysfunctions. It therefore means there is a given threshold below or above which oxidative stress could either become beneficial or detrimental. Thus, the need for elucidating the mechanisms of action of the biochemical antidote agents-"antioxidants" for these agents continues to attract more attention every now and then. The damage to cellular macromolecules and tissues caused by free radicals is known as oxidative stress. Such damage can be effectively controlled by a functional antioxidant system that maintains a balanced redox state necessary for normal tissue homeostasis. Reactive oxygen species (ROS) is the collective term used to describe oxygen atom carrying charges and other oxygen atoms carrying no charges that can easily form free radicals and/or cause damage to cellular components and tissues. Examples of oxygen atoms carrying charges include hydroxyl ($OH^{\cdot}$) and superoxide anion ($O_2^{-\cdot}$); and the oxygen atoms carrying no charges include hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl). However, there are other groups that contain nitrogen atoms that have been shown to induce oxidative damage to cellular constituents as well [34]. The above listed are said to contain unpaired electron (s) in their outermost shell, thus named free radicals. Even though these chemical species have high reactivity and cause damage, they are still essential components of certain biological processes [75]. Free radicals modulate the sulphydry (SH) groups of antioxidant enzymes and other regulatory proteins [19, 70]. The biochemical processes taking place in the mitochondria, peroxisome and cytochrome P450 of a living cell lead to the formation of these chemical species [65]. Inability of the body system to scavenge these chemical species using its antioxidants potentiates the chemical imbalance known as oxidative stress [33], characterized by oxidative damage to cellular molecules. The extent to which ROS damage the cellular constituents depends on its concentration, cell type, and the time frame of the oxidative stress. At relatively low concentration, ROS activates mitogenic proliferation; high concentration of ROS can result in cellular necrosis or apoptosis; and growth arrest or senescence results at moderate concentration of ROS. However, a high concentration of oxygen atoms carrying charges does not induce cellular damage due to the intrinsic mechanisms that prevent and repair such damage, according to a hypothesis [84]. Weidinger and Kozlov [92] affirmed that reactions of free radicals can be reversed and such reactions are crucial for signaling within cells. Some antioxidants have no direct effect on these groups of atoms carrying charges and their activities within a living cell, but instead modulate some signaling pathways of cells [3]. There is variability in the mechanism and structure of antioxidant [84], and this is characterized by their different modulatory effects on disease as they tend to have ameliorative effect on some oxidative-stress induced diseases, while on others, they aggravate the condition. Sayin *et al.* [73] observed that antioxidants stimulate tumour growth and increase the risk of metastasis [63]. Low levels of free radicals might be the cause of diabetes mellitus and not oxidative stress itself [91], although others have reported the implication of oxidative damage in the disease [47, 10, 20, 46, 72]. Antioxidants that target mitochondrial-induced oxidative stress can decrease inflammation and damage of organ in a model of animal [45]. Agents that can neutralize the damaging effects of free radicals and other molecules capable of generating free

radicals via maintenance of tissue homeostasis are known as antioxidants [1]. The oxidative damage caused by ROS can be effectively controlled by a functional antioxidant system that maintains a balanced redox state necessary for normal tissue homeostasis [65]. A natural defense mechanism has evolved to mop up these free radicals in order to maintain chemical balance between antioxidants and free radicals [65, 1]. Superoxide dismutase, glutathione, catalase, retinol, glutathione peroxidase/reductase, vitamin C, thioredoxin, vitamin E, etc. are antioxidants [65]. Many scientific works have reported the failure of these free radical-mopping up molecules to prevent some diseases despite the increased scientific interest in understanding the beneficial roles of antioxidants [84].

II. ROLE OF IMMUNE SYSTEM IN CENTRAL DEFENSE

The human body has been naturally built to protect itself from dangerous external and internal agents [52]. Several components which unite in protecting man against harmful substances make up the immune system [52]. The immune system works together with endocrine, nervous, and cardiovascular systems [52]. The intrinsic capacity of an immune system enables it to discern cells of the body from those which are foreign [5, 80, 52]. The viral disease, acquired immune deficiency syndrome (AIDS) clearly illustrates the importance of an effective immune system. An immune response is often elicited by a stimulus, and such response leads to a cascade of different reactions. A typical illustration of such is the immune response elicited by the specific binding of antigens to immune receptors [2]. In the same way, any agitation in other systems of the body affects the immune system. Leukocytes and other cells of common origin bring about immunity. In addition to cells, immune system comprises the lymphoid organs. Protective immunity is mediated by the various cells of the spleen, the largest lymphoid organ [15]. The spleen can generate, and store immune cells that drive humoral and cellular responses [82]. An immune response may be innate or acquired. The first line of protection against foreign agents is the innate immunity [2, 43]. The immune response elicited during a re-encounter with a particular foreign substance is the acquired immunity [66, 37].

The humoral and cellular immune systems are the two complementary systems of the immune response. Humoral immunity protects the body against disease-causing agents and it is mediated by soluble proteins which mark and destroy such pathogens [82, 15]. On the other hand, cell-mediated immunity is carried out by various T-cells [2, 28]. T-cells occupy a central position in the regulation of immune response. Cells of the T-lymphocytes are the master regulators of the immune response. The assessment tests for possible immunotoxicants stemmed from interaction of T-cells.

For further knowledge of the relevance of T-cells in tumour surveillance, transplantation rejection, among others, see the reviews of Gerloni and Zanetti [22], Hayakawa and Smyth [24] and Romero et al. [69]. Cytokines (tumour necrosis factor-alpha, interferon-gamma and interleukins) which are cellular messengers required for the modulation of immune response become increased in aflatoxin B1-induced oxidative stress [41, 44]. Cytokines are specific cell recruiting messengers. Some cytokines stimulate the production of immunoglobulins whereas others inhibit such production to prevent damage of host tissue. The production of cytokines is in relatively low concentration and their activity is at the site of production [40]. The largest immune cells called macrophages are involved in the phagocytosis and ingestion of foreign pathogens during inflammation [98]. Various types of cancer cells including other infected cells are destroyed *in vitro* by another group of lymphocytes known as natural killer cells [69, 21, 27]. T-cells play crucial role in protection against certain pathogens during which respiratory burst that releases free radicals takes place [71, 39].

III. THE IMPLICATION OF OXIDATIVE STRESS IN IMMUNOTOXICITY

The adverse effect to which the immune system is subjected when exposed to harmful agents is termed immunotoxicity [31]. Immunotoxicity is charcterized either by a suppressed immune response, or an upregulated immune response [8]. Immunotoxicity takes place due to hypersensitivity,autoimmunity, and immunosuppression arising from the damaging effects of substances that modulate the physiologic activities of the immune system. The administration of immunosuppressive drugs during transplant is another form of immunotoxicity. High morbidity and mortality are associated with the continuous exposure to such immunotoxicants, making them a high risk to human health [56]. The extensive review by Rodney [68] highlighted some risk factors of immunotoxicity. Immunotoxicants bring about bioactivation of cytochrome P450, induction of lipid peroxidation, formation of DNA adducts, inhibition of ATP production, apoptosis of haematopoietic stem cells and immune cells, alteration in immunoglobulins and alteration of cell cycle [77]. A typical immunotoxicant such as aflatoxin B1 brings about dysregulation of Nrf2 signaling pathway [89, 90] as a result of its ability to form free radicals, cause cell death in humans and other animals [77]. Chemicals disrupt immune functions through several mechanisms. Oxidative stress, alteration in homeostasis of calcium, and programmed cell death are some mechanisms through which chemicals disrupt immune functions [78]. Atrazine is one chemical which induces immunotoxicity via Fas-mediated apoptosis among splenocytes [99]. Two week treatment of mice with atrazine via oral route was reported to be immunotoxic as characterized by a significant increase in $CD8^+$ T-cells and a concurrent reduction in spleen with respect to its mass, its cells and overall mass of the thymus [30]. Atrazine-induced immunosuppression is of great concern because it increases the risk for contracting disease [78]. Another typical pesticide known to induce oxidative stress, neurotoxicity and immunotoxicity is endosulfan [29, 58]. Endosulfan at 8 and 16mg/kg doses significantly suppressed interferon (IFN-gamma) and cytokine (IL-4) levels [58].

A correlation has been shown to exist between free radical-induced damage and a compromised immune response based on animal studies [23]. Sies *et al.* [79] opined that oxidative stress is not only a pathophysiological process in inflammatory response that damages cellular macromolecules, but also a vital biological process that enhances immune system to handle pathogens and cell signaling. The formation of free radicals is an essential process in immune response because they are used to destroy foreign particles and adsorbed contaminants by phagocytes. The oxidative burst due to formation of free radicals is a mechanism utilized by innate immune cells for defense against disease-causing agents [17, 50, 57, 35, 85]. The activity of phagocytes is measured by the level of ROS generation. ROS despite their damage promoting effects have however been shown to be an emerging central signaling molecule in recent studies [9]. Mitochondria perform crucial function in ROS signaling, apoptotic process, and innate immunity [76]. Mitochondria modulate the fission and fusion activities necessary for the development of T-cells towards memory or effector phenotypes [7]. T-cells utilize oxidative phosphorylation and ROS for their activation [9], and they can either use oxidative phosphorylation or glycolysis for proliferation. Upregulated autophagy, decreased ATP and impaired redox homeostasis have been observed in rheumatoid arthritis [96, 97]. Increased cardiolipin has been reported in multiple sclerosis [88]. Monocyte activation and adhesion was upregulated by the expression of intercellular adhesion molecule which results from a compromised integrity of mitochondria within the endothelial cells secreting pro-inflammatory cytokines [11]. Abnormal generation of nitric oxide (NO) from monocytes [51] correlates with the elevated ROS production in systemic lupus erythematosus [21]. The substantial downregulation of ROS during hepatitis B virus infection is due to the concentration of various cellular processes on mitochondria [9]. Cells of the epithelium are metabolized when under stress via the binding of specific receptors that prevent mitochondrial damage and apoptosis of such cells, a process mediated by innate immunity [81]. ROS triggers inflammation through binding with specific receptors [74]. Such binding is necessary for the immune cells to ward off disease-causing agents or elicit inflammation. ROS induction via NADPH oxidase complex is common with the most abundant circulating white blood cells known as polymorphonuclear leukocytes (PMNs) [38, 50]. The phagocytic effect of PMNs on opsonized bacteria enhances the production of ROS [54]. The cytosolic domain of NADPH oxidase gains electrons from NADPH to form superoxide anion by transferring the electrons across the membrane [14, 55, 60, 18]. Infections by the bacterium, *Staphylococcus aureus* can be effectively killed by phagocytes [12, 83]. This phagocytosis is enhanced by the different free radicals generated by leukocytes. These reactive species modulate the macromolecules of cells causing defective growth [94], which the bacterium now easily evades. NADPH oxidase and myeloperoxidase (MPO) mediate the functioning of neutrophil, a phagocyte against *S. aureus.* The activity of MPO during oxidative burst forms special traps of neutrophils [59, 61]. Defective ROS generation favours bacterial survival and repetitive colonization of different types of tissue [4, 26, 86, 25, 36, 95]. The generation of free radicals may probably account for their downstream antibacterial activities, and not necessarily the damage caused by reactive species directly [49]. Binding of intercellular adhesion molecule-1 to β2 integrin during the movement of neutophils is inadequate to generate free radicals [32], illustrating the involvement of other factors in regulating NADPH oxidase in disease conditions. Nauseef [53] observed that the release of granule protease facilitates neutrophil migration and it is also partially involved in the activity of neutrophil and other enzymes against microbes. The oxidative burst during inflammation is potentiated by the formation of singlet oxygen anion radical and nitric oxide. Neurotransmission and immunity are some of the biological processes where the reactive nitrogen species, nitric oxide plays crucial roles as signaling molecule [6].

IV. CONCLUSION

One of the ways of inducing immunotoxicity is free radical-induced stress and its implication herein is not always detrimental. Some of the free radicals being generated confer beneficial roles in their fight against foreign invaders depending on their concentration. It therefore becomes necessary to further elucidate the particular threshold above or below which supplementary antioxidants should be used to ameliorate immunotoxicity potentiated by oxidative stress.

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