Chapter 35
Selenium and Inflammation

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Abstract It is becoming increasingly clear that over-production of reactive oxygen and nitrogen species (RONS) by immune cells, resulting in oxidative stress, plays a prominent role in several disease states, where inflammation forms the underlying basis. Emerging evidence from many studies in humans and animals strongly suggest that the beneficial effects of selenium-supplementation in prevention and/or treatment of some of these diseases occur via the mitigation of inflammatory signaling pathways. Selenium supplementation, over the minimal nutritional requirements, has gained popularity and there is some scientific evidence to support benefits of super-supplementation of Se. However, despite the therapeutic potential of selenium in many inflammatory diseases, very little is known about the mechanism and regulation of inflammation by Se. To explain the health benefits of selenium and define its biochemical role in mitigating oxidative stress-mediated expression of proinflammatory genes and initiate the recovery or resolution phase, it is important to identify those signaling pathways and genes whose expression is regulated strictly by selenium status in macrophages. Given that RONS serves as a double-edged sword in the modulation of inflammatory signaling pathways, it is not surprising to find that selenium-deficiency defects may be related to an "over-worked" system that fails to mitigate oxidative stress. Thus, studies relating to the modulation of signaling of inflammatory gene expression by selenium may open new opportunities to understand the redox-regulation of complex signal transduction pathways.

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35.1 Introduction

Inflammation is a common biological phenomenon that lies at the helm of many pathological states including cancers, atherosclerosis, autoimmune disorders, diabetes, and neurodegenerative diseases. As part of a complex biological response, inflammation provides the first line of defense against harmful stimuli, infections, and pathogenic invasions and, thus, may be considered as a "necessary evil." A variety of specific mediators are released from tissues and migrating cells in response to stress, free radicals, and infections to activate inflammatory pathways, where prostaglandin (PG) E_2, thromboxane (TX)A_2, and leukotriene (LT)A_4 and (LT)C_4 play critical roles. Biological systems have evolved a variety of anti-inflammatory strategies to combat this phenomenon. Alongside, pain management strategies have also advanced with numerous anti-inflammatory agents such as steroids, antibodies to proinflammatory cytokines, and nonsteroidal anti-inflammatory drugs (NSAIDs). Interestingly, many naturally occurring dietary supplements and nutrients have been shown to modulate low-grade inflammation [1]. These molecules or compounds reduce inflammation by specific mechanisms. Selenium is one such well-known antioxidant that has gained significant attention in the recent past due to its diverse role in the etiology of numerous physiological and pathological processes. Selenium has been found to possess anti-inflammatory properties by modulating a number of cellular signaling pathways.

35.2 Selenium and Inflammation: Human trials

Literature is replete with studies that suggest a critical role for selenium in stress-induced inflammatory processes and diseases of viral or bacterial origin. High levels of C-reactive protein (CRP), which is a commonly used biomarker of inflammation, is associated with reduced serum selenium levels [2]. It has been found that increased RONS production induced by low selenium levels has pathological implications as seen in systemic inflammatory response syndrome (SIRS) and patients afflicted by sepsis that is characterized by extensive tissue damage and organ failure [3, 4]. Studies also suggest the ability of selenium supplementation to reduce the rate of secondary infections in patients with burn injuries and trauma that are characterized by low serum selenium levels and glutathione peroxidase (GPx) activity [5]. In a randomized multi center study, selenium administration reduced the mortality in patients with severe sepsis and septic shock [6]. On the contrary, in another randomized placebo controlled study, infusion of high doses of selenium failed to provide any protective outcome [7]. Although the reasons for such discrepancies are not clear at present, these studies suggest the need for further studies to understand the role of Se in mitigating inflammation.

Selenium possesses protective roles in pathologies involving inflammation associated with rheumatoid arthritis, pancreatitis, autoimmune disorders, cancers,

and asthma. Numerous epidemiological studies in different geographical areas support this fact. In a case-control study involving 18,709 men and women who had no arthritis at baseline, the adjusted relative risk between the highest and lowest tertiles of serum selenium was 0·16 (p for trend = 0.02) for rheumatoid-factor-negative arthritis [8]. In another double-blind randomized trial in a small group of patients with rheumatoid arthritis, supplementation of 200 μg selenium (as selenium-yeast) for 3 months significantly reduced pain [9]. Similarly, the protective effect of selenium was evident in pancreatitis, a disorder associated with a high level of oxidative stress and inflammation. Administration of selenium (600 μg/day) along with other antioxidants to patients with chronic and recurrent pancreatitis significantly reduced pain and frequency of attacks [10]. In a small controlled trial in Rostock, Germany, intravenous administration of selenium to patients with acute necrotizing pancreatitis significantly reduced mortality [11].

An inverse relationship was found between dietary selenium intake and asthma in adults in a large population-based case–control study in London [12]. In a small nested case–control study, current wheeze among New Zealand children was more common in those with low concentrations of selenium in serum samples [13]. Hasselmark et al. [14] demonstrated significant clinical improvement in asthma upon supplementation with selenium at 100 μg per day as sodium selenite.

Several interventional studies over the past few years have demonstrated a variable decrease of anti-thyroid-peroxidase (TPO) in patients with autoimmune thyroiditis (AIT) supplemented with selenium [15–17]. In pregnant women with AIT, selenium supplementation was found to alleviate hypothyroidism and impede the manifestation of postpartum thyroiditis by suppressing anti-TPO levels [18]. A recent study from Austria revealed existence of an inverse causal relationship between AIT and serum selenium levels [19]. Furthermore, in celiac disease (CD), an intestinal inflammatory syndrome, malabsorption-induced selenium deficiency was proposed as a major cause of intestinal mucosal damage as well as a predisposition to AIT via the decreased expression of selenoproteins [7]. Selenium has been recommended as a therapeutic measure in CD to block IL-15-dependent epithelial damage and complications as seen in AIT [20, 21] highlighting the role of selenoproteins as critical regulators of RONS-dependent inflammatory signaling pathways that involve interplay of many immune cells.

35.3 Selenium as an Anti-Inflammatory Agent: Mode of Action

The exact mechanism by which selenium serves as a protective agent in mitigating inflammatory insults is not clear. In immune cells, selenium status is known to modulate a variety of pathways that are pivotal in defining the proinflammatory repertoire. Multiple pathways have been proposed for modes of action of selenium pertaining to its anti-inflammatory properties. These pathways are interrelated to each other, but work at different levels of molecular hierarchy as discussed below.

35.4 Selenium Mediated Scavenging of ROS via Selenoproteins

RONS occupy a major role as key modulators central to many pathways of inflammation. RONS, particularly H_2O_2 and $ONOO^-$, have the ability to interact with many cellular molecules, including proteins, to elicit pathways that lead to increased expression of inflammatory mediators. While the effects are, in part, mediated by the ability of selenoproteins to detoxify ROS, including H_2O_2, lipid and phospholipid hydroperoxides, the consequence of such a process to impact gene expression signatures is intriguing. For instance, changes in the cellular redox tone brought about by the reduction of cellular peroxides have an impact on the activation of key enzymes, such as the cyclooxygenases (COX) and lipoxygenases (LOX), which produce lipid mediators in the form of prostaglandins, thromboxanes, prostacyclins, and oxidized fatty acids, respectively [22]. As an example, PGE_2, TXA_2, LTA_4, and LTC_4 are well-known biomarkers of inflammation. Thus, suppression of the production of such mediators by selenium may attest to its role as an anti-inflammatory agent.

The role of selenium in ROS-mediated pathways of inflammation cannot be complete without addressing the effect of selenium on the mitochondria. Given that the mitochondrial electron transport system also serves as an additional source of RONS, mitochondrial redox imbalances can have serious consequences leading to the activation of signal transduction pathways of inflammation and apoptosis. The loss of mitochondrial integrity and activity could be the main cause of tissue oxygenation and development of inflammatory conditions, which are critical events in cell death processes [23]. Thus, protecting mitochondria may prevent tissue damage during inflammation. Subcellular analysis of selenium distribution in human liver samples indicates that this element is preferentially concentrated in mitochondria and nuclei [24]. Recently, it was documented that high selenium diets could affect liver mitochondrial parameters in vivo as a possible mechanism for its chemopreventive effects [25]. Furthermore, high selenium completely prevented the inflammatory and necrotic conditions by directly interacting with mitochondria in an in vivo inflammatory model of colitis. High selenium treatment was also shown to increase the levels of two important mitochondrial transcription factors, nuclear respiratory factor 1 (NRF-1), and mitochondrial transcriptional factor A (mtTFA) upon treatment with inflammatory stimuli [26]. NRF-1 regulates the expression of mitochondrial electron transport chain protein cytochrome C; whereas mtTFA regulates the transcription, maintenance, and replication of the mitochondrial genome. Thus, the protective mechanism of selenium during inflammation may be explained, in part, by its ability to directly target mitochondria leading to upregulation of mitochondrial transcription factors [26]. On the contrary, under selenium deficiency, modulation of the mitochondrial proteins may cause disturbances in the respiratory chain leading to increased free radical production and subsequent activation of inflammatory signaling pathways.

In favor of the anti-inflammatory role of selenium, selenium deficiency is known to impair some of the phagocytic cell functions, while selenium supplementation

completely corrected the defect [27]. For instance, peritoneal macrophages from rats fed with a selenium-deficient diet exhibited increased H_2O_2 production [28]; and granulocytes from selenium-deficient animals were unable to metabolize H_2O_2 leading to the destruction of their superoxide generating system [29]. Many studies demonstrate the importance of selenium in the pathobiology of disease processes. Decreased chemotaxis in selenium-deficient rats [30] and goats [31] were corrected with selenium supplementation [32]. Studies by Pertuz et al. [33] suggest that selenium may function as one of the physiological factors responsible for reducing inflammation, particularly in the joints in rheumatoid arthritis (RA) patients, by downregulating the "respiratory burst" that is critical for neutrophil activation and generation of oxygen-derived free radicals. While the disturbances are explained, in part, by the low GPx level of cells, the role of many uncharacterized selenoproteins need to be elucidated. More importantly, the ability of selenoproteins to impact key signaling pathways to modulate proinflammatory or anti-inflammatory outcomes needs to be addressed to provide a complete understanding of the role of selenium in anti-inflammation.

35.5 Selenium-Mediated Modulation of COX/LOX Pathways of Arachidonic Acid Metabolism

Cellular exposure to stress is reflected by increases in the levels of circulating proinflammatory cytokines, chemokines, and lipid mediators such as PGs and LTs, some of which are already recognized as bonafide biomarkers of inflammation. As discussed earlier, in addition to its role in the detoxification of peroxides during the activation of phagocytic cells, selenium is also involved in the modulation of COX and LOX pathways of PG and LT from arachidonic acid (AA), a common polyenoic fatty acid esterified in the sn-2 position of membrane phospholipids. The initial step in eicosanoid production requires the release of AA from membrane phospholipids through the activity of phospholipase A_2 (PLA_2), which is activated under conditions of oxidative stress. Because of accumulation of peroxides in Se-deficient conditions, selenium status has been indirectly implicated in increased PLA_2 activity through decreased GPx activity [34]. In addition, selenium participates in several steps of both the COX and LOX pathways of the arachidonic acid cascade through the activity of GPx1, which can reduce lipid hydroperoxide intermediates to their corresponding alcohols. GPx1 reduces the COX product PGG_2 to PGH_2 efficiently (Fig. 35.1). In platelets, GPx1 mediates the reduction of 12-lipoxygenase product, 12-hydroperoxyeicosatetraenoic acid (12-HPETE) to 12-hydroxyeicosatetraenoic acid (12-HETE) [35]. Platelets from selenium-deficient rats produce more trihydroxyeicosatetraenoic acid (THETE) and less 12-HETE than platelets from control rats, indicating that THETE is an alternate pathway when the peroxidase-mediated conversion of 12-HPETE is impaired [33]. Increased 12-HETE levels, particularly in keratinocytes, could play an important role in shaping the immune response during bacterial infections [36]. Similarly, the conversion of 5-HPETE to the inactive

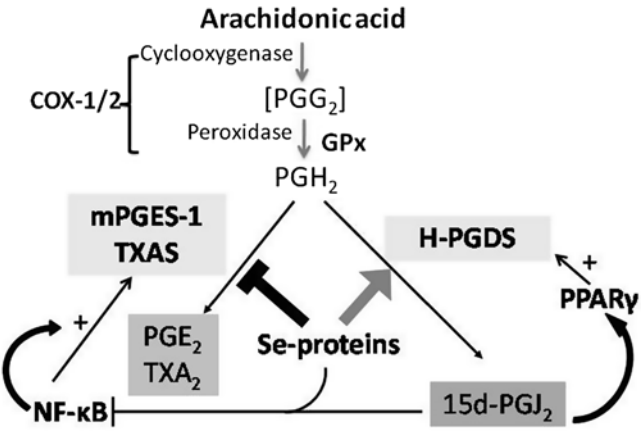

Fig. 35.1 Schematic illustration of the shunting of arachidonic acid metabolism by selenoproteins in macrophages. Macrophages cultured in the presence of bioavailable selenium leads to the enhanced expression of H-PGDS and its product, PGD_2 and 15d-PGJ_2; while pro-inflammatory PGE_2 and TXA_2 that are products of m-PGES-1 and TXAS, respectively, are decreased. Inhibition of NF-κB and activation of PPARγ are two major pathways that are affected by selenoproteins in these cells to modulate pathways of shunting. Increased activation of PPARγ facilitates a positive feedback upregulation of H-PGDS leading to increased levels of CyPGs. COX, cyclooxygenase; mPGES-1, microsomal PGE_2 synthase; H-PGDS, hematopoietic PGD_2 synthase; PPARγ, peroxisome proliferator activated receptor-γ

metabolite, 5-HETE, in leukocytes is also mediated by GPxs [33]. Many of the lipid hydroperoxides display a higher proapoptotic potential in many cell types, apart from activating upstream kinase (MAPK) pathways that increase the expression of many proinflammatory genes, including COX and LOX enzymes. Thus, selenium status serves as a critical determinant of the levels of these reactive intermediates, which appears to be critical in the pathophysiology of many diseases.

Based on these findings, it is speculated that selenium supplementation alters the synthesis of LTs from 5-HETE, while selenium deficiency promotes the conversion of AA to LTA_4, and other products derived from LTs. On the contrary, selenium was shown to promote the synthesis of LTs. Indirect evidence for such a phenomenon comes from studies of pulmonary alveolar macrophages isolated from selenium-deficient rats that produce less LTB_4. Thus, some investigators suggest that GPx activity should be inhibited rather than enhanced in inflammatory diseases [37]. Despite these conflicting data, there is a general consensus that selenium and GPxs play a significant role in PGs and LTs biosynthesis via the ability of these enzymes to modulate the cellular redox tone, particularly to impact such redox-sensitive transcription factors as NF-κB, whose activation has a direct bearing on the production of these lipid hydroperoxides and inflammatory lipid mediators (Fig. 35.1). Therefore, optimal levels of selenoproteins, mainly those with high peroxidase activity, may be clinically beneficial in inflammatory disorders. To determine their relative importance, further in vivo studies are required.

35.6 Selenium-Dependent Modulation of the NF-κB Pathway and Its Role in Macrophage Activation

The NF-κB family of transcription factors, comprising p50, p65 (RelA), p52, RelB, c-Rel, is termed as the "central mediator of immune and inflammatory responses." Diverse stimuli, including cytokines, bacterial and viral products, oxidants, and mitogens, lead to phosphorylation of two regulatory serine residues on IκB, which targets it for polyubiquitination and proteolytic degradation. This leads to nuclear translocation of NF-κB, where it binds to and stimulates the transcription of target genes, including COX-2, iNOS, and several other proinflammatory cytokines and chemokines. Consistent with the notion that decreased selenium deficiency increases intracellular ROS levels, our laboratory has previously demonstrated an increased activation of NF-κB in selenium-deficient RAW 264.7 cells when compared with macrophages supplemented with supraphysiological levels of selenium [38, 39]. More importantly, our studies have further demonstrated that changes in the cellular selenium status serve as a critical regulator of pathways of macrophage activation.

Classical macrophage activation is characterized by the production of several proinflammatory mediators such as IL-1β, IL-6, TNFα, PGE_2, and TXA_2 [40]. PGE_2, TXA_2, PGD_2, and 15d-PGJ_2 are the major eicosanoids derived from arachidonic acid in macrophages. The initial step of PG synthesis involves formation of PGH_2 from arachidonic acid by the action of COX-1 and COX-2, which is subsequently acted upon by specific PG synthases microsomal PGE synthase-1 (mPGES-1), thromboxane synthase (TXAS), and PGD synthase (PGDS), to form PGE_2, TXA_2, and PGD_2, respectively. While the initial phases of inflammation involve increases in levels of proinflammatory mediators like PGE_2, TXA_2, a switch toward the pro-resolving and anti-inflammatory mediators like PGD_2 and 15d-PGJ_2 during the latter stages suggests the involvement of a critical regulator. NF-κB serves as a key transcription factor for mPGES-1 and TXAS, leading to the upregulation of PGE_2 and TXA_2, respectively [41]. Our laboratory has shown that selenium supplementation of macrophages downregulated NF-κB with a corresponding increase in the activation of peroxisome proliferator activated receptor, PPARγ, through the increased production of 15d-PGJ_2 (also called cyclopentenone prostaglandins, CyPGs) [42] (Figs. 35.1 and 35.2). 15d-PGJ_2 serves as an endogenous ligand for PPARγ in addition to acting as an inhibitor of NFκB. On the contrary, Nrf-2 is activated by 15d-PGJ_2 perhaps as a compensatory mechanism to keep the levels of CyPGs under check via detoxification by glutathionylation. Interestingly, recent studies in our laboratory have demonstrated that selenium supplementation of macrophages caused the eicosanoid pathway to be shunted toward PGD_2 and 15d-PGJ_2 rather than PGE_2 and TXA_2 by the differential modulation of NF-κB and PPARγ (Fig. 35.2). Furthermore, preliminary studies have demonstrated the requirement of selenoproteins to effect the switching of eicosanoid pathways. Thus, the role of selenoproteins as key regulators involved in this "switch" toward anti-inflammatory mediators is intriguing and needs to be further elucidated. More importantly, the

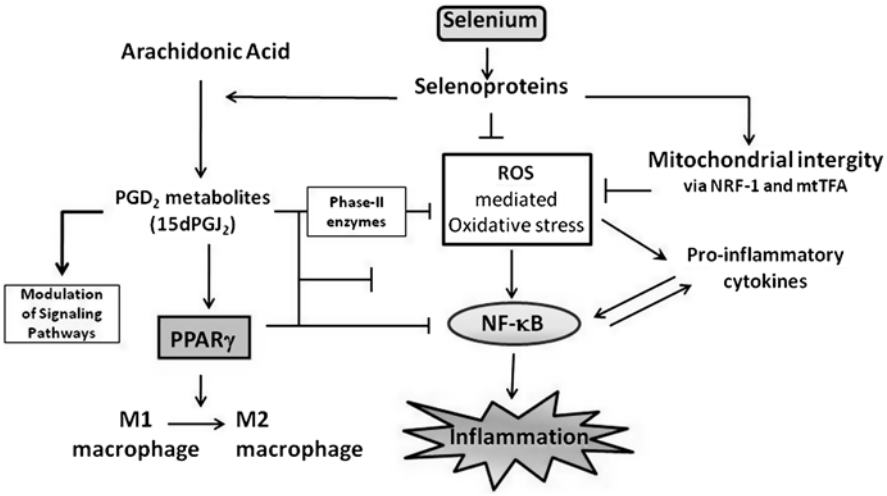

Fig. 35.2 Schematic representation of the implication of selenium-dependent eicosanoid shunting on pathways of anti-inflammation by macrophage phenotype switching. Based on our recent studies, selenoproteins are essential for the upregulation of cellular markers of M2 (anti-inflammatory) macrophages. Selenoproteins effectively mitigate RONS production by protecting the integrity of the mitochondria as well as downregulating the NF-κB pathway. As a result of shunting of arachidonic acid metabolism towards CyPGs, changes in the transcriptional programs within the pro-inflammatory (M1) macrophages facilitates their switching to anti-inflammatory (M2) macrophages to activate proresolution pathways. Such a process is inhibited by treatment of cells with COX or H-PGDS inhibitors or even organoselenium compounds that do not increase selenoproteins in cells

shunting of the arachidonic acid pathway, particular in macrophages, may have many implications; the most notable being a switch from the classically activated "M1" macrophage to the alternatively activated "M2" macrophage phenotype that are endowed with wound-healing and resolving properties [43] (Fig. 35.2).

In addition to producing proinflammatory eicosanoids, M1 macrophages produce proinflammatory cytokines and mediators, such as IL12, IL1β, TNFα, and nitric oxide (NO) [44]. Stimulated by factors like LPS and IFNγ, M1 macrophages lead to tissue damage and cellular immunity [43]. Within the macrophage, the specific enzyme, inducible nitric oxide synthase (iNOS), acts on L-arginine (L-Arg) to produce nitric oxide (NO) [43]. Our laboratory has shown that Se supplementation decreases the presence of iNOS, leading to decreased production of NO [39]. Interestingly, the abundance of the substrate L-Arg does not increase when NO is inhibited, indicating it may be available for the competing enzyme, arginase (Arg-I). Arg-I acts on L-Arg to form urea and L-ornithine, which help in polyamine (collagen) synthesis and enhance the production of anti-inflammatory cytokines and mediators [45].

Alternatively activated macrophages are recognized by their production of anti-inflammatory cytokines, such as IL-10, the expression of distinctive cell surface markers, like mannose receptor, and the secretion of mediators like Ym-1 and

FIZZ-1 [43]. While a function of M2 macrophages is to initiate wound healing through the production of collagen and granuloma formation, M2 macrophages also serve to resolve inflammation. Numerous studies have shown that uncontrolled inflammation can lead to tissue injury and cell death [44]. Based on the preliminary studies, we believe that selenium supplementation positively regulates Arg-I expression to mitigate inflammation and initiate wound-healing (catabasis) responses. Such a switch in macrophage phenotype by selenium could be important in the immune responses to parasites, which remains to be tested.

35.7 Modulation of Inflammatory Pathways by Selenium and Its Effect on HIV Transcription

While micronutrient deficiencies may contribute to HIV/AIDS, selenium deficiency has been singled out as being a major cause for disease progression and mortality in individuals infected with HIV [46, 47]. The significance of selenium against autoimmune disorders is seen in a recent cohort study indicating increased mortality and morbidity among children born to HIV-infected mothers with selenium deficiency [48]. It has also been shown that HIV infection shifts cellular processes toward a prooxidant state leading to increased levels of oxidation products [49] and, hence, accelerated oxidative stress. These changes are concurrent with a simultaneous decrease in plasma selenium levels and depletion of selenoproteins in T cells and erythrocytes [50, 51]. On the contrary, selenium supplementation was found to improve the immunity, diffusion pattern of HIV/AID'S and health of the HIV infected patients [52–54]. Furthermore, the spread of *Mycobacterium tuberculosis* that is commonly associated with HIV-positive patients was reduced with selenium supplementation with a decrease in neuropathy and genital ulcers, accompanied by an increase in $CD3^+$ and $CD4^+$ cells [55].

It is well documented that oxidative stress induces the expression of the transcription factor NF-κB, which is a key molecular event in the initiation of proviral transcription. Increased activation of NF-κB in selenium deficient monocytes or T cells lowers the threshold for increased proviral expression. Thus, the redox modulation of NF-κB by selenium in immune cells could play a regulatory role in the modulation of HIV transcription and replication. Consistent with the observation of Gladyshev et al. [50], our laboratory has recently reported that HIV infection leads to a decrease in the expression of selenoproteins, GPx1, and Txnrd1 in macrophages [56]. Supplementing such infected cells with selenium (in the form of sodium selenite) not only increased the expression of GPx1 and Txnrd1, but also inhibited HIV transcription and replication. These positive effects of selenium on GPx1 and Txnrd1 may be attributed to alleviation of oxidative stress and decreased expression of NF-κB and other pro-inflammatory cytokines that are required to establish a successful HIV infection.

A recent study from our laboratory has shown that selenium, via the increase in Txnrd1 activity, modulated the redox status of a key HIV protein, Tat, a viral protein

expressed early during infection, by reduction of two disulfide bonds to inhibit its transactivation activity, and expression of other viral (structural) genes [56]. In addition, the selenium-dependent production of Δ^{12}-PGJ_2 and 15d-PGJ_2 also impacted the activity of Tat by covalently modifying the thiols that are reduced by Txnrd1. Thus, by a concerted effort, selenium affects the proviral transcription of HIV-1 possibly leading to a reduced rate of disease progression. Such evidences are suggestive of selenium supplementation as a potent adjuvant therapy alongside conventional therapies against HIV/AIDS. Studies are being performed to further characterize the cross talk of HIV with inflammatory signaling pathways, and the role of specific selenoproteins, in downregulating pathways of oxidative stress.

35.8 Selenoprotein S, Its Polymorphism, and Inflammation

Genetic and environmental factors are likely to influence the inflammatory response, but little is known about the genes underlying its regulation. Selenoprotein S (SEPS1) is an endoplasmic reticulum (ER) membrane protein and human homolog of Tanis protein [57], which putatively functions in stress responses of ER that are closely linked to immune and inflammatory signaling pathways [58, 59]. SEPS1 has been found to have a role in inflammatory pathways as an interacting protein of serum amyloid A, which is an acute phase inflammation response protein [58, 60]. SEPS1 participates in the processing and removal of misfolded proteins from the ER to the cytosol [61]. This selenoprotein has a critical role in mediating inflammation through its protection of the ER from unfolded protein stress responses. When the ER is functionally impaired by the build-up of such misfolded proteins, the expression of a number of genes is induced leading to activation of the transcription factor NF-κB [62]. Activated NF-κB induces the expression of SEPS1 in a positive feedback loop. Increased expression of SEPS1 in turn suppresses cytokine production by its ability to remove misfolded proteins from the ER. This system constitutes a SEPS1-dependent regulatory loop in the presence of inflammation. Variations in the SEPS1 gene are known to affect circulating levels of the inflammatory cytokines, IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). Interestingly, polymorphism in the 5′ upstream sequence (−105G→A) was associated with impaired expression of SEPS1 and siRNA suppression of SEPS1 resulting in the increased production of inflammatory cytokine production in macrophages [61].

Inflammation in the arterial wall is recognized to be an important component in the development of acute coronary disease syndromes [63]. Given the known association of SEPS1 with inflammation, the effect of genetic polymorphisms in SEPS1 on the risk of cardiovascular disease was investigated in two independent prospective Finnish cohorts. A significant association was found with increased coronary heart disease risk in females carrying the minor allele of rs8025174 in the combined analysis of both cohorts (HR 2.95; 95% CI 1.37–6.39). Another variant, rs7178239, increased the risk for ischemic stroke significantly in females (HR 3.35; 95% CI 1.66–6.76) and in the joint analysis of both sexes in both cohorts (HR 1.75; 95%

CI 1.17–2.64). Suggestive associations of both variants were also seen with the known cardiovascular risk factors of BMI and waist to hip ratio implicating the selenoprotein SEPS1 in cardiovascular disease risk [64]. These studies indicate that genetic variation in selenoproteins, particularly SEPS1, affect cytokine production that could impact cellular stress and inflammation.

35.9 Selenium Containing Drugs and Compounds as Anti-Inflammatory Agents

As a consequence of the growing recognition of the role of selenium in human health, a number of novel pharmaceutical agents are being developed. The beneficial effects of selenium, in the form of selenoproteins and organo-selenium compounds, have been studied for their role as antioxidants, cytokine inducers, enzyme inhibitors, and anticancer agents. Selenium may complement the actions of COX inhibitors and anti-histamines to effectively reduce major inflammatory mediators. Previously it has been described that derivatives of sulfonamide drugs bearing the selenophene with pyridine, pyridazine, and quinoline nuclei, such as selenolo[2,3-Ib]pyridine, selenolo[2,3-c]pydriazine, selenolo[2,3-b]quinoline, respectively, possess anti-inflammatory and analgesic activities [65]. These sulfa drugs with selenium-containing heterocyclic compounds were demonstrated to increase their biological activities in the form of anti-inflammatory, analgesic, fungicidal, and bactericidal agents [66]. Such novel findings of selenium-based drugs have opened new vistas to explore the enhanced spectrum of biological activity of sulfonamides (sulfadiazine, sulfadimidine, and sulfacetamide) with organo-selenium derivatives.

Along these lines, 1,4-phenylenebis(methylene)selenocyanate (*p*-XSC), a selenium-derivative of benzylthiocyanate was shown to have significant chemopreventive properties in a few rodent cancer models [67]. Interestingly, *p*-XSC effectively inhibited COX-2 expression via the inactivation of NF-κB [68] and displayed enhanced chemopreventive activity in rodents when compared with its sulfur counterpart, 1,4-phenylenebis(methylene)thiocyanate (*p*-XTC). Along the same lines, recent studies by Desai et al. [69] demonstrated that substitution of sulfur in PBIT (S,S′-(1,4-phenylenebis[1,2-ethanediyl])bisisothiourea), a well known iNOS inhibitor, with Se [Se′-(1,4-phenylenebis[1,2-ethanediyl])bisisoselenourea (PBISe)] increased the proapoptotic ability of the isosteric analog toward many cancer cell lines by inhibiting the PI3-kinase and Akt pathway. Recently, we demonstrated a similar strategy with celecoxib, a well-known nonsteroidal anti-inflammatory drug that selectively inhibits COX-2 activity. Interestingly, clinical trials are in progress using a combination of celecoxib and selenium yeast for the prevention of colon cancer [70]. Thus, the concept of synthesis of selenium-derivatives of celecoxib with anti-inflammatory and chemopreventive properties could, thus, represent an effective method to treat inflammatory processes, a hallmark of tumorigenesis. Therefore, to enhance the anti-inflammatory properties at extremely low doses and protect against potential side effects of these drugs, selenium-containing

derivatives were synthesized. One of the selenium-derivatives of celecoxib, namely, 4-(3-selenocyanatomethyl-5-*p*-tolyl-1-yl)-benzenesulfonamide (selenocoxib-2) significantly inhibited bacterial endotoxin LPS-induced activation of NF-κB leading to the down-regulation of expression of pro-inflammatory genes, *COX-2*, *iNOS*, and *TNFα* more effectively than the parent celecoxib at least in a murine macrophage model [71]. Surprisingly, these studies also revealed that selenocoxib-2 effectively suppressed NF-κB activation without increasing the selenoprotein pool, which suggests that such placement of selenium within the celecoxib molecule is critical to target key inflammatory signaling axes in immune cells to mitigate inflammation [[71]]. The ability of selenium in these pharmacophores to interact with Cys thiols in proteins to (redox) modulate their activity could be one of the mechanisms of action, which needs to be further investigated. Nonetheless, these interesting findings open possibilities for a new generation of inhibitors with significant and broader anti-inflammatory potential.

35.10 Concluding Remarks

Increasing evidence shows that selenoproteins and possibly selenium metabolites play a pivotal role in down regulating cellular signaling pathways critical in the expression of proinflammatory mediators. It is now clear that selenium status of immune cells, particularly macrophages, leads to the decreased activation of NF-κB through a variety of mechanisms, including the production of novel anti-inflammatory PG metabolites. The implications of such an increased CyPGs production is vast and can explain many anti-inflammatory properties of selenium. However, defining the mechanism(s) by which selenoproteins increase CyPGs to dampen pathways of proinflammatory signaling while increasing pathways of anti-inflammation still remain to be investigated.

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