Chapter

Reactive Oxygen Species in the Development and Resolution of Autoimmune and Inflammatory Disease

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Abstract

Reactive oxygen species (ROS) have been associated with a wide variety of human diseases and disorders. The ability of these molecules can incapacitate antioxidant activity leading to an imbalance between oxidants and anti-oxidants, with the latter being more pronounced. ROS are no strangers to immune cell relationships and function and consequently the development of autoimmune and inflammatory diseases. The collateral damage of excessive ROS (collectively called Oxidative stress) to the cells or tissue due to nucleic acid damage and oxidation of macromolecules such as proteins and lipids is linked to the manifestation, malfunction and translation to the disease state of cells. Contrary to this view, recent studies have shown that ROS have protective roles in certain autoimmune and inflammatory diseases. Despite significant advances in our understanding of inflammatory and autoimmune diseases, therapeutics for these diseases still need further development and identification of new targets for improved therapeutic effect. ROS molecules and inflammation modulators appear before disease development making them great therapeutic targets with the potential to inhibit disease manifestation.

Keywords: reactive oxygen species, antioxidants, immune cell, autoimmune, inflammatory disease, oxidative stress

1. Introduction

1.1 Reactive oxygen species

Reactive Oxygen Species (ROS) are by-products of chemical reactions that involve a one-electron reduction of oxygen, leading to the production of a diatomic oxygen radical known as superoxide. Superoxide serves as a precursor for multiple ROS generation. The oxygen anion can be produced mainly by enzymatical or non-enzymatical means. Enzymes such as Phagocytic Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH Oxidase), cytochrome P450–dependent oxygenase,

and the proteolytic conversion of cytosolic Xanthine dehydrogenase can produce singlet-oxygen molecules [1, 2]. The enzymatic generation of superoxide is the main generator of superoxide, especially NADPH oxidase. However, non-enzymatic generation can also cause a significant increase in reactive species. This occurs mostly in the mitochondria during ATP synthesis. The electron transport chain (ETC) has been reported to consist of centers that can leak electrons to oxygen, thereby causing a reduction of the oxygen [1]. Additionally, reduced coenzymes and prosthetic groups such as flavins and metal ions can directly transfer an electron to oxygen. The produced singlet-oxygen undergoes dismutation, catalyzed by the enzyme superoxide dismutase, to produce hydrogen peroxide, a more stable and less reactive molecule. The increased availability of ROS can lead to an imbalance between oxidants and antioxidants, resulting in a state that is known as oxidative stress [2]. During this state, the various deleterious effects of ROS such as disruption of cellular homeostasis, structures and function are manifested in the cell. Therefore, ROS overproduction has a pathological role in the development of various conditions and diseases, including inflammation and autoimmune disease.

1.2 Inflammation

Inflammation is a none-specific immune response of cells or tissues to a stimulus such as a pathogen, cell damage, or toxicity that plays an important role in host defense. This response involves the signaling molecules, immune cells and blood vessels. The process is marked by the proliferation of inflammatory cells like monocytes, neutrophils, and lymphocytes. These cells release various molecules such as ROS, pro-inflammatory cytokines and various enzymes that have the ability to induce oxidative stress in the target tissues [3]. Therefore, inflammation and oxidative stress can co-occur, and one process can induce the other and vice versa.

Inflammatory responses can be complex as they involve multiple interactions of many cells and mediators. There are four major patterns of inflammatory response that are also common mechanisms of diseases. These patterns depend on the type of hypersensitivity. Two or more types of hypersensitivity can occur at once in a patient.

1. Type 1: This type of hypersensitivity is mediated by immunoglobulin (Ig) E that is found on the surface of mast cells. The interaction between this antibody and a respective antigen causes the release of inflammation mediators such as serotonin and histamine, among others. The release of these molecules causes diminished blood pressure due to vasodilation, increased vascular endothelium permeability, and bronchoconstriction [4]. Interestingly, increased activation of mast cells can cause a systemic response that causes anaphylactic shock. Mediators that are released by mast cells can also recruit inflammatory cells such as eosinophils and increase the production of PAF, leukotrienes, prostaglandins and cytokines like TNF-α, IL-1, IL-3 and IL-5 [5]. This results in a sustained inflammatory response and reduces transient respiratory efficiency.

2. Type 2: This type of hypersensitivity is triggered by the binding of antibodies, IgG and IgM to the cellular antigens, causing tissue destruction. The binding of antibodies results in lysis of the cell via the in-situ fixation complement. Ig M is an effective inducer of this process [5]. Fixation of complement is an important cause of cell injury, and it can cause opsonization as well as being an active recruiter of inflammatory cells.

3. Type 3: This is heavily marked by serum sickness due to increased circulating immunocomplexes. The deposition of these immunocomplexes can lead to injury at the site of deposition (usually vascular beds). This is because the complexes are efficient activators of the classical pathway of the complement cascade [6]. The properties of the complexes determine which vascular bed they are deposited in. This deposition is precise and distinct in pathophysiology of different diseases such chronic autoimmune diseases such as systemic lupus erythematosus [5, 6]. Certain inflammatory responses have a confection of features of type 2 and type 3 hypersensitivity.

4. Type 4: This type of hypersensitivity usually takes longer to occur after antigen exposure and is also referred to as delayed-type hypersensitivity. It is typified by antigen-specific T cells activation after 24–48 hours of exposure to antigen. The antigens modify cellular proteins and these proteins are targeted by T cells. CD8+ T cells interact with the antigen presented by MHC-I and become activated [7]. This causes the T cell to kill all the cells that are presenting that antigen. Antigen-presenting cells also display antigens via the MHC-II that activates CD4+ T cells and causes the release of cytokines [5]. Activation of the two T cell activation leads to an increase in antigen-specific response, leading to hypersensitivity reaction over time. In some events, an immediate inflammatory response is initiated due to a positive response. The positive response occurs when the T cells are pre-primed as a result of prior ongoing exposure to the pathogenic antigen [6]. During this event, the interaction between the T cells and macrophages causes the release of TNF- and IFN, which are responsible for the inflammatory response. Other types of hypersensitivity responses that are triggered by cellular components of the immune system can also be referred to as type 4 even without being antigen specific (**Table 1**).

Inflammation is triggered to eliminate harmful agents so as to minimize the effects of the injuries. However, minimal inflammation (acute inflammation) usually does not inhibit these effects and prolonged inflammation (chronic inflammation) is associated with multiple diseases and conditions [3]. Acute inflammation is known to be part of the innate immune response as it is the initial response to a stimulus. In this phase of inflammation, platelets and granulocytic cells like basophils, eosinophils and mast cells are activated. These cells migrate from the blood vessels to the site of injury and release molecules that initiate, stimulate and attenuate inflammation for a short period [8]. For this to occur, the blood vessel becomes more permeable, consequently leading to the escape of proteins, outflow of fluids known as exudate and migration of other blood cells from the vessels to the site of inflammation, causing a swelling known as edema on the site. Neutrophils are the primary cells during this phase and they tend to engulf the foreign materials and organisms together with other debris. As neutrophils are short-lived cells, they are replaced by monocytes that differentiate into macrophages [8]. The acute phase usually resolves after hours or days, or even within a week. The persistent presence of monocytic cells due to ongoing and long-term response to stimuli leads to the development of chronic inflammation.

During chronic inflammation, there is a continuous accumulation of macrophages and lymphocytes at the site of inflammation due a persistent stimulus from the immune system [9]. The prolonged inflammatory response that might last for a week, months and in some cases a lifetime, will eventually lead to tissue injury. This can be induced by viral or certain bacterial infection and in some individuals,

Type	Mediator	Components	Antigen & Antibody	Principle	Phenotype	Time/Period	Example
1	IgE	Mast cells, Basophils, Histamine	Antigen: exogenous, free in circulation Antibody: fixed on mast and basophil cells	Destruction of cells via antibody mediated degranulation of granulocytes.	Weal and Flare	Early ≤3 hours	Asthma, Bee sting, Rhinitis
2	IgG/IgM	Neutrophils, Complement system components	Antigen: endogenous or exogenous, fixed on cells Antibody: Free in circulation	Annihilation of normal tissue cells via antibody mediated pathway.	Lysis and Necrosis	Intermediated 5–8 hour	Rhesus hemolytic disease, autoantigen-induced cell damage, Drug-induced anemia
3	IgG/IgM	Compliment system components, Phagocytes, Killer cells	Antigen: free in circulation, with exogenous or endogenous origin Antibody: free in circulation	Antigen–antibody complex mediated cell death	Erythema and Edema	Early - Intermediate depending on stimulant 2–8 hours	SLE, Lung arthritis, glomerulonephritis, vasculitis
4	$CD4^+$ Th cells, $CD8^+$ Tc cells	Antigen presenting cells (APC), Macrophages, Cytokines	Antigen: from exogenous or endogenous sources, soluble or fixed on cell. Antibody: none	T lymphocytes mediated cell damage	Erythema and Induration	Delayed ≥ 24 hrs from stimulation	Granuloma formation, Diabetes Mellitus,

Table 1.
Summary of types of hypersensitivity.

genetic polymorphism of inflammation mediators and cell receptors can also induce and favor extensive chronic inflammation [10]. In addition to the accumulation of macrophages, chronic inflammation is also marked by the proliferation of fibroblasts and small blood vessels. In rare cases when the inflammatory response encounters an agent that is difficult to eliminate, the response proceeds to granulomatous inflammation.

Granulomatous inflammation is a specific type of chronic inflammation that is marked by the presence of crystalline materials embedded into the tissues. Macrophages are the predominant effectors and they are recruited by T cells. Th1 cells have been reported to be the major mediators of granulomatous inflammation reactions [11]. Following the activation of Th1 cells by the antigens presented on MHC-II on the macrophages, Th1 secretes IFN-γ and other cytokines. These molecules then transform macrophages into activated tissue macrophages. Although the activated macrophages have increased capacity to eliminate foreign pathogens, they have a tendency to fuse and form multinucleated giant cells which forms concentric nodules that are known as granulomas [12]. Central necrosis can develop in these granulomas. This phenomenon has have been observed in infections caused by *M. tuberculosis* and other pathogens [13]. Such a phenomenon has also been reported in some autoimmune diseases.

Although inflammation is an essential process to the host defense, it can easily induce excessive tissue damage, resulting in acute or chronic tissue damage, organ or system dysfunction with fatal outcomes. Studies have shown increasing evidence of the involvement of chronic inflammation in autoimmune diseases, including but not limited to rheumatoid arthritis (RA), inflammatory bowel disease (IBD) systemic lupus erythematosus (SLE), gout, and diabetes [14]. This happens when inflammatory activity causes the production of autoimmune molecules and reactive species that sensitizes the immune system to a non-pathogenic component of the body.

1.3 Autoimmune diseases

Autoimmune diseases are chronic conditions that result from the loss of immune tolerance to self-antigens, causing the immune system to attack the organisms' healthy cells, tissues, and/or organs. Autoreactive T cells and autoantibodies are identified as the major attackers of self-antigen [15]. The differentiation and activation of these key attackers are still not fully elaborated. These disorders can be classified into two major groups, organ-specific autoimmune diseases and multiple organs or systemic autoimmune diseases. Different types of autoimmune diseases have been found to share common phenotypic features, from clinical signs and symptoms to genetic factors and pathophysiology mechanisms [16–18]. However, it is likely that some inducing factors may differ as different autoimmune diseases target different cells, organs and systems. Additionally, environmental factors also play a role in the onset of these diseases.

Factors that are common in different autoimmune diseases include but is not limited to the following features.

1. Pathology: The phenotypic manifestation of autoimmune varies, depending on the affected or target cell or system. However, the major pathogenic role is contributed by the phagocytic T cells and B cells. Other predominant cells include macrophages, neutrophils, and CD8+ T cells. Other cells that also contribute to the pathogenesis of autoimmune diseases are T helper cells, especially Th1, Th9

and Th17 [19]. The array of complex biological functions displayed by these cells such as cytokine production, antigen presentation, exosome release, the release of neutrophil extracellular traps (NETs), ROS, Arginase 1 and programmed death-ligand 1 have been implicated in the induction of autoreactive T cells and B cells as well as tissue damage and inflammation [20]. Abnormalities in the function of cells that participate in the classic immune response such as higher expression of IL-6, interferon-α, APRIL and BAFF can cause the dysregulation of adaptive immune cells [21]. These cells then go on to cause cell death either directly or indirectly by releasing cytokines, ROS, RNS and prostaglandins. Interestingly, specialized pro-inflammatory neutrophils with enhanced NETs and inflammatory cytokine production capacity have been found in the peripheral blood of patients suffering from different autoimmune diseases [15]. These cells have a low density due to altered buoyancy properties.

Peripheral tissues contain activated regulatory T cells that control inflammation and autoimmunity responses by eliminating malfunctioning neutrophils, lymphocytes and macrophages. Cells such as CD25+ and CD4+ T cells can secrete anti-inflammatory cytokines that can reduce Th1, Th9 and Th17 activity, thereby preventing autoimmune disease development [22]. However, their function can be inhibited by environmental agents such as pathogenic toxins or smoking.

2. Risk factors

   a. Gender: Statistically women are more susceptible to autoimmune diseases than men. With nearly 5% of the total global population suffering from these diseases, 80% of the reported cases are women [23]. Pathophysiology in the progression of autoimmune diseases in women tends to be different from men and can cause polyautoimmunity. Factors that contribute to this are differences in hormonal orientation and genetic factors [24]. High levels of estrogen, progesterone and prolactin have been implicated in the development of autoimmune diseases.

   b. Age: Diseases like systemic lupus erythematosus (SLE) and type1 diabetes mellitus tend to have a high severity when the onset is early [25]. However, other autoimmune diseases are not influenced by the time of onset, e.g. rheumatoid arthritis and Sjogren's syndrome.

   c. Environmental agents: One of the most crucial environmental autoimmunity triggers is infectious agents. Viruses like the Epstein–Barr virus and cytomegalovirus have been implicated in multiple autoimmune inductions [26]. However certain viruses like the hepatitis B virus have the putative ability to protect against autoimmune disease development.

   d. Genetics: The genetic risk factors of autoimmune diseases can be divided into two groups, the common factors and the specific factors. Autoimmune phenotype is determined by a combination of common and disease-specific alleles interacting with environmental and epigenetic factors [27]. Autoimmune phenotypes have also been confirmed to be the outcomes of nonspecific diseases genes [28]. Additionally, genetic ancestry can also influence the heterogeneity and variation of the clinical manifestation disease [29]. Certain population

subgroups and races have been associated with having a relatively high frequency of autoimmune diseases risk alleles. However, genetic risk factors only confer a small risk and can only explain a limited proportion of heritability in relation to autoimmune diseases [30]. Investigated population and additive and non-additive factors should be considered when assessing heritability in autoimmunity.

e. Other autoimmune conditions: People with a history of autoimmunity or who have an existing autoimmune infection are at higher risks of developing another autoimmune disease [31]. Diverse manifestation of disease phenotype originating from the same gene causes a condition known as polyautoimmunity [17]. The coexistence of more than two autoimmune diseases in a patient leads to a syndrome known as multiple autoimmune syndromes (MAS). MAS is known to favor the pathogenesis of other autoimmune diseases. Dermatological autoimmune disease is present in most MAS. Aside the existence of other autoimmune conditions, the development of MAS is associated with genetic, immunologic, infectious, and psychological factors.

3. Subphenotype: Signs and symptoms of autoimmunity are shared across a wide range of autoimmune diseases. Symptoms such as fatigue, dizziness, arthritis, alopecia, and Raynaud's phenomenon and high levels of cytokines are common in most autoimmune diseases [32]. However, these diseases can have a heterogeneous spectrum if the disease course is dependent on the patient. Additionally, the disease phases differ from one patient to another and even within the same

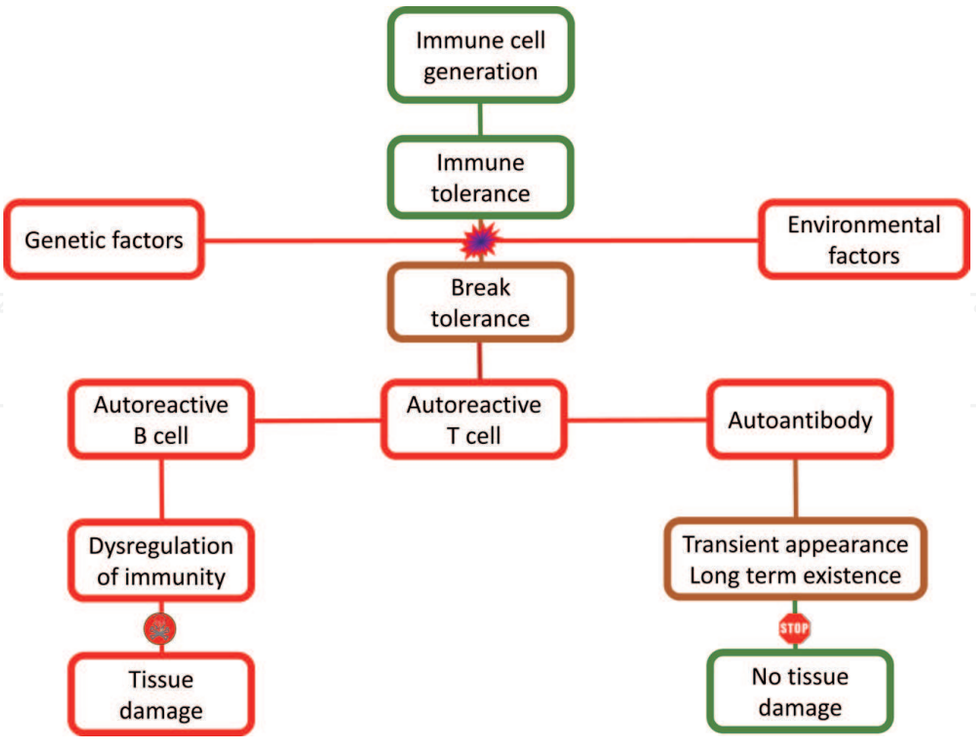

Figure 1.
Development of autoimmune disease. Following the generation and maturation of immune cells in the bone marrow and thymus, the cells undergo a series of processes to produce immuno tolerant cells. A small number of T and B cells evade this process and form autoreactive T and B cells. However these cells are harmless until acted upon by genetic or environmental factors autoantibody can trigger autoimmunity for long term.

patient [33]. This can increase the challenge in acquiring a better understanding of autoimmune diseases because although subphenotypes are similar, they can change depending on the diseases activity and duration [34].

4. Recurrence risk: Complex diseases such as autoimmune diseases tend to cause phenotype clusters in the family of the infected individual. This aggregation usually occurs in a higher frequency than what is observed in the general population [29]. The presence of different autoimmune diseases in the members of the nuclear family is known as familial autoimmunity. When a specific autoimmune disease occurs in the family, it is known as familial autoimmune diseases [18]. Familial autoimmunity is common than a familial autoimmune disease (**Figure 1**).

2. Pathogenic foreign bodies, ROS, inflammation and autoimmunity

Production of ROS in phagocytic cells during the oxidative burst is essential to the elimination of pathogens during an immune response. However, it is also connected with the promotion of inflammation and tissue damage. Interestingly, recent studies have demonstrated that phagocyte derived ROS plays a role in the regulation of inflammation as well as providing protection against autoimmunity. This is mainly because chronic inflammation in multiple pathologic conditions has been associated with ROS deficiency.

The activation of the oxidative burst is highly marked by increased uptake of oxygen in the neutrophils. The consumed oxygen is primarily converted to singlet-oxygen molecules. This leads to an increase of the membrane-permeable hydrogen peroxide due to elevated dismutation activity within the phagocytes. This initiates the generation of various radical and non-radical ROS molecules via the activity of myeloperoxidase. In the events of oxidative burst, the NADPH oxidase complexes serve as one of the major generators of ROS but the localization and timing of the products depend on the stimulus [35]. Despite the localization and efficiency of ROS production, a high concentration of the molecules has been reported to cause the inactivation of proteins and enzymes via the adduct formation due to lipid peroxidation products [36]. Among the enzymes that are inactivated by this mechanism is NOX2, a potent producer of superoxide molecules. To counter this inhibition, phagocytic cells recruit cytochrome-b558 from the lysosomal pool via the soluble NSF attachment receptor 23 (SNARE) [37]. This enables the continuous production of ROS even after the inactivation of NOX2. This mechanism ensures the efficient eradication of pathogens and has been reported to potentially play a vital role in the regulation of autoimmunity [38]. The failure to move the NOX2 to the endosomes due to decreased Ncf4 expression in phagocytic cells can cause autoimmune responses but without the elimination of pathogenic molecules. Notably, increased activity of NOX2 is known to cause the destruction of membranes because of lipid peroxidation and this results in the leakage of the endosome contents such as antigens [39]. This process allows the presentation as well as cross-presentation of antigens to MHC-I. ROS production is therefore essential for the eradication of intracellular pathogens [39, 40].

Some evidence of the role of ROS in the maturation of dendritic cells and the increased expression of MHC-II molecules has been proposed, however, this is met with conflicting research results that NOX2-ROS production does not play a role in the maturation, differentiation and production of cytokines. This is despite its

important role in the elimination of intracellular foreign stimuli. Nevertheless, ROS enables regulated presentation of antigen by MHC-II via the oxidation of cathepsin cysteinyl thiols which prevents excessive protein degradation in early phagosomes. Intracellular foreign pathogen infections such as bacterial and fungal infections have been reported to be persistent in conditions where NOX2 activity is lacking [41]. NOX2 is also involved in backup mechanisms of pathogen capturing such as the formation of neutrophil extracellular traps (NETs) [42]. NETs are mainly composed of chromatin coated in antimicrobial peptides and proteases. During NETs formation, ROS are required for the release of elastase while myeloperoxidase participates in the formation of azurophilic neutrophils granules that facilitate histone degradation in the nucleus [42].

2.1 ROS in inflammatory and autoimmune development

Oxidative damage caused by ROS can generate deleterious byproducts consisting mainly of proteins and lipids that are modified into peroxides. These molecules play important roles in the pathogenesis of several diseases. These molecules have also been implicated in the pathophysiology of cell death and tissue damage. Some of these have the ability to cause immunogenic reactions by inducing pathogenic antibody release in diseases such as systemic lupus erythematous, alcoholic liver disease, diabetes mellitus, inflammation, degenerative diseases, and rheumatoid arthritis. Aldehydic by-products that form adducts with proteins make up two-thirds of molecules that have been implicated in these conditions.

Stress-induced by ROS or any other factor compromises the antioxidant activity within a cell can lead leading to an imbalance in the pro-oxidant/antioxidant balance. The prevalence of this phenomenon has been shown to increase lipid peroxidation. Lipid peroxidation is the degeneration of polyunsaturated fatty acids by free radical activity. The process involves three steps: initiation, propagation and termination. In the first step, a reactive radical extracts a hydrogen molecule from the methylene group. This leaves an unpaired electron on the carbon that combines with molecular oxygen in the propagation phase which then forms reactive peroxyl radicals that react with other lipids thereby forming hydroperoxides. Notably, peroxyl can produce fatty acid radicals and this can cause a chain reaction that causes lipid peroxide toxicity. Lipid peroxidation can also be induced by incidences of exacerbated conjugated dienes, 4-hydroxyl-2-nonenal modified proteins, malondialdehyde modified proteins and 4-hydroxynonenal among other molecules. Products of lipid peroxidation such as 4-hydroxy-2-alkenals can form the an adduct with the amino groups of proteins, leading to ROS induced protein modification. Modified proteins that gain the function of an aldehyde are highly immunogenic. ROS-induced lipid peroxidation and protein modification are likely to co-occur, and the two processes can mutually induce each other. Some products of these processes can avidly react with antioxidants including glutathione and cofactors of ketoglutarate dehydrogenase causing further damage to the antioxidant response.

Lipid peroxides are not bystanders when it comes to the destruction of cellular membranes, cell-matrix and the accelerators in the development of conditions such as atherosclerosis in arthritis especially rheumatoid arthritis. The destruction of the cell membrane can cause the leakage of cellular content, thereby inducing an inflammatory response as the phagocytic cells attempt to clean the debris. The process of debris clearance can percussively cause tissue damage. During this process two sets of macrophages are activated, the first set is M1 which is classically activated, and the

second set is M2, which is alternatively activated. M1 is known for excessive production of toxic production which M2 tries to resolve by producing molecules like EVG and VEGF. The difference in function is made vivid by the distinction in the cytokine profile of the two sets. M1 releases excessive proinflammatory cytokines IL1, IL6 and ROS which ultimately causes cell death by activating death receptors and/or caspases. M2 on the other hand releases anti-inflammatory cytokines like IL-4 and IL-10. In situations that lead to excessive tissue injury, there is little to no anti-inflammatory response as compared to proinflammatory. Aside from this, oxidation of low-density lipoproteins can cause the upregulation of chemokines, adhesion molecules and glycan end-products, thereby inducing an increased inflammatory response. Inflammation in the presence of oxidative stress is known to result in the nonenzymatic degradation of proteins through glycoxidation. Glycoxidation of immunoglobins produces modified immunoglobins which can induce a systemic inflammatory response. Neo-epitopes created by protein modifications can be recognized by toll-like receptor-4, advanced glycan end-product receptors, and scavenger receptors as invasive and can induce pathogen-associated molecular patterns in the immune system that will ultimately lead to autoimmunity. Additionally, there is a correlation between ROS-altered biomolecules and the severity score of autoimmune and inflammatory diseases.

2.2 Examples of inflammatory and autoimmune diseases and the ROS

2.2.1 Systemic lupus erythematosus

SLE is a complex autoimmune disease that affects at least 0.04% - 0.2% of every 100,000 people. The disease has a high prevalence in childbearing age women. This disease is marked by the increased presence of autoantibodies that target nuclear components and inflammation. This usually occurs in organs like the lungs, kidney, and joints. Although the exact cause of SLE remains not fully understood, a genetic predisposition that promotes the formation of lupus has been purported. Additionally, single nucleotide polymorphism in the Ncf2 gene that causes reduced ROS production is known to increase the likelihood of SLE occurrence. The promoting role of ROS deficiency in lupus-like phenotype has been demonstrated in mice where mutation of the Ncf1 shows high levels of anti-DNA, anti-histone, and anti-RNA antibodies with elevated deposits of Ig G and complement C3 in the glomeruli [43]. This contributes to the development of clinical signs of Arthritis, lung hemorrhage and enhanced glomerulonephritis. Increased risk of atherosclerosis is another feature of SLE. Atherosclerosis is developed due to endothelial dysfunction which is linked to a diminished bioavailability of nitric oxide and an increased generation of ROS. Studies in lupus-prone mice have shown increased activity of NADPH oxidase coupled with elevated systolic blood pressure and renal disease, a typical symptom of lupus [44]. ROS in SLE can play a double role depending on the stage of the disease. On one hand, it can be essential in the prevention of autoimmune diseases during the early stage, but it may exacerbate damage during the late stage of the disease.

2.2.2 Type 1 diabetes (diabetes mellitus)

Type 1 diabetes is a metabolic disease that results from the dysregulation of insulin due to the autoimmune destruction of β-cells in the pancreas. The disease emerges at an early age and is manifested as high levels of blood sugar.

The hyperglycemia-induced onset of diabetes has been linked to excessive oxidative stress damage. Mouse model-based experiments have demonstrated that ROS plays a key role in disease development of the disease [45]. For example, non-obese diabetic mice that produce is prone to type1 diabetes, contrary to their ROS deficient counterparts [46]. Reducing the ROS levels is known to help in transforming macrophages to M2 phenotype. Unlike M1, M2 is not a proinflammatory phenotype and does not cause diabetes mellitus. Cells taken from diabetic patients have been found to exhibit increased production of singlet oxygen molecules and a depletion of antioxidants or loss of antioxidant enzymes activity. Hyperglycemia coupled with oxidative stress can lead to macromolecule damage such as protein damage, DNA, and lipids. Islet β-cells are highly susceptible to this damage, which displaces the activation of signaling pathways [47].

2.2.3 Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune and inflammatory disorder characterized by persistent joint inflammation, which can result in the production of autoantibodies, destruction of the bone and cartilage at the site of inflammation. Mutations in the genes that encode components involved in oxidative stress have been found to play a role in the progression of rheumatoid arthritis. By using murine-induced arthritis, pristine-induced arthritis (PIA), gene regions that are involved in the regulation of different phases of the disease and its severity have been identified using mouse models [48]. The loss of NOX2 function due to polymorphism of the *Ncf1* gene is associated with the manifestation of the arthritis phenotype. Recovery of NOX2 function shows protection against the development of the disease. Sever collagen-induced arthritis with excessive cartilage destruction has also been found in mice with a mutated *Ncf1* gene [43]. Additionally, female mice with a mutated *Ncf1* gene develop spontaneous arthritis postpartum. Autoimmune responses that target cartilage-derived molecules play a vital role in the development of arthritis. The recognition of type II collagen bound to MHC-II by T cells is important for disease initiation. However, this alone is not enough to break the immune tolerance. When the recognition of type II collagen by T cells is coupled with the dysregulation of NOX2, chronic collagen-induced arthritis is initiated [49]. Notably, tolerance break can still occur by modulation of T cell activation. Single nucleotide polymorphism in genes that encode for components of NADPH oxidase complex such as *Ncf4*, *Ncf2*, and *Rac2* and genes of antioxidants enzymes have been linked to arthritis incidence. Low copy numbers of the *Ncf1* gene are a common occurrence in patients with rheumatoid arthritis. Therefore, an increased copy number of the gene can lead to protection against the development of rheumatoid arthritis.

The protective role of ROS in rheumatoid arthritis seems to oppose its destructive role in joint inflammation. During arthritic inflammation, reactive species can exacerbate inflammation while contributing to tissue damage via collagen degradation. Overproduction of ROS is also known to cause cartilage degradation in osteoarthritis. This is achieved by inducing apoptosis in the chondrocytes, cells that are essential for the formation and function of the cartilage [50]. The prevalence of ROS coupled with inflammation causes the disruption of tissue homeostasis and depletion of antioxidants. Hydrogen peroxide and hydroxyl species react with membrane lipids, causing lipid peroxidation and promoting cartilage degeneration while inhibiting self-repair [51]. Cartilage degeneration is achieved by affecting the structures of the structural proteins found on the joint, such as collagen and proteoglycan, causing

the chondrocytes to enter the stage of senescence or cell death, which can eventually lead to subchondral sclerosis and meniscal and ligament damage. ROS and inflammatory cells are contained in the synovial fluid in the joint. Their intense activity not only causes the thinning of the proteoglycan layer and collagen fiber but can also cause functional impotence to the DNA mismatch repair system. This activates the NF-kB and the overproduction of metalloproteinase and DNA adducts such as 8-oxo-hydroxy-7,8-dihydro-2′-deoxyguanosine there by contributing to DNA damage and cell arrest. With reduced antioxidant activity, arthritis progression is favored.

2.2.4 Chronic granulomatous disease

Chronic granulomatous disease (CGD) also known as Bridges-Good or Quie syndrome is a rare inheritable immunodeficiency disorder that affects phagocytes such as neutrophils, monocytes and macrophages. These phagocytes lose their capability to form reactive oxygen compounds such as superoxides, and their capability to eliminate invasive pathogens will therefore, become greatly reduced. CGD is characterized by recurrent bacterial or fungal infection and other dysregulated inflammatory responses, leading to the formation of granulomatous and development of other inflammatory disorders such as colitis. Clinical manifestation of CGD includes pneumonia, adenitis, subcutaneous and hepatic cellulitis, lymphadenitis, osteomyelitis, and sepsis. Clinical studies have also shown the involvement of the genitourinary system and gastrointestinal tract in granulomas [52]. CGD is caused by a reduction in ROS production due to defective activity of the NADPH complex's NOX2. The defect is a result of mutations in the NOX2 catalytic subunit gene gp91phox. About 70% of all reported CGD cases are found in males and they are X-linked. Mutations in the Ncf1 and Ncf2 which are recessive autosomal inherited account for a large number of cases [53]. These mutations can cause reduced ROS production and disable the ability to form NETs, leading to reduced efficiency in pathogen elimination. Interestingly, CGD patients have reduced long term memory immunity. A reduced long term memory in CGD patients and mice may can be due to the relation between the number of neutrophils, NOX2 normal activity and percentage of memory B cells. ROS is known to directly influence the process of memory B cells, and hence a loss of function of NOX2 will reduce this process. Contrary to a reduced number of memory B cells, Cd19+ B cells and immature Ig, the D + CD27- B cells availability increases in patients [54]. ROS also plays a role in the activation and proliferation of B cells. According to *in vitro* studies, the neutralization of ROS in B cells is associated with the attenuation of B cell receptor signaling. CGD patients with Ncf1 mutation have increased expression of type 1 IFNs, which is comparable to 1 IFNs in SLE patients. Type 1 IFNs are known to cause autoimmune disease by inducing the differentiation of dendritic cells capable of presenting organisms own materials to the phagocytic immune cells [55]. This puts CGD patients at a high risk of developing SLE and other autoimmune diseases, including juvenile idiopathic arthritis, antiphospholipid syndrome, and IgG nephropathy.

2.2.5 Sepsis

In septic patients, the loss of redox balance is usually the common cause of severe inflammatory response syndrome. The inflammation is caused by the reactive species from neutrophils and macrophages. The inflammation phase of the disease is marked by reduced mitochondrial ATP synthesis and continuous uptake of antioxidants by

affected cells. The antioxidants aim to fight the deleterious activity of ROS and RNS such as reversible and irreversible oxidative modifications of nucleic acids, lipids, and proteins. The oxidative modification of complex lipids of the mitochondrial inner membrane such as cardiolipin worsens the mitochondrial dysfunction by causing the release of cytochrome c [56, 57]. This causes further reduction of ATP synthesis while elevating the production of reactive species. Excessive and persistent ROS in turn inhibits the translocation of Nrf2, which jeopardizes the antioxidant response mechanism.

2.2.6 Psoriasis

Psoriasis is an immune-mediated chronic inflammatory skin disease that speeds up the growth cycle of skin cells. The disease comprises numerous comorbidities and the multifactorial etiology of cardiovascular diseases, metabolic syndrome, and type 2 diabetes [58]. The pathogenesis of psoriasis is heavily marked by oxidative stress. However, ROS is reported to have protective effects in psoriasis. In mice models with induced psoriasis, elevated levels of ROS will increase the functionality of T regulator cells as well as the expression of indoleamine 2,3-dioxygenase. Increased functionality of T regulator cells results in the reduction of circulating Th17 cells [20]. The protective effects of ROS are further supported by evidence showing the exacerbation of Psoriasis in Ncf1 mutated mice [59]. This suggests that the normal functionality of NOX2 plays a role in the attenuation of psoriasis.

2.2.7 Gout

Gout is one of the most understood and manageable systemic rheumatoid diseases. It is a disorder of purine metabolism that results in the formation of monosodium urate crystals that are deposited in and around the joints. This is mostly due to longstanding hyperuricemia. The urate crystals can induce the release of inflammatory cytokines from monocytes and neutrophils, which cause immense inflammation [60]. The onset of gout attack can last for at most 10 days and then disappear, but the crystals remain present in the joint area. These crystals can induce the formation of large NETs aggregates that end up trapping and degrading the pro-inflammatory mediators. This in turn will limit and resolve the inflammation [61]. The formation of NETs in gout is dependent on the availability of ROS, and a deficiency in ROS can result in a chronic state for the disease. Therefore, a functional oxidative burst is critical for the maintenance of immune tolerance and the resolution of inflammation in gout.

3. ROS in inflammation resolution and autoimmune regulation

The effects of ROSs autoimmunity appears to be more complicated than previously anticipated. ROS is thought to be solely a by-product of the process involved in the cellular response to inflammation or infectious stimuli. However, recent findings have attributed ROS to have vital roles in cellular regulatory and inflammation restraining processes. As their role in numerous cell functions is elaborated, it is now understood that these functions cannot occur without the presence of ROSs. Despite this, the tissue, cell type and time point on which ROS act as anti-inflammatory and immunoregulators are not yet elucidated.

The deficiency of NOX2 has been found to play a key role in the induction of multiple autoimmunity conditions. This is true even in severe bacterial and fungal infections. Inflammatory and autoimmune diseases such as Corhn-like inflammatory disease, idiopathic arthritis and CGD can co-occur. Animal model experiments as well as genome-wide studies have shown a relationship between the polymorphism of Ncf1 and the occurrence of many arthritic diseases [62]. Ncf1 is a cytosolic subunit of NOX2 whose polymorphism signifies diminished production of superoxide. Mutation in the Ncf1 gene which results in loss of NOX2 function has been reported to increase susceptibility to T cell autoreactive activation, cartilage oligomeric matric protein-induced arthritis, and collagen-induced arthritis among others [28]. Additionally, NOX2 derived ROS have been found to have regulatory roles in T-cell dependent nervous system diseases such as multiple sclerosis and Guillan-barre syndrome. Interestingly, NOX2 is also a regulator of autoantibody production and autoimmune inflammation. Therefore, NOX2 activity, especially ROS generation has a crucial preventative effect on the development of autoimmunity and can regulate chronic inflammation [63]. However, it is important that NOX2 is viewed not as a regulator of disease susceptibility but as a regulator of disease severity.

The protective role of ROS in inflammatory and autoimmunity is not universal. In type 1 diabetes, ROS deficiency is associated with safeguarding from diseases, especially in non-obese diabetic animal model. Thayer et al. reported the essential role of macrophage ROS in mediating effector function for CD4+ T cells autoreactivity and autoimmune diabetes pathogenesis [64]. NOX2 generated ROS is also vital in the execution of islet reactivity. However, mutations in the Ncf1 gene which eventually leads to NOX2 malfunction and reduced ROS availability has been found to significantly alter the effector function of macrophages and T-cell subsets [43]. Additionally, collagen antibody transfer which develops independently of phagocytic immune cells can induce arthritis. This phenomenon can be exacerbated by an increase of Ncf1 gene expression. Furthermore, non-classical autoimmune diseases such as monosodium urate crystal-induced inflammation and zymosan show signs of increased inflammation even in the absence of NOX2 and ROS [41, 63]. This shows that certain cases ROS deficiency can be linked to the protection against disease.

4. Conclusion

The development of autoimmunity is defied by a wide range of mechanisms, regulatory cells and tolerance mechanism, which when not properly functioning or are inefficient, fail to decelerate the effects of the interplay of environmental, genetic, and immunological factors. Faults in the immune tolerance mechanism consequentially leads to inappropriate cell death or survival or failure to clear debris which are involved in the pathogenesis of autoimmune diseases. The failure of these systems and the eventual development of autoimmune diseases is aided by inflammatory modulators. Interestingly, this process occurs before the full development of diseases, making the modulators a potential therapeutic target. As such, they can also be used as control points to prevent the exacerbation of the autoimmune diseases. Targeting inflammatory modulators can, therefore, offer opportunities for the development of novel diagnostic methods and effective therapy in the future.

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