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REVIEW

Crosstalk between reactive oxygen species and pro-inflammatory markers in developing various chronic diseases: a review

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Abstract The inflammation process in the human body plays a central role in the pathogenesis of many chronic diseases. In addition, reactive oxygen species (ROS) exert potentially a decisive role in human body, particularly in physiological and pathological process. The chronic inflammation state could generate several types of diseases such as cancer, atherosclerosis, diabetes mellitus and arthritis, especially if it is concomitant with high levels of pro-inflammatory markers and ROS. The respiratory burst of inflammatory cells during inflammation increases the production and accumulation of ROS. However, ROS regulate various types of kinases and transcription factors such nuclear factor-kappa B which is related to the activation of pro-inflammatory genes. The exact crosstalk between pro-inflammatory markers and ROS in terms of pathogenesis and development of serious diseases is still ambitious. Many studies have been attempting to determine the mechanistic mutual relationship between ROS and pro-inflammatory markers. Therefore hereby, we review the hypothetical relationship between ROS and pro-inflammatory markers in which they have been proposed to initiate cancer, atherosclerosis, diabetes mellitus and arthritis.

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Abbreviations

ROS	Reactive oxygen species
NO	Nitric oxide
TNF-α	Tumor necrosis factor-alpha
COX	Cyclooxygenase
PG	Prostaglandine
NF-κB	Nuclear factor-kappa B
IL	Interleukin
MCP-1	Monocyte chemotactic protein-1

Introduction

Inflammation has been considered biologically for long time as the earliest defense and healing process against tissue damage. The customary marks of inflammation are redness, pain, heat and swelling that are result of confronting the host tissue by toxic microbe, tissue damage or cancerous circumstances [1]. In addition, pro-inflammatory markers have appeared, in the recent decades, as a potently interfering agent in the pathophysiological age-related diseases and in the major chronic diseases of developed populations, including cardiovascular disease, type 2 diabetes mellitus, arthritis disease, and many types of cancer [2, 3]. Furthermore, there is a grave concern about the contribution of reactive oxygen species (ROS) in supporting the inflammation process.

Free radical, highly reactive molecules, is created by normal cellular processes, environmental stresses, and UV

irradiation. In the other hand, the reaction of ROS, at high concentration, with biological components lead to damage in DNA, carbohydrates, proteins, and lipids causing injury on the cellular and tissue level by which can lead to inflammation, premature aging disorders, and several disease states, including cancer, diabetes, and atherosclerosis [4].

A currently acceptable hypothesis is that the relationship between ROS and pro-inflammatory markers is directly interactive. At the same time, various scenarios have elucidated that the more ROS produce, the more pro-inflammatory markers produce. Meanwhile, a considerable body of experimental evidence has shown that ROS activate NF-κB [5], which results in the transcriptional activation of genes relevant for pro-inflammation. Thereby, we hypothesize that ROS and pro-inflammatory markers are sharing relatively the same results with respect to initiate various diseases.

The purpose of this review is to focus on the following points; (A) the role inflammation in human body and its effect, (B) the interaction between ROS and pr-inflammatory markers, (C) the role of ROS and pro-inflammatory markers in initiating cancer, diabetes mellitus, atherosclerosis, and arthritis.

Definition of inflammation

Inflammation is defined as a primary response of the immune system to reinstall the homeostasis after injury to any tissue made by harmful stimuli such as pathogens, irritants, or damaged cell [6]. Generally, it can be divided into two different types.

Initiation and progression of inflammation

During the first few seconds of inflammatory state, several types of symptoms appear directly such as expansion of blood vessels, rising in blood flow, increasing in capillary permeability, and neutrophils emigration to the interstitial spaces. As result of these activities, the classical symptoms such as redness, heat, swelling, and pain have been shown. The cells where is existed in inflammatory site release inflammatory mediators like leukotrienes, histamines, and prostaglandins [7]. Some of these mediators are responsible for pain feeling and accumulation and activation of other cells involved in inflammation. Binding these mediators with endothelial cell receptors leads to vasodilation and diapedesis [7]. Prostaglandines which are enzymatically derived from arachidonic acid by the action of COX enzyme are a pro-inflammatory mediator with a contribution in vasodilation and blood flow [7]. Because of the rearranging of capillaries surrounding the basement membrane in reaction to inflammatory mediators, the filtration of plasma macromolecules is facilitated to the juxtaposed (placed side by side) tissue. Smooth muscles inside blood vessel, at the injury site, shrink which in turn lead to a low blood flow through the small capillaries [8]. Therefore, more leukocytic cells can stick to the capillary wall. As a result of shrinking endothelial cells, the space between those cells in smaller blood vessels increases. Thus, the diameter of blood vessels expand and this process name a vasodilation [9]. Released by endothelial cells, adhesion molecules bind with the integrin, a protein that links the outside of a cell with its interior, present in leukocytic cell [10]. The previous process by which leukocytes flatten and filtrate from the capillaries into the surrounding tissue is so-called extravasations.

Neutrophils are considered as an immune cell which is the primary cells typically present at the site of injury during acute inflammation [11]. Naturally, this cell has a capability not only to function as a phagocyte but also to ingest and destroy particles and microorganisms through creating reactive oxygen specious and hydrolytic enzyme [11]. The process by which neutrophils move chemotactically toward the injury site has characterized by releasing interleukin-8, interferon gamma and complementary proteins from the cells at afflicted site in response to injury [12, 13]. As a result of its being inside the cell, the granules of neutrophils contain lactoferrin, bactericidal increasing proteins, cathelicidin, cathepsins, defensins, and gelatinases which are collectively released at the injury site either to kill foreign particles or to regulate physiological and pathological process such as inflammation [11].

The practical benefit of acute inflammation process is to maintain the tissue in homeostasis. For example, this process leads to activation of blood platelets providing antibodies [14], and facilitate phagocytosis [3]. The production of lysozymes, defensins, and cathelicidins from granules of neutrophils degrade peptidoglycan, cleave peptides, equalize LPS, and contribute in penetrating the cytoplasm membrane of bacteria [15]. During acute inflammation, the compensation of nutrients at the site of injury and the releasing of transferrin to deprive the microbes from iron has been documented [16].

During chronic phase inflammation, the primer accumulation of granulocyte at the site of injury is made by neutrophils. To resolve this inflammatory state, elimination of neutrophils is required. Released by the macrophage, interleukin-1 (IL-1) tumor necrosis factor (TNF-α) exerts a stimulation on natural killer and T-lymphocyte to liberate interferon gamma (IF-γ). The binding of IF-γ with macrophage lead to a releasing of Fibroblast Growth Factor to begin the operation of reconstructing tissue [17]. Then, the fibroblast and endothelial cell grow rapidly with creating a

network of capillary vessels followed by collagen to make a cicatrix in the opened area.

Endogenously inflammatory mediators derived from lipid have a significant role in resolving inflammation [18]. The two cell interactions, platelets and leukocytes, are the main generator of lipoxin A_4 and B_4 during inflammation. These enzymatically biosynthetic compounds are considered as an indicator for resolving inflammation. After lipoxins suppress the recruitment of granulocyte from the post-capillary venules [19], prostaglandin has shown a transcriptional effect on 15-lipoxygenase which stimulate the biosynthesis of lipoxins from arachidonic acid instead of prostaglandin [20]. Moreover, the stimulation of lipoxin A_4 to liberate IL-10 and transforming growth factor-β (TGF-β) could assist in fibrosis [21, 22]. Before leaving the inflammatory site, macrophage cleans the wreckage and moves to lymph node [23].

The opportunity of transforming acute inflammation into chronic inflammation has been dwindled throughout successful resolving of acute inflammation. Several factors have lead to chronic inflammation such as, success of endogenous anti-resolving mediators, deficiency of overcoming the inflammatory stimuli, and existed attack of stimulus [17]. The characteristics of chronic inflammation can be expressed by increased angiogenesis [23], monocyte infiltration [24], necrosis [25], and fibrogenesis [26]. Angiogenesis is a process by which new vessels are created from another one, but if it is not well-controlled, chronic inflammation may be noticed. Angiogenesis process has been stimulated by different kind of cells; mast cells, fibroblast and macrophage [17]. Macrophage has the capability to release potently angiogenic factors and cytokines to begin angiogenesis [27]. Several mediators such as vascular endothelial growth factor (VEGF), TGF-β, TNF-α, prostaglandin E_2 (PGE_2), nitric oxide (NO), IL-1, IL-6, and IL-8 have indirect or direct effect on promoting angiogenesis and on endothelial cell [17]. Released by macrophage, TGF-β motivates fibroblast and allows entering fibrosis [28]. With a pro-inflammatory action, thrombin is released during the coagulation process and stimulates endothelial cell to produce monocyte chemotactic protein-1 (MCP-1) [29]. Then, inflammatory monocyte is attracted by MCP-1 to infiltrate through endothelial cells and they immigrate to special tissue with transforming to macrophage for other inflammatory actions [30]. After transforming from monocyte to macrophage in chronic inflammation, lymphocyte, complementary proteins, and immune complexes activate macrophage [31]. It has been proven that stimulated macrophages produce highly pro-inflammatory mediators such as IL-6, IL-1β and TNF-α in rat with chronic inflammation [32]. The presence of stimuli and overwhelming the surrounding tissue with pro-inflammatory mediators enable the activated macrophage to dismantle the tissue to be damaged seriously leading to chronic inflammation [33].

Biological markers of inflammation

COX-2 and NO are assumed to be one of the most important inflammatory biomarkers in cells. The pro-inflammatory cytokines such as IL-1, TNF-α, IL-8 can be stimulated from various lymphocyte and leukocyte as a result of NO, being a key role in the pathophysiological actions of inflammation. It has been shown that NO have the ability of stimulating neutrophil to produce IL-8 which in turn have chemotactic actions on polymorphonuclear leukocytes in a dose dependant manner [34]. Wang et al. [35] has demonstrated that NO has up-regulated TNF-α in human blood monocular cell (U937). Additionally, the genesis of NO through the inflammatory state leads to DNA damage which increases the opportunity of cancer in some cases [36]. NO also can up-regulate COX-2, an important inflammatory marker [35]. Prostaglandin endoperoxide synthase 2 or COX-2 is an inducible enzyme which can convert arachidonic acid to PGs through a series of radical reactions similar to that in fatty acid oxidation [37]. Considered as a key role in inflammation, PGE_2 has a productive ability to produce several pro-inflammatory cytokines such as IL-6, IL-1 [37]. Other study has shown that arthritis induced in rats has increased the expression of COX-2 mRNA [38]. By using COX-2 inhibitors, the expression of COX-2, IL-6 and IL-6 mRNA level is reduced in serum [39]. Ultimately, the previously mentioned studies reflect the impact of COX-2 in inflammation. Additionally, C-reactive protein (CRP), naturally produced hepatic and adipocyte tissue, is also included in the list of inflammatory biomarkers [40]. Along with different important functions, CRP takes part in immunity where that binds the foreign particles and facilitates phagocytosis [41]. The production of IL-6 triggers on liver cells which is stimulated by COX-2 and NO to release CRP in serum [41]. The increasing level of CRP is attributable with several diseases such as atherosclerosis [42], osteoarthritis [43], and cancer [44].

Reactive oxygen species (ROS)

Reactive oxygen species is divided into two types; oxygen-centered non-radicals and oxygen-centered radicals. Of those are super oxide anion ($O_2^{\cdot-}$), hydroxyl radical ($OH^{\cdot}$), peroxyl radical ($ROO^{\cdot}$), singlet oxygen (O_2), hydrogen peroxide (H_2O_2), and alkoxyl radical ($RO^{\cdot}$) [45]. Despite of considering reactive oxygen species as a free radical in the biological system, there are non-radical compounds related

to reactive oxygen species such as singlet oxygen and hydrogen peroxide. The three main characteristics of free radicals, in general, are unstable, highly reactive and excited molecules [46]. The formation of free radicals can be by pro-oxidant enzymes, irradiation, lipid peroxidation, smoking, air pollutants, and glycoxidation [46]. It has been mentioned in several clinical researches that ROS are linked with different type of diseases such as cancer, atherosclerosis, trauma, asthma, retinal damage, vasospasms, and liver damage [47]. The mentioned above is thought to be the outcome of ROS reactions with lipids, carbohydrates, proteins, and DNA which in turn become a free radical itself after stealing the electron [48].

Reactive oxygen species and pro-inflammatory markers

Reactive oxygen species (ROS) exert potentially a decisive role in human body, specifically in physiological and pathological process as well as pro-inflammatory markers [49]. Unpaired valence electrons and unstable bounds are the main characteristic of all ROS type. Because of their high activity, ROS is able to act, at high concentration, with the biological materials such as protein, lipid, and nucleic acid causing either negative functional alterations or destructive actions [50]. In addition, many chronic diseases related to inflammation are attributable with high levels of ROS [4]. At the same time, respiratory burst made by inflammatory cells, during inflammation, lead to an increased production and accumulation of ROS at the site of damage [51]. However, ROS interfere in the regulation of several types of kinases and transcription factors such iNOS and COX-2 [52, 53]. ROS also play as a second messenger in intracellular signal transduction pathways [54].

In a murine fibrosarcoma cell line namely L929, ROS production was induced under TNF-α stimulation [55]. In addition, ROS motivate the production of IL-6 from skeletal myotubes through transcriptional activation of IL-6 expression gene [56]. Notably, mitochondrial ROS inhibitor has reduced the production of LPS-induced IL-6, suggesting to other inhibitions for inflammatory mediators [57]. Using cells from tumor necrosis factor receptor-associated periodic syndrome (TRAPS) patients showed that mitochondrial ROS affect significantly on the promotion of transcriptional factors of pro-inflammatory cytokines [58]. However, the ROS inhibitors was suppressed the activation of mitogen-activated protein kinases (MAPK) and the production of IL-6 and TNF in TRAPS patients cells [58]. The previous finding comes along with a study demonstrating that ROS inhibitors make MAPK ineffective [59]. Nuclear factor-kappa B (NF-κB) has a potent role in regulating the pro-inflammatory gene expression [59]. Several cytokines such as IL-6, IL-1, TNF-α as well as cyclooxygenase-2 (COX-2) are synthesized as result of NF-κB mediation [60]. At the same time, ROS have been thought to be involved in NF-κB activation [61]. Another study has considered the interplay between ROS and eicosanoids through suppressing RAC-1-dependent ROS generation by 5-LOX inhibitors [62].

The previous mentioned studies show a strongly overlapping relationship between ROS and pro-inflammatory mediators through NF-κB and MAPK cascades mainly. This relationship can be translated in the persistent of inflammation along with high concentration of ROS leading directly to chronic inflammation which in turn render the immune system to continue its efforts to recover from damage. Consequently, a changing in the physiological surrounding tissue and destruction of nearby cells follow the immune efforts. We hypothesize that the continuous release of cytokine and chemokine along with ROS in bloodstream could contribute in demonstrating general responses by which several maladies such as cancer, atherosclerosis, arthritis, and diabetes could be generated.

Diseases associated with ROS and pro-inflammatory markers

Cancer

In 2013, the estimation of new cases for all kinds of cancer (except non-melanoma skin cancer) is 1,660,290 and the mortality due to cancer is expected to be 580,350 with economic burdens around $219.2 billion [63]. Cancer is identified by uncontrolled divide of cells in which occupy around tissues with impairing their physiological roles. These changes can be noticed also in other tissue through metastasizing the carcinogenic cells. Three phases (initiation, promotion, and progression) are involved in the carcinogenic process. In chronic inflammation, releasing NO from inflammatory cells can strongly trigger the process of carcinogenesis through supporting mutagenic changes including alterations in DNA sequence and bases, breaking DNA strands, suppressing the expression of anti-cancer genes, and promoting oncogenes [64]. In addition, DNA repair enzyme (ligases) is not active to repair the interruption of single strand when exposure to reactive nitrogen species [4]. Moreover, reactive nitrite species has the ability to achieve mutations in DNA, altering protein, RNA, and trigger carcinogenesis [51]. Additionally, ROS has been widely accused to cause damage in DNA causing cancer [65]. Gallo et al. [66] demonstrated the effect of NO on angiogenesis and tumor developing in head and neck cancer. Tumor sample and human squamous carcinoma

cell (A-431), supplemented with NO, were expressed more angiogenesis compared with control group. The increased rate of angiogenesis can trigger forming a neoplastic tissue. Through inducing proliferation, migration, and invasion, NO acts on complete tumor cell causing metastasis and progression [67]. Chronic inflammation is related to the developing of cancer affected by variety of factors such as virus, bacteria, dangerous chemical exposure, and epigenetic change.

Helicobacter pylori-induced cancer is a well-documented design of gastric cancer initiated by infection [65]. The attachment of H.pylori with epithelial tissue stimulates multi-immune responses containing interferon γ, TNF-α, IL-12 and other pro-inflammatory cytokines, macrophage inflammatory protein α and chemotactic protein of monocyte by activation of transcription factor NF-κB [68]. Additionally, the long persistent of bacteria in intestine consider as the source of antigens continuously. The immune system has the ability to increase the response of chronic inflammation leading to cellular damage followed by increased cell turnover and finally inducing cancer. Furthermore, white blood cells accumulate and release reactive oxygen and nitrogen specious that increase the expression of COX-2 enzyme which in turn lead to formation of prostaglandins [65]. A large number of previous studies demonstrate that the production of prostaglandin and pro-angiogenic factor causes migration in endothelial of colon cancer cell and angiogenesis as a result of overexpression of COX-2 [69, 70]. In addition, the increased angiogenesis induced by COX-2 has been noticed in hepatocytes carcinoma throughout the activation of VEGF pathway [71]. Shi et al. [72] have shown during their study on human cervical cancer that the increased growth of tumor and metastasis by VEGF expression was associated with high-rates expression of COX-2.

There is a massive body of reviews that shows ROS as a key player in several malignant diseases [73–76]. Bohr and Dianov [77] discussed the ability of ROS in deteriorating the carcinogenic suppressor genes and supporting the expression of proto-oncogenes. Further study has demonstrated the promotion of malignant transformation induced by ROS in different cell cultures as a result of multi-mutations [76]. Mostly, these mutations have been occurred through transversion of guanine with tyrosine [78]. Thus, ROS have mutagenic effects in promoting carcinogenesis. Furthermore, the presence of hydrogen peroxide and superoxide, at low concentrations, has stimulated the proliferation and improved the survival of many cells types [79]. The elevation of ROS, also, has been studied in various cancer cells during the administration of antioxidants which in turn increase the inhibition of cell proliferation, indicating the role of ROS in mediating cancer cell growth [74]. Further biological evidence supporting the theoretical contribution of ROS in carcinogenesis is well-discussed. When a tumor tissue confronts hypoxia condition, which is very common, cancer cells induce the development of blood vessels (angiogenesis). ROS can increase the process of angiogenesis throughout several trends; (1) promote the production of IL-8 and VEGF (Vascular Endothelial Growth Factor) which are angiogenic factors, (2) enhance the secretion of matrix metalloprotease MMP-1 which promote vessels growth in tumor tissue, (3) trigger vasodilatation [80, 81]. In addition, a recent review has reported clearly about the role of ROS in tumor metastasis during the process of cancer initiation [82].

Atherosclerosis

Heart diseases which the main cause of death and pain globally will become soon the dominant health issue [83]. Several theories have been published in order to describe the association of inflammation with atherosclerosis. At the same time, the science of inflammation applied to atherosclerosis has promoted to understand the underlying mechanism by which various inflammatory elements participate in. To explain more, the initiation of atherogenesis is associated with the beginning of chronic inflammation because of stimulation of immune system and endothelial dysfunction. The production of two types of auto-antigen, namely heat shock proteins (HSP) and oxidized low density lipoprotein (oxLDL), in endothelial cell has been triggered by several factors such as oxidative stress, cytokines, infections, smoke, and dust [84, 85]. The increased production of ROS at mitochondrial level and changeable activity of NO ultimately can result in alteration of permeability, inflammatory, and vasodilatory characteristics of endothelial cells, so-called endothelial dysfunction [86]. As a result of ROS accumulation, HSP has been produced from the outer and inner side of endothelial cells [87]. Produced naturally due to stress, HSP helps in disposition of functional and structural protein [88, 89]. Then, the innate immune cells target these proteins which imitate some pathogenic HSPs [90]. To elaborate more, endothelial and macrophage cells treated with HSP60 have increased the expression of iNOS and COX-2 [91]. Collectively, this process leads to recruitment of inflammatory cell and initial inflammation.

OxLDL is the second auto-antigen in cardiac diseases. It is well-established that LDL is used to transport the cholesterol into peripheral tissues for appropriate cellular function and high-density lipoproteins picks up the invalid cholesterol and carry it internally from cells to the liver. The retention of LDL within the cells causes local inflammation in which transforming growth factor-α is produced by surrounding cells followed by increased

production of proteoglycans [92]. This latter can negatively charge sulfate group that bind to the positive charge of apo B-100 of LDL [93]. In the presence of this inflammatory state, some enzymes oxidize LDL molecule. This oxidation liberates lipid peroxides which in turn induce the inflammatory reaction in near cell [94]. The previous data have been supported experimentally by Norata et al. [95] who indicated that oxidized LDL raises the level of COX-2 expression in human endothelial cells. Thus, anti-inflammatory drugs along with antioxidant supplements have been always studied on heart diseases. In a pharmaceutical study, using of selective COX-2 inhibitors so-called celecoxib in a dose of 200 mg each day improves the endothelial vasodilation and in 14 men (Age 63–70 years) affected with atherosclerotic heart diseases [96].

Arthritis

Arthritis, which effect around 1% of the worldwide population, is defined as a joint disorder associated with inflammation and characterized by joint pain, synovial inflammation, swelling, and abnormal reaction of humoral [97]. The thick subchondral bone that causes pain and stiffness results from changing the underneath bone and destructive action of hyaline articular cartilage leading to osteophyte (abnormal outgrowth of small bone) [98]. The immune cells and inflammatory mediators have a crucial role in the pathophysiology of arthritis. Furthermore, the primary cause of osteoarthritis is inflammation according to Bonnet and Walsh [99]. The expression level of COX-2, angiogenesis, VEGF, TNF-α, and IL-1β has been found to be increased in synovial tissue of patients afflicted with early osteoarthritis [100]. The stimulation of chondrocyte by using pro-inflammatory mediator like IL-1β has been resulted in increased expressions of COX-2 and iNOS leading to up-regulation in the synthesis of PGE2 and NO [101]. Simultaneously, the recruited macrophages and neutrophils, in the damage site, secrete chemotoxic materials and pro-inflammatory mediators such as PGE_2, NO, TNF-α, IL-1β, IL-8, and IL-6 [102]. The existence of various cytokines (IL-1, IL-6, IL-15, TNF-α) secreted from macrophages and synoviocytes is considered as a primary determinant in the pathological persistence of arthritis [103]. To be more specified, the level of TNF-α has increased independently in mouse model of arthritis [104, 105]. Surprisingly, using TNF-α blockade has shown an improvement in inflammatory cells and arthritis in mice model [106]. However, the main cause of cytokines biosynthesis in arthritis has not fully understood while other researchers have suggested that nutritional status, bone density and obesity could contribute in cartilage destruction [107].

Being a crucial bio-factor, ROS has relatively a complicated pathogenic contribution in arthritis. In different joints diseases, ROS and pro-inflammatory mediators such as cytokines are present at the site of disease according to Montecucco and Mach [108]. As a kind of ROS, the production of superoxide anion (O_2^-) along with nitric oxide (NO) by chondrocytes creates peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2) [109]. The mechanism by which oxygen and nitrogen injure the component of cellular elements and extracellular matrix in cartilage is either by direct attack or by increasing the reduction of matrix components synthesis (proteoglycans, type 2 collagen) and decreasing the sulfation of recently synthesized glycosaminoglycans [110]. Lloyds et al. [111] supported the previous findings where ROS was increasingly presence at the site of inflammation in arthritis patients. Similarly, the oxidative enzymes have been found a high ratio in the serum and synovial of arthritis patients [112]. Thus, the improvement of SOD (super oxide dismutase) level in the arthritis patients has been considered as one of the arthritis-attenuating approaches [113].

Diabetes

The growing concern of diabetes reflects the increasing ratio of its incidence and also it is predicted to increase further [114, 115]. Because of its various and serious complications which are burden on human health, there is a grave concern about the rapid prevalence of diabetes. Of those are nephropathy, cardiovascular diseases, neuropathy, and retinopathy. The different factors that contribute in the pathogenesis of diabetes and its complications are plenty such as diet, genetics, age, obesity, and lifestyle [116]. The role of ROS and inflammation in the etiology of diabetes has received a lot of attention. The inflammatory process is involved in the initiation of diabetes type 1 and 2.

Several controversial discussions have been documented around the ability of inflammatory processes in the pathogenesis of diabetes type 1. CRP (C-reactive protein) which is a circulatory biomarker for inflammation have been found in normal range with subjects recently diagnosed with diabetes type 1 compared with healthy subjects, but subjects with long-term diabetes were higher [117]. CRP and IL-1β released by monocyte have been existed increasingly in patients with diabetes type 1 [118]. Meanwhile, Schram et al. [119] has demonstrated that CRP, IL-6, and TNF-α of plasma were elevated noticeably in type 1 diabetic patients. Total of 168 hypertensive patients have been followed up during 32 months to observe their C-reactive protein in serum and development of diabetes. In total, 13% of the subjects have developed diabetes with high elevation of C-reactive protein [120]. However, the usage of IFN-γ-antibodies to block IFN-γ in NOD mice has decreased significantly the impulsive diabetes type 1 and

prohibited the adaptation of the disease, suggesting that IFN-γ plays a role in the pathogenesis of diabetes [121]. Being a crucial inflammatory cytokine, TNF-α produced by $CD8^+$ T cells has been shown a toxic impact against pancreatic β-cells [122].

The focus of research on the function of inflammation in developing diabetes type 2 has taken the attention more than diabetes type 1. Several studies have documented an increase in the inflammatory markers of healthy individuals who later develop diabetes type 2 [123, 124]. Frank et al. [125] has supported the previous findings where IL-6, CRP, and TNF-α have been higher in women who had developed diabetes type 2. Taken together, the involvement of pro-inflammatory cytokines in the initiation and/or developing diabetes is well-observed in the previous findings.

There are various biochemical pathways describe the relationship between hyperglycemia and the increased production of ROS. Beside of that, the existence of diabetes is considered to be escorted with elevated level of ROS and/or damaged anti-oxidative defense [126, 127]. Thereby, the participation of ROS in diabetes genesis has been mentioned in several articles, suggesting different mechanisms in the etiology [128]. Recently hypothesized, ROS is accused to be a pathogenic player leading to damaging β-cells, insulin resistance, impaired glucose intolerance which collectively causes diabetes [129]. Similarly with type 1 and 2 diabetes, the generation of ROS, in autoimmune diabetes, is attributed to the infiltration of T cells in pancreas cells [130]. Depending on different assays to measure the cellular damage-mediated ROS, ten studies have obviously found an increase in the cellular damage caused by ROS in diabetic patients [131]. In the same context, a review article published in *Journal of Biochemical Molecular Toxicology* has mentioned more than 20 in vivo diabetic studies that unanimously focused on the toxic role of ROS in developing diabetes mellitus and the importance of antioxidants administration as a preventive and attenuating approach against diabetes [127].

Discussion

The aim of this review is primarily to focus on the literature supporting the role of pro-inflammatory mediators and ROS as a mechanistic link in the initiation and progression of various chronic diseases. This review hypothesize that the persistent production of ROS and pro-inflammatory markers is associated with each other (Figs. 1, 2). The increased production and accumulation of ROS is made by the respiratory burst of inflammatory cells during inflammation [51]. However, ROS do regulate several types of kinases and transcription factors such NF-κB which is

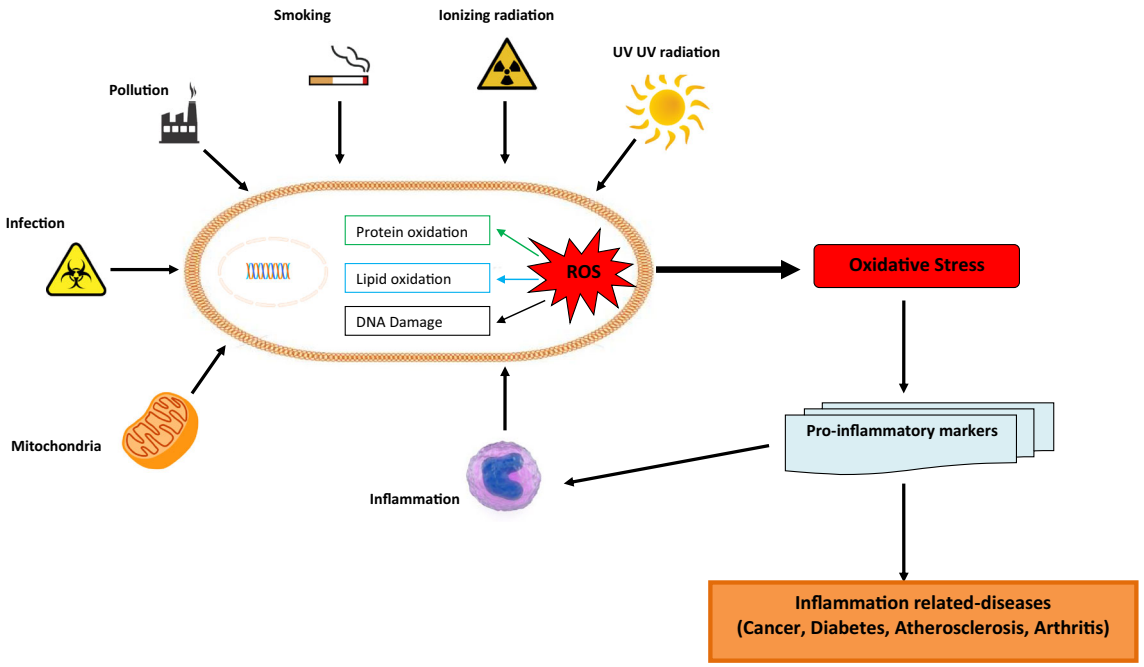

Fig. 1 Reactive oxygen species (ROS) can be produced by (1) exogenous sources such as (air pollutions, infection, UV light, radiations, stress, and smoking); or (2) endogenous sources during the oxidation reactions of metabolic pathways in mitochondria, drugs metabolism, and inflammation. An accumulation of cellular ROS can affect or oxidize the cellular contents (cell membrane phospholipids, lipid, protein, and DNA) and thus promote pro-inflammatory mediators releasing. The oxidative cellular damage can thereby lead to formation the oxidative stress manifestation, which in turn causes many age-related diseases particularly cancer, early aging, cataractogenesis, arthritis, neurodegenerative diseases, and diabetes

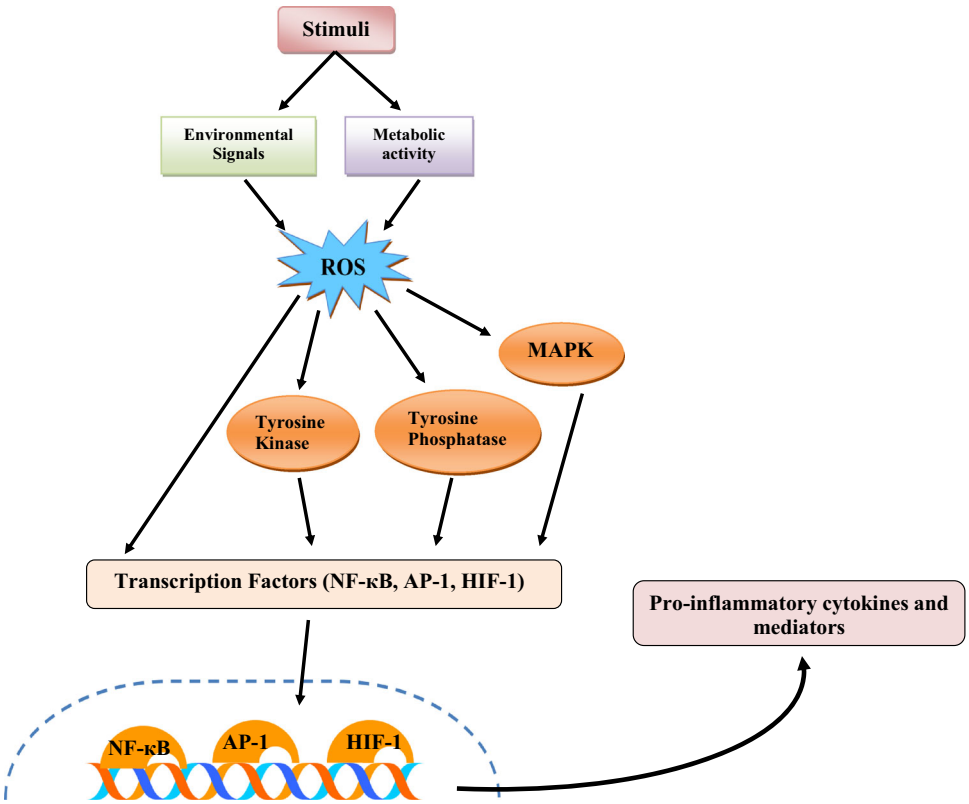

Fig. 2 The major signaling pathways activated in response to oxidative stress and its relation with inflammation. Reactive oxygen species (ROS) originating from environmental signals or from metabolic activity are modulated by antioxidants to non-toxic levels, at which point they serve as signaling molecules that can trigger pro-inflammatory gene expression leading to a state of chronic inflammation. ROS can activate gene transcription-related to inflammation in two ways: (a) via transcription factors, such as NF-κB, AP-1, and ARE-binding proteins (ARE-BP) that can interact directly with specific DNA motifs on promoters of target genes, or (b) via activation of MAPK cascades, which in turn activate transcription factors that trigger target gene transcription. The degree to which a given pathway is activated depends on the nature and duration of the stress, as well as on cell type and developmental stage. NF-κB = nuclear factor-kappa B; AP-1 = activator protein-1; HIF-1 = Hypoxia Inducible factor 1

related to the activation of pro-inflammatory genes [53]. In summary, the studies above show a strong evidence for the hypothesis that ROS and pro-inflammatory markers could be involved in the production of each other which in turn lead to generating cancer, diabetes mellitus, atherosclerosis and arthritis (Fig. 1). Surprisingly, the above exciting discussion comes up with highly important admonitions. Initially, although the number of trails has assessed prospectively the relationship between ROS and pro-inflammatory markers, few studies have included measurement of ROS and pro-inflammatory markers in cancer, diabetes mellitus, atherosclerosis, and arthritis, simultaneously. Revealing the relationship between ROS and pro-inflammatory markers is the key for developing underlying mechanisms by which the pathogenic development of chronic diseases become understood.

While this review sets out an extensive mechanistic relationship (ROS and pro-inflammatory markers) that may provide an explanation for the incidence and/or developing of the mentioned above diseases (Fig. 1), it is very important to realize that direct, prospective, high quality, human evidence to provide a significant role of ROS in the relationship between pro-inflammatory markers and the mentioned above diseases is lacking. Despite of this fact, these mediators provide a promising approach for future studies with materialistic translational benefits in prevention and treatment areas.

It is worth to mention that patients with cancer, atherosclerosis, arthritis, and diabetes mellitus could be essentially good candidates for novel anti-inflammatory and antioxidant therapy. Current clinical trials of anti-inflammatory and anti-ROS agents have shown relatively promising outcomes. The administration of ROS inhibitors to TNFR1-associated periodic syndrome has shown an inhibition in MAPK activation, IL-6, and TNF-α production [58]. Using Sulindac, as a kind of NSAIDS, for 1 year has reduced the polyp multiplicity and induced polyp regression in patient population [132]. Several genetic, pharmacological manipulations that used COX-2 inhibitors demonstrated tumor formation in both human and animal

model suggesting a novel therapy for cancer [132]. Funk and Fitzgerald [133] reported that aspirin confer cardioprotective benefits from the incidence of atherosclerosis by decreasing the inhibition of COX-1. The usage of NSAIDS by patients with active arthritis within 1–2 weeks had a superior efficacy comparing with placebo [134]. Additionally, it has been reported by Tahereh et al. [135] that selective COX-2 inhibitor could be potentially preventive therapy for insulin-dependent diabetes.

For better preventive applications, a further understanding of the relationship between ROS and pro-inflammatory markers may provide a profound biological understanding for the well-established benefits of diet rich in antioxidant and anti-inflammatory compounds in the prevention of ROS- and inflammation-associated diseases. In addition, it could enhance the developing of novel preventive strategies to dwindle the emerging of the mentioned above diseases.

Conclusion

This review has assigned to discuss the possible mutual relationship between ROS and pro-inflammatory markers (Figs. 1, 2). Several studies have concluded that overproduction of ROS triggers the pro-inflammatory process through activation of several regulatory proteins in the tissue. However, further prospective studies on the relationship of ROS and pro-inflammatory markers at cellular and molecular markers are also needed to increase the confirmation of this evidence base.

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Authors' contribution YR involved in study design and concepts, manuscript and figure preparation, editing of manuscript. FA helped in editing manuscript and revising. AMA involved in final approval and editing manuscript. HA and HK helped in revising manuscript and final approval. AF contributed to editing manuscript and final approval.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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