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Relationship between selenium status, selenoproteins and COVID-19 and other inflammatory diseases: A critical review

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ABSTRACT

The antioxidant effects of selenium as a component of selenoproteins has been thought to modulate host immunity and viral pathogenesis. Accordingly, the association of low dietary selenium status with inflammatory and immunodeficiency has been reported in the literature; however, the causal role of selenium deficiency in chronic inflammatory diseases and viral infection is still undefined. The COVID-19, characterized by a severe respiratory syndrome and caused by the novel coronavirus 2, SARS-CoV-2, has infected millions of individuals worldwide since late 2019. The severity and mortality from COVID-19 have been associated with several factors, including age, sex and selenium deficiency. However, available data on selenium status and COVID-19 are limited, and a possible causative role for selenium deficiency in COVID-19 severity has yet to be fully addressed. In this context, we review the relationship between selenium, selenoproteins, COVID-19, immune and inflammatory responses, viral infection, and aging. Regardless of the role of selenium in immune and inflammatory responses, we emphasize that selenium supplementation should be indicated after a selenium deficiency be detected, particularly, in view of the critical role played by selenoproteins in human health. In addition, levels of selenium should be monitored after the start of supplementation and discontinued as soon as normal levels are reached. Periodic assessment of selenium levels after supplementation is a critical issue to avoid over production of toxic metabolites of selenide because under normal conditions, selenoproteins attain saturated expression levels that limits their potential deleterious metabolic effects.

1. Introduction

1.1. The chemical physiology of selenium: selenoproteins

The trace element selenium (Se), a nonmetal (sometimes considered a metalloid) that belongs to the Group 16 (Chalcogens) of the periodic table, is a central component of the 21st proteogenic amino acid selenocysteine, which is part of selenoproteins in humans. Various selenoproteins are part of the body’s most important antioxidant defense mechanisms. For instance, as an integral component of Se-dependent glutathione peroxidase isoforms (GPxs), the Se atom [in the form of selenol (-SeH) group in selenocysteine; Fig. 1] is involved in the reduction of various forms of peroxides. The glutathione peroxidase 1 (GPX1) enzyme is the most abundant of the GPxs and is found in the cytosol of different mammalian tissues where it degrades hydrogen peroxide (H2O2) to water (H2O). Glutathione peroxidase 4 (GPX4) is an essential selenoenzyme in mammals and is found associated with biomembranes, where it decomposes organic peroxides of fatty acids from phospholipid [1,2]. Selenocysteine residues are also found in the active site of human thioredoxin reductases (TXNRD), where its selenol group plays an important role in the reduction of oxidized thioredoxin isoforms at the expense of electrons from NADPH. Consequently, Se is essential for optimal functioning of the antioxidant TXNRD system in mammals [3]. Of particular importance for human health, the glutathione and the

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The antioxidant effects of Se (as component of selenocysteine) has been demonstrated by its role in the antioxidant enzyme methionine-R-sulfoxide reductase, which can reduce methionine-R-sulfoxide back to methionine, thus contributing to preserve the biochemical properties of methione-containing proteins. There are lines of evidence indicating that some selenoproteins are thought to be involved in the physiological regulation of inflammatory and immunological response [4,5]. However, the molecular mechanisms mediating such regulation are unknown. The association of low Se dietary status with inflammatory and immunodeficiency has been extensively reported in the literature, but it should be emphasized that the causal role of Se in those pathologies is still elusive. For instance, in the case of type 2 diabetes, observational studies have indicated an association of Se levels and an increase risk of developing the diseases, but in randomized clinical trials of Se, a higher risk of type 2 diabetes was not observed for those who received Se compared to a placebo (for a meta-analyses review see Kohler et al. [29]). It has been also hypothesized that the increase in Se levels can even be consequence of diabetes than the cause of the pathology [30] and, in another study with type 2 diabetes subjects, high blood selenium levels (the highest quartile) was associated with a decrease in the risk of all causes of death, when compared to the lowest quartile group. In contrast, Huque and Shi [31] found that selenium levels was associated with increased risk of diabetes, but with a decrease in the risk of all-cause mortality, but only in white subjects of the study.

### 1.2. Nutritional Se status and COVID-19

The COVID-19, characterized by acute respiratory syndrome, and caused by the novel coronavirus 2 (SARS-CoV-2), has infected millions of individuals worldwide since the end of 2019 [32]. The severity and mortality from COVID-19 have been associated with several factor, but age, sex, and the Charlson Comorbidity Index (CCI, a weighted index that predicts the one-year mortality risk of subjects with comorbidities) seem to be the most reliable risk factors [33]. The role of low serum Se status in COVID-19 has been investigated [18,34] as Se-deficiency has been previously associated with the severity of a few viral infections [16, 19,35–41]. However, available data on Se status and COVID-19 are limited, and a possible causative role for Se-deficiency in COVID-19 severity has yet to be fully addressed. For instance, the severity of COVID-19 is increased by age and a variety of chronic pathological conditions, which are normally associated with chronic inflammatory states and oxidative stress [42–45]. Thus, the first issue to be clarified is whether lowered Se status found in the preliminary published data was a consequence of age and comorbidities associated with increased rates of death in COVID-19, or a causal factor in the etiology and ensuing death upon SARS-CoV-2 infection. Another critical aspect is whether or not Se status is directly related to control of virus replication, or if it indirectly modulates inflammation and cell redox balance via the expression of

![SELENIUM STATUS](image-url)

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**Fig. 1.** The selenocysteinyl (Sec) residue in human glutathione peroxidase 1. Here a monomer is presented but the active form of the enzyme is homotramer. The rare amino acid selenocysteine (Sec) is not found free in the body fluids of vertebrates, but it is found in the structure of 25 selenoproteins in the human body. The three-dimensional crystal structure (left) and the selenocysteinyl residue found in its active site are indicated in the left part in green with the Se atom in orange. The amino acids before (leucyl residue) and after (glycyl residue) the Sec are depicted with the free amino (NH) and carboxyl groups (CO). The Se atom (orange) is depicted as the big ball linked to one hydrogen (white) forming the selenol group. The structures are based on the analysis of GPX1 performed by Epp; Ladenstein; Wendel [8] (PDB ID: 1GP1). The hydrogen atoms were hidden for the sake of clarity (in the left). Details of Sec and the two adjacent amino acids (leucine and glycine) are shown on the right. The whole GPX1 structure and three amino acids (in the right) are depicted as sticks, except the selenol group (-SeH). The selenol group is represented by scaled balls.

TXNRD systems are pivotal for the maintenance of cellular redox balance in mammalian cells.

The antioxidant effects of Se (as component of selenocysteine) has been demonstrated by its role in the antioxidant enzyme methionine-R-sulfoxide reductase, which can reduce methionine-R-sulfoxide found in oxidized proteins back to methionine, thus contributing to preserve the biochemical properties of methionene-containing proteins. The three-dimensional crystal structure (left) and the selenocysteinyl residue found in its active site are indicated in the left part in green with the Sec atom in orange. The amino acids before (leucyl residue) and after (glycyl residue) the Sec are depicted with the free amino (NH) and carboxyl groups (CO). The Se atom (orange) is depicted as the big ball linked to one hydrogen (white) forming the selenol group. The structures are based on the analysis of GPX1 performed by Epp; Ladenstein; Wendel [8] (PDB ID: 1GP1). The hydrogen atoms were hidden for the sake of clarity (in the left). Details of Sec and the two adjacent amino acids (leucine and glycine) are shown on the right. The whole GPX1 structure and three amino acids (in the right) are depicted as sticks, except the selenol group (-SeH). The selenol group is represented by scaled balls.

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**Fig. 2.** Inverted U-shaped relationship between Se status (in microgram/liter of serum) and risk of human disease.
specific selenoproteins. In this regard, Se may participate indirectly by modulating the anti-inflammatory and antioxidant status of the cells, either by impairing (deficiency) or improving the synthesis and biochemical activity of critical 25 human selenoproteins. For example, it is known that glutathione peroxidase 2 (GPX2) and GPX1 are able to modulate the levels of cyclooxygenase (COX)-derived prostaglandins PGE2 and PGD2 [46,47]. In this context, here, we will review the relationship between Se, immune response, selenoproteins, and COVID-19. Regardless of the role of Se in immunological and inflammatory responses, we emphasize that Se supplementation should be indicated only after a Se-deficiency had been detected. In addition, the levels of Se should be monitored after the start of supplementation and discontinued as soon as normal levels are reached.

2. Se involvement in the immune and inflammatory responses

The immune system has important roles in protecting the organisms against physical damage or microbial infection. After such a kind of insult (for example, an infectious agent), its activation typically involves the action of pro-inflammatory molecules, thus stimulating inflammation. However, this initial pro-inflammatory response is subsequently accompanied by the activation of anti-inflammatory mechanisms. The resolution of inflammation, which is necessary to reestablish cellular and organismal homeostasis, is mediated and regulated by various classes of chemical mediators, and the adequate (neither insufficient nor exaggerated) immune response to infectious agents requires a chronologically orchestrated interplay between pro- and anti-inflammatory mediators [47-53].

2.1. Se in immunity: direct or indirect roles?

Adequate Se intake is crucial for the appropriate functioning of cellular and humoral immune processes (Table 1) [16,36,37,54-57]. For instance, the inclusion of sodium selenite in the diet of pigs (0.05–0.1 ppm) [58], lambs (1 ppm) [59], and mice (0.5 or 2 ppm) [60] has been shown to modulate the activity of adaptive immune response by stimulating the appropriate proliferation of T and B lymphocytes in response to mitogens [54], and by preventing the apoptosis of T lymphocytes and natural killer (NK) cells [54]. On the other hand, some negative effects of high in vitro concentrations of inorganic Se - Se (IV) and Se (VI) - supplementation on leucocyte function (particularly in natural killer cells) have been reported [61,62]. However, it remains unclear how selenoproteins participate in human immune and inflammatory responses. There are only few reports on the direct role of specific selenoproteins in immune cell function [46,53]. For instance, Ma and Hoffmann [63] have indicated that selenoprotein K (SELENOK) is essential for adequate palmitoyl acyltransferase activity of the protein DHH6 and for the proper function of inositol 1,4,5-trisphosphate receptor. Of immunological significance, SELENOK/DHH6 interaction has a critical role in the palmitoylation of AS1, a process that is required for proper phagocytosis in mouse bone marrow derived macrophages [64,65].

Studies have also demonstrated that Se can influence leucocyte function both in vitro and in vivo models. Intake of Se-enriched diet (0.3 mg/Kg diet) by goats has been associated with improvements in the function of the most abundant circulating phagocytic polymorphonuclear neutrophils, when compared with the selenium deficient diet (0.08 mg/kg diet) [78-80], which are important players in the innate immune system [85-87]. It has been suggested that Se can protect against bacterial infections of bovine mammary gland by increasing the velocity of neutrophil migration to the site of the infection [77]. However, in an in vitro model of Se-deficiency using primary bovine mammary arterial cells [2], the TNF-α and IL-1-induced adhesiveness of neutrophils to endothelial cells was greater in Se-deficiency than in control endothelial cells (Se supplemented group).

The excessive adherence of neutrophils to endothelial and other non-target tissues can compromise proper immune responsiveness (e.g.,

| Table 1 | Modulation of the immune system by Se. |
|---------|--------------------------------------|
| Species | Se Function | Assay | Reference |
| Chicken | Increased leucocyte migration. | in vivo | Swain et al. [66] |
|         | Increased mRNA expression of interleukin 1 receptor (IL-1R) and interleukin 1 beta (IL-1β). | in vivo | Pan et al. [67] |
| Mice    | Increased mRNA expression levels of selenoprotein T (SELENOT), interleukin 2 (IL-2) and interleukin-2 (INF-γ). | in vivo / in vitro | Beck [68] |
|         | Increased severity of inflammation in Influenza A infection. | in vivo / in vitro | Beck et al. [36] |
|         | Increased in antigen-specific responses, cell proliferation, and differentiation in CD4+ T lymphocytes. | in vivo / in vitro | Hoffman et al. [69] |
|         | Reduced mature T cell pool and T cell-dependent antibody responses. | in vivo / in vitro | Carlson et al. [70] |
|         | Decreased macrophage migration, exaggerated T cells production of reactive oxygen species (ROS), and impaired T cell response to receptor stimulation. | in vivo / in vitro | Nelson et al. [71] |
| Sheep   | Increased GPX and phagocytic activity of monocytes and neutrophils against ruminal bacteria and protozoans. | in vivo | Cobanová et al. [75] |
| Cattle  | Increased GPX and phagocytic activity of neutrophils against Candida albicans. | in vivo | Boyne and Arthur [76] |
|         | Increased polymorphonuclear neutrophils activity. | in vitro | Smith et al. [77] |
|         | Increased neutrophil adherence to endothelial cells after stimulation with TNF-α, IL-1, and H2O2. | in vitro | Maddox et al. [2] |
| Goats   | Increased the function of polymorphonuclear neutrophils associated with increased levels of GPX. | in vitro | Aziz et al. [78] |
|         | Decrease the leutokaxis towards chemotaxis. | in vitro | Aziz and Klesius [79] |
|         | Decreased production of migration factor in leukocytes. | in vitro | Aziz and Klesius [80] |
| Horses  | Suppressed cell-mediated immunity, associated with lowered GPX activity. | in vitro | Brummer et al. [81] |
| Pigs    | Decreases the levels of selenozymes, selenoproteins, IL-2 and INF-γ. | in vivo | Yang et al. [82] |
| Humans  | Decreases phosphoglycan function and cytotoxicity of immune system cells. | in vivo | Dworkin [83] |
|         | Decreases T cell count. | in vivo | Baum et al. [84] |
|         | Increased T cell proliferation. | in vivo / in vitro | Ivory et al. [57] |
clearance of infectious agents from target tissues). The migration of neutrophils to non-target tissues can have pathological consequences and aggravate chronic or acute inflammatory diseases. However, mechanistic data on how Se status modulates the neutrophil migration to target or non-target tissues in infectious diseases are scarce. The increase in neutrophil adherence to endothelial cells maintained in a Se-deficient medium has been shown to be associated with increased mRNA expression of endothelial cells adhesion molecules, ICAM-1 and E-selectin. In contrast, the levels of P-selectin were increased in Se supplemented in relation to Se-deficient cells. Selenite supplementation in human umbilical vein endothelial cells increased the activity of antioxidant selenoenzymes (GPX1 and 4 and TXNRD) and inhibited the synthesis of TNF-α-induced ICAM-1, VCAM-1, and E-selectin expression [88,89].

Se has also been reported to induce an increase in the endothelial reactivity, synthesis of adhesion molecules associated with neutrophil infiltration, and exacerbate inflammatory response both in vitro and in vivo models of Se-deficiency [88,90–92]. Se-deficient diet intake caused vasculitis in chicken, which was associated with an increase in several molecular endpoints of inflammation [91].

In accordance with an anti-inflammatory role of adequate Se status, Se-deficiency has been associated with enhanced pro-inflammatory response by increasing the synthesis of cyclooxygenase 2 (COX-2) in the RAW 264.7 macrophage after a challenge with bacterial endotoxin lipopolysaccharide (LPS) [93]. The production of pro-inflammatory prostaglandins has been reported to increase during Se-deficiency, whereas Se supplementation changed the arachidonic acid metabolism from the synthesis of pro-inflammatory to anti-inflammatory prosta-
glandins [47,53,94].

In contrast, Se-deficiency has been linked with decreased production of leukotriene B4, which is an important chemotactrant involved in leukocyte activation [79,80,95]. In various mammalian species (goats, cows, horses, and mice), Se-deficiency has been associated with impaired synthesis or release of migration factors by leukocytes, neutrophils, and macrophages [73,79–82,96]. Consequently, Se-deficiency can impair leukocyte activation, differentiation, migration and adhesion to infected tissues; however, whether this represents an indirect response to redox unbalance caused by disruption of antioxidant selenoproteins synthesis is presently unclear. The direct involvement of specific selenoproteins in the normal functioning of immunological cells have been described in a few studies [53,64,97]. For instance, the expected decrease of SELENOK under Se-deficiency can also impair the phagocytosis by macrophages and neutrophils [64], because SELENOK has been demonstrated to be a cofactor for acyltransferase activity of DHH6 in mice macrophages [64].

Notably, the increase in the production of reactive oxygen and nitrogen species (RONS) has been associated with an increase in the expression of pro-inflammatory agents. For instance, RONS stimulate the synthesis of nitric oxide synthase (iNOS), IL-1β, IL-10, IL-12, NF-κB, prostaglandin E synthase (PTGES), TNF-α, IL-8 levels, interferon-γ (IFN-γ) and interferon-β (IFN-β) [16,37,53,98,99]. Together, the increased adherence of pro-inflammatory cells and the absence of proper modulation of ROS production can exacerbate the inflammatory response and impair the resolution phase of inflammation. In corroboration, individuals with decreased serum Se levels can have higher chronic oxidative stress caused by the overproduction of ROS by neutrophils [100]. One important point that has not been investigated is the potential inactivation of selenoproteins by the reactive species formed directly by myeloperoxidase in phagocytizing cell [86,101]. In chondrocytes, the deletion of selenophosphate synthetase 1 (SEPHS1), a protein with antioxidant properties, exacerbated oxidative stress and downregulated the mRNA levels of glutathione peroxidase 1 (GPX1), selenoprotein W (SELENOW) and methionine sulfoxide reductase-B1 (MSR1) [102]. While N-acetylcysteine decreased the oxidative damage in SEPHS1 deficient cells, the effects of N-acetylcysteine on the levels of selenoproteins were not investigated. From these observations, it appears that selenoproteins can modulate oxidative stress in the inflammatory and immune responses. For instance, GPX4 has recently been implicated in the stimulation of NLRP3 inflammasome in the kidneys of broilers maintained in a Se-deficient diet [103]. The mechanism was associated with increased synthesis of the microRNA 1656 (miR-1656), pro-inflammatory cytokines and ROS production. Of note, the synthesis of all 25 broiler selenoproteins were decreased (including GPX4) [103]. There are only a few studies showing that a specific selenoprotein (e.g., SELENOK) has direct molecular role in immune cells (macrophages) phagocytosis [64] (more details will be discussed below). Thus, it will be important to determine the expression of selenoproteins (selenoproteome analyses) under conditions of dietary Se excess, adequacy, and deficiency in different types of white blood cells and correlate Se status with changes in the production of pro- or anti-inflammatory mediators. Most importantly, the assessment of how the fluctuations in Se status (from deficiency to supranutritional levels) and selenoprotein interfere with the immune and inflammatory responses of specific white-blood cells against pathogenic microorganisms is highly needed both in vitro, ex vivo and in vivo.

2.2. Se as an important factor in inflammation resolution

Another point that needs further investigation is whether or not Se has a more critical role during the resolution of inflammation than in the initial pro-inflammatory phase [47,53]. Indeed, a critical role for Se supplementation (in vitro) has been advanced in the transition from a pro-inflammatory to an anti-inflammatory phase in macrophages [39,71,74]. In macrophages obtained from the bone marrow of mice fed a Se adequate diet (0.1 mg sodium selenite/Kg of diet), incubation with LPS or IL-4 enhanced the expression of anti-inflammatory macrophage (M2) markers, while blunted the stimulation of pro-inflammatory macrophages (M1) phenotype, when compared with the bone marrow derived macrophages from mice maintained in a Se-deficient diet. The bone marrow derived macrophages obtained from mice maintained in a supranutritional level of Se (0.4 mg selenite/kg) did not differ from the adequate Se group [71].

The participation of selenoprotein P (SELENOP) in the modulation of polarization of macrophages has also been demonstrated in mice infected with Trypanosoma congolense. The infection of wild mice was associated with increased expression of SELENOP and M2 macrophage phenotype-linked genes [104]. The knockout of SELENOP increased the susceptibility to T. congolense infection. In contrast, mice with deletion only in the C-terminal region of SELENOP (the Se-rich region involved in the transport of Se) but with the preserved putative antioxidant N-terminal domain, were able to control the T. congolenses infection. Notably, the levels of pro- and anti-inflammatory cytokines were not modified by SELENOP knockout. These results suggest that in this model of infection, the role played by SELENOP was possibly indirectly related to modulation of oxidative stress or by the expression of M2-associated genes (including SELENOP itself), allowing for the proper modulation of inflammation and infection by wild and SELENOPΔΔ240-260(SELENOP containing only the antioxidant domain) muted mice [104]. The data also point that the fine balance between the M1 and M2 macrophages phenotype was modulated by the N-terminal part of SELENOP, indicating that the full understanding on how Se regulates the inflammatory and immune responses towards microorganisms will require complex experimental manipulation of selenoprotein domains synthesis both in vitro and in vivo.

In a recent elegant study, Korwar et al. [74] demonstrated that murine macrophages isolated from the bone-marrow cell cultures supplemented with sodium selenite (250 nM) facilitated the shift from a pro-inflammatory (M1) to anti-inflammatory (M2) phenotype of macrophages in a model of peritoneal inflammation induced by LPS. In
contrast, macrophages isolated from the Se-deficient (0 nM) bone-marrow cultures had the predominance of the pro-inflammatory (M1) phenotype. The study of Korwar et al. [74] was the first study to indicate that Se status can have a complex role in the adequate immune and inflammatory response to the LPS bacterial endotoxin.

At some variance with the study of Korwar et al. [74], Barrett et al. [105] demonstrated that heterozygous SELENOP-deleted mice had enhanced tumorigenesis in a model of colitis and increased M2 macrophages in the colonic tumors. It is noteworthy that the complete deletion of SELENOP did not result in an increase in tumorigenesis and M2 macrophage phenotype. The complex in vivo data with a modification in the levels of a single selenoprotein indicate that efforts should be made to scrutinize the role of each individual selenoprotein in relevant models in vitro.

### 2.3. Se Deficiency, selenoproteins, and cellular immune and inflammatory responses

As noted above, Se-deficiency has been associated with impaired leukocytes, neutrophils, and macrophages' function [72,83,106,107] (Table 1). Se-deficiency and non-adaptative synthesis of selenoproteins have been shown to modulate negatively the adequate immune response of macrophages [70], particularly the proper resolution of the inflammatory response [74].

In studies carried out in pigs and chickens, Se-deficiency has been associated with the downregulated synthesis of the selenoenzymes (TXNRD-1, GPX1, GPX2, GPX3, GPX4), selenoproteins (SELENOP, SELENOH, SELENOS, SELENJ, SELENOM, SELENO, SELENOK, SELENON, and SELENOW) [82], IL-2 and INF-γ, and with an increased expression of IL-1R and IL-1β mRNA [67]. Thus, Se status can modulate the inflammatory and immune response either by changing the synthesis of critical selenoproteins, chemotractant mediators, and the level of reactive oxygen and nitrogen species both in target and non-target tissues.

In a recent study, Wolfram et al. [108] demonstrated that Se did not modulate the differentiation of human THP-1 leukemic monocytes into macrophages after treatment with phosphor myristate acetate (PMA). However, protein levels of GPX4, SELENOH, SELENOS, and selenoprotein F (SELENOF) increased after selenite inclusion in the cell culture medium. The levels of GPX4, SELENOH and SELENOS decreased as the PMA concentration increased, independently of Se supplementation. The mRNAs expression of all selenoproteins were also evaluated and in the presence of selenite only the mRNA levels of SELENOH and SELENOP were increased. PMA increased the mRNA levels of all selenoproteins both in absence and presence of selenite. In the presence of PMA, selenite caused a further increase in SELENOF mRNA. The mechanism involved in the general increase selenoproteins mRNA induced by PMA was not addressed, but PMA treatment caused a significant decrease in GSH levels and catalase expression, suggesting a possible role for an oxidative cellular environment as modulator of selenoprotein synthesis.

The authors also demonstrated that LPS–selenite caused a general increase in the levels of various lipid mediators when compared with LPS-treated monocytes. In PMA-differentiated macrophages selenite supplementation caused an increase only in the levels of docosahexaenoic acid (DHA), but selenite–LPS–PMA increased the level of various lipid mediators. However, a potential correlation of selenoproteins levels with lipid mediators was not investigated.

The general role of all selenoproteins expression in T-cells was studied in mice with selenoprotein-deficient T cells by deletion of the gene codifying the selenocysteinyl-tRNA synthetase (sec) (trsp) [109]. Mice consuming Se-deficient diets (see Table 1) displayed selenoprotein-deficient T-cells with decreased pools of mature T cells and exhibited marked impairments in spleen, thymus, and lymph node size and number of cells. The T Cell Receptor (TCR) signaling was also compromised in the T cells of mutant mice and the stimulation of the mutant T cell with CD3 and CD28 caused only a modest increase in the incorporation of thymidine when compared with the T cells from wild mice [109]. T cells with deleted tRNA[Ser]Sec gene exhibited oxidative stress and the inclusion of N-acetylcysteine (1 and 10 mM) together with CD3 plus CD28 restored the capacity of T-cells to respond to CD3-TCR complex-induced cell proliferation. Taken together, it seems that both dietary Se-deficiency (Table 1) and the impairment of all selenoproteins causes an overall oxidative unbalance in T cells, which impaired their responses to CD3 plus CD28 stimuli.

Additional studies from the same group [70] corroborated and expanded the previous findings by Shirmali et al. [109]. In the study by Carlson et al. [64], selenoprotein-deficient T cells responded to a lesser extent to IL-2 receptor activation than normal T cells, with selenoprotein deficient T cells displaying exaggerated ROS production and impaired T cell activation and the global immune response [70,109].

The effects of all selenoproteins deficiency in macrophages on in vivo models of inflammation (peritonitis induced by zymosan, LPS endotoxicemia, and chemical irritant (12-O-tetradecanoylphorbol-13-acetate dermatitis)) were investigated in mice [70]. The authors observed that all selenoproteins deficiency did not change neutrophil infiltration nor cytochrome c release, nor mortality in these above-mentioned models of inflammation. Notably, differences between the in vivo results from Carlson et al. [70] and the data described above in Section 2.1, where neutrophil migration and adhesion to tissues were altered by Se-deficiency are apparent. However, though the inflammatory responses in these models were not modified by selenoprotein deficiency in macrophages, in vitro migration of macrophages in the gel-Landén Trans well model was impaired [70,110]. The impairment of macrophage migration results is in agreement with the data reported previously both after in vivo or in vitro models of Se-deficiency (see Table 1 and Section 2.1.). Thus, the deficiency of all selenoproteins in macrophages seemed to modify the inflammatory response in a complex way. As already noted, knockout of SELENOK modifies the normal chemistry of phagocytic cup and impairs the phagocytosis in mouse bone-marrow derived macrophages [64]. In accordance, the knockout of SELENOK in mice was associated with a deficient TCR activation and with impaired intracellular Ca^{2+} fluxes with macrophages and neutrophils [63,97].

Se has also been implicated as an important modulator of an adequate inflammatory response in infectious and autoimmune diseases [84,111–113]. In fact, the beneficial effects of Se can be mediated indirectly via modulation of the antioxidant activity (i.e., maintaining the adequate selenoprotein synthesis) [70]. For instance, antioxidant selenoenzymes (e.g., GPX isoforms and TXNRD isoforms) can modulate the inflammatory response indirectly by regulating the peroxide tone that is critical for the adequate activity of lipoxigenases and cyclooxygenases [53,60,114,115]. The products of these pathways (leukotrienes, thromboxanes, prostaglandins, resolvin, etc.) are involved in the synthesis of pro-inflammatory mediators (for instance, TNF-α) [53,99,116,117]. In agreement, GPX1 has been demonstrated to have indirect anti-inflammatory functions by inhibiting the pathway involved in the synthesis of the nuclear factor kappa beta (NF-κB). By negatively modulating this signaling pathway, Se can reduce the production of inflammatory mediators, such as IL-1β, interleukin 6 (IL-6), TNF-α, and interleukin 17 (IL-17) [47,53,60,113,118,119].

Se can also mitigate the occurrence of exacerbated inflammatory responses by regulating the eicosanoid metabolism, for instance, the synthesis of cytokines and chemokines in leukocytes and endothelial cells [47,53,120]. Additionally, Se has been described to regulate the expression of pro-inflammatory genes, for instance, COX-2 and TNF-α, in murine macrophages [94,114]. These authors demonstrated that in vitro sodium selenite supplementation (0.05 – 0.5 nmol/mL) decreased the expression of COX-2 and TNF-α, compared to the Se-deficient group (0 nmol/mL). Furthermore, sodium selenite supplementation (0.05 – 1.5 nmol/mL) increased concentration-dependently macrophage GPX1 expression. It is important to emphasize that a causal relationship between GPX1 expression and inflammatory markers was not clearly established. Apparently, GPX1, GPX2 and GPX4 modulate the
inflammatory process by reducing the peroxide tonus. However, the whole picture is rather complex because the modulation of the enzymes involved in the synthesis of lipid mediators (e.g., 5-LOX; 12-LOX, 15-LOX, COX-1 and COX-2) by GPXs can modify both inflammatory and anti-inflammatory synthetic pathways [46,53]. On the other hand, GPX isoforms can reduce lipid peroxides derived from 12-LOX- and 15-LOX-mediated arachidonic acid oxidation [121].

In mice, moderate Se-deficiency has been associated with decreased splenic leukocytes total GPX and TXNRD activities and impaired expression of the GPX1 and SELENOF, SELENOW, and SELENOH genes [122]. Of note, moderate Se-deficiency disrupted the expression of several genes associated with the inflammatory response (for instance, the expression of more than 30 NF-κB target genes was repressed under Se-deficiency) [122], suggesting that indirectly Se may modulate the production of pro- and anti-inflammatory agents by modulating the adequate selenoprotein synthesis.

Selenoproteins in the endoplasmic reticulum (for instance, the SELENOS, selenoprotein N (SELENON), SELENOK, and iodothyronine deiodinase 2 (DIO2)) could be directly involved in the modulation of inflammation by facilitating the inhibition of pro-inflammatory pathways or stimulating the anti-inflammatory signaling. Knockout of SELENOK, which is highly expressed in human and mice polymorphonuclear blood cells, mice spleen, and lymph nodes, caused defective receptor-triggered Ca²⁺ fluxes in mice T cells, neutrophils, and bone marrow-derived macrophages [63,97]. Ex vivo neutrophil chemotaxis was impaired by SELENOK knockout. The in vivo infiltration of neutrophils induced by a peritonitis model and the serum level of two cytokines (KC and MCP-1) were decreased in SELENOK deficient mice. However, no changes in the number of CD4⁺, CD8⁺ and CD4⁺CD8⁻ cells from the thymus, lymph node, and spleen of SELENOK knockout mice were detected [97], suggesting that SELENOK deletion did not play a critical role in immune system development.

In an elegant study, Norton et al. [64] demonstrated that bone marrow-derived macrophages (RAW 264.7) from SELENOK knockout mice exhibited impaired phagocytosis of IgG-coated beads, a process dependent on the activation of Fc gamma Receptor. The same authors investigated these cells transfected with V5-tagged SELENOK proteins that could interact with SELENOK. They identified one fragment corresponding to the multidomain protein ASAP2, a protein that participates in the phagocytosis activated by the Fc gamma receptor. The fluorescent detection of ASAP2 during Ig-G coated beads phagocytosis by bone marrow-derived macrophages from SELENOK knockout mice demonstrated that ASAP2 accumulated in the phagocytic cups. The accumulation was associated with impairments in palmitoylation and proteolytic ASAP2 processing by Calpain 2 under SELENOK deficiency. The data obtained in macrophages expanded previous studies from the same group where SELENOK/DHHC6 complex formation was demonstrated to be important for the palmitoylation of Inositol-1,4,5-triphosphate receptor (IP3R) [65]. The authors concluded that SELENOK is a cofactor for the palmitoylation of proteins ASAP2 by DHHC6, a critical metabolic step in the macrophage phagocytosis mediated by Fc gamma receptor.

However, in addition to having specific molecular roles in the modulation of immune cells function (e.g., SELENOK is a critical cofactor in macrophages phagocytosis [64], selenoproteins, such as SEPS1, SELENOK, and SELENON can also have antioxidant properties or modulate the endoplasmic reticulum stress response [123,124]. In short, Se and selenoproteins have significant roles in both inflammatory and immune responses mediated by antioxidant selenoenzymes (e.g., GPX and TXNRD isoforms), and possibly some specific selenoproteins can participate directly in the control of neutrophils, T cells macrophages functions and in the immune response to the infection with West Nile virus the SELENOK knockout was associated with high mortality and virus titers in the mice brain [125]. However, experimental data supporting specific direct molecular roles for the majority of selenoproteins in the inflammatory and immune response are still preliminary.

2.4. Selenoproteins as modulators of inflammation: undefined or only general modulatory roles?

As discussed above, Se status can modulate the immunological and inflammatory responses by changing the synthesis of selenoproteins. Here we will discuss the general role of antioxidant selenoenzymes as indirect modulators of inflammation and some few in vitro and in vivo data pointing out a possible direct role for a few selenoproteins as modulators of the inflammatory response [64,71,74].

The antioxidant selenoenzymes can play a role against infection by modulating and preventing the excessive production of reactive species associated with the host’s inflammatory response against infectious agents. During the inflammatory response, the initial and transitory increase in reactive species is physiologically involved in the process of microbial clearance; however, the persistence of reactive species over-production can blunt or delay the resolution phase of inflammation [126]. In this context, modulation of the inflammatory response by Se has been implicated in the proper resolution of inflammation [74]. One point to be addressed chemically is the potential inactivation of selenoproteins by reactive species with highly reactive selenocysteinyl residues, particularly those produced in immune cells during the initial phase of inflammation caused by pathogens (e.g., those from hypochlorous and hypohalous acids) [86,101].

As briefly commented, several lipid mediators participate in the orchestration of the inflammatory response. These mediators are derived from the metabolism of membrane phospholipids through phospholipase A₂ (PLA₂)-mediated hydrolysis. For instance, arachidonic acid (AA) can be oxidized by two enzymes: COX and lipoygenase (LO). AA can be oxidized by COX, forming prostaglandins (PGE₂ or PGF₂α), prostacyclin (PGI₂), and thromboxane (TXA₂). Alternatively, AA can be sequentially oxidized by LO, forming 5-hydroperoxyl-eicosatetraenoic acid (5-HPETE) and converted to leukotrienes (LTc₄) [47,53,56,127–130]. In this scenario, the potential modulation of lipid inflammatory mediators derived from AA by Se has previously appeared in the literature as a hypothesis (Fig. 3). McCarty [127] proposed that Se could decrease indirectly the production of the pro-inflammatory leukotrienes in inflammatory diseases, such as asthma, and rheumatoid arthritis by decreasing the peroxide tone via upregulation of GPX activity [131,132]. The participation of the antioxidant selenoproteins GPX1 and GPX2 as indirect modulators of inflammation by negatively controlling NF-κB pathway activation has recently been described [46].

Se deficiency (and selenoproteins, such as GPX, SELENOP, SELENOS, SELENOK) have been involved to modulate the inflammation pathways and the cellular redox balance [46,124,133]. For instance, the activity of Se-dependent GPXs is involved in the reduction of hydrogen peroxides and lipid peroxides that are essential in the synthesis of lipid mediators of inflammation [46,134–136]. In other words, AA metabolism to lipid mediators of the inflammatory response can be modulated (typically downregulated) by Se not only by changing the prostaglandins metabolism but also by decreasing the ROS production [56,135,137,138].

As briefly mentioned in Section 2.2, Se-deficiency can modulate the expression of selenoproteins. For instance, Luan et al. [139] demonstrated that Se-deficiency decreased the expression of all the 24 selenoproteins and cytokines (IL-2, IL-4, IL-8, IL-19 e IL-12), TGF-β and IFN-α in chicken. Besides, the expression of the pro-inflammatory cytokines (IL-1γ, IL-6 e IL-7) were increased in the Se-deficient group. The authors reported a positive correlation between the cytokine expression levels with IL-2, IL-4, IL-8, IL-19 e IL-12). TGF-β and IFN-α. In contrast, the correlation between selenoproteins gene synthesis (mRNA levels) with the pro-inflammatory cytokines IL-1γ, IL-6 e IL-7 was negative. Nevertheless, the regulation of cytokines levels under Se deficiency was associated with a decrease in the mRNA expression of GPX1, GPX3, GPX4, SELENOP, SELENON, SELENOS, SELENOM, SELENON, SELENOP, SELENOW and with an increase of TXNRD1 and SELENOT. The study also demonstrated a modest but significant increase in the
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concentration of pro-inflammatory markers (e.g., IL-1β, IL-6, TNF-α and NFκ-B in the muscle of Se-deficient animals [140]. As just discussed for Luan et al. [139], the data of Zhang et al. [140] were only descriptive and did not explore the chronological correlations between inflammatory markers with the mRNA levels of selenoproteins.

A study by Li et al. [141], demonstrated that Se-deficiency decreased the expression of SELENOP, GPX4, and TXNRD in the blood and spleen of pigs. They also demonstrated that Se-deficiency decreased the levels of anti-inflammatory cytokines (IL-10, IL-13, and TGF-β) and increased the synthesis of proinflammatory cytokines (IL-1β, IL-6, IL-8, IL-17 and TNF-α), COX-2 and induced iNOS inducing inflammation. In short, the study of Li et al. [141] corroborated previous studies where the Se-deficiency induced a pro-inflammatory state in pigs and that three selenoproteins may be involved in the regulation of the inflammatory response. However, the precise role played by each of the 3 selenoproteins in the installation or resolution of inflammation was not elucidated.

Of potential implications for COVID-19 (the importance of Se status on COVID-19 severity will be discussed in Section 3.1), Wang et al. [142] proposed a link between infection with the COVID-19 virus and selenoproteins by demonstrating that, although infection of Vero E6 cells with SARS-CoV-2 did not alter the expression of GPX1 mRNA, it significantly reduced the expression of selenoproteins involved in the modulation of redox balance and ferroptosis, such as GPX4 (69 %), TXNRD3 (37 %), and selenoproteins from the endoplasmic reticulum (SELENOF (76 %), SELENOK (71 %), SELENOS (61 %) and SELENOM (56 %)), and increased expression of the inflammatory cytokine IL-6.

2.4.1. DIO2 as a negative modulator of inflammation in chondrocytes

In addition to the modulation of peroxide tonus by the classical antioxidant GPX isoforms, there are some studies in the literature indicating that DIO2 can have a role as a negative modulator of inflammation in vivo. DIO2 is an enzyme of the endoplasmic reticulum that is part of the subfamily of selenoproteins that regulate thyroid hormones metabolism, and catalyzes the conversion of T4 to the active hormone T3 [143–145]. Recently, it was demonstrated DIO2 silencing (50 % reduction in the DIO2 protein) in human cardiomyocytes derived from pluripotent cells caused oxidative stress and impaired mitochondrial function [141]. The effects of DIO2 deficiency in mitochondria was related to non-adequate fold of mitochondrial proteins, particularly those associated with respiratory chain complexes [146]. Although the pro-oxidant consequences of down-regulation of DIO2 protein synthesis was indirectly mediated by mitochondrial dysfunction, a potential direct antioxidant effect of DIO2 was not investigated.

The reduction of DIO2 in vitro by using specific small interfering ribonucleic acid (siRNA) for DIO2 caused an increase in markers of inflammation in chondrocytes, for instance, a 2-fold increase of basal and IL-1β-induced COX2 gene expression [147]. Correspondingly, the same authors have also observed that suppression DIO2 increased (around 9-fold) IL-1β induced IL-1β gene expression and resulted in a downregulation of the Liver X receptor-α (LXRα), but had no effect on LXRβ [147]. The LXRs are regulators of macrophage physiology, including their role in modulating inflammation [148]. In contrast to DIO2, the silencing of GPX1 and TXNRD1 in chondrocytes did not change the levels of inflammatory markers [147]. The study by Cheng; Bolognesi; Kraus [147] was one of the pioneering studies demonstrating that a selenoenzyme that has no direct antioxidant catalytic activity could modulate the levels of inflammatory markers in chondrocytes in vitro. The data about the silencing of GPX1 and TXNRD1 in chondrocytes are intriguing and point out the necessity of similar and systematic studies with human leukocytes. The results in chondrocytes are somewhat discrepant with the general modulatory role of antioxidant selenoenzymes as negative modulators of inflammation (Section 2.3) and with early studies on Se-deficiency associated with a decreased in GPX activity and with an increase in inflammatory markers. It is interesting also to comment that the data of Cheng; Bolognesi; Kraus [147] can be consonant with the study of Wang et al. [142], where the inflammatory effects caused by SARS-CoV-2 infection in Vero 6 cells were associated with impaired synthesis of GPX4, TXNRD3, SELENOF, SELENOK, SELENOS, SELENOM, but not with GPX1. The data from Cheng; Bolognesi; Kraus [147] and Wang et al. [142] suggest that the early correlations between total GPX activity with disrupted inflammatory and cellular immune responses need additional clarification.

The general negative association between mRNA levels of all selenoproteins with the pro-inflammatory cytokines may indicate the broad influence of selenoproteins in immune and inflammatory responses. In accordance, Se-deficiency disrupted selenoprotein mRNA synthesis and caused immunological impairments in the thymus and spleen of chickens [99,149]. Nonetheless, it is important to emphasize that the changes in mRNA of selenoproteins do not always correlate with the changes in the selenoproteins expression [108]. Consequently, it would be essential to perform both seleno-transcriptome and selenoproteome integrated analyses in models of insufficient, sufficient, excess and toxic levels of Se and determine how they correlated with inflammatory
markers (including lipidic analyses of lipid mediators of inflammation) and cellular immunological responses. Such kind of integrative analyses based on transcriptomics, proteomics and lipidomics approaches will allow for a better understanding on the main roles of selenoproteins in modulating immune and inflammatory events, as well as their relationships with the metabolism of oxidized pro-inflammatory lipid mediators derived from LOX and COX activities.

2.5. Potential role of selenoproteins in the regulation of neutrophil extracellular traps (NETs) activation

Neutrophils play an important role in the elimination of pathogens via the Neutrophil extracellular traps (NETs) formation. NETs are part of the defense process of the immune system where neutrophils create physical barriers to capturing and preventing the spread of pathogens (viruses, bacteria, and other microorganisms) in the extracellular medium [150–152]. Regarding the inflammatory process, it appears that Se-deficiency (possibly associated with the reduction of SELENOS) plays a role in the ROS-mediated NETs formation in an avian model of arthritis [153,154].

In an elegant study by Chi et al. [154], the authors demonstrated that a Se-deficient diet given to chicken for 42 days caused a decrease in the plasma Se level (from near 110 to 40 µg/kg of plasma) and arthritis in the aorta of broilers. Furthermore, the TNF-α and IL-1β levels were increased in the aortic tissues from Se-deficient broilers when compared with controls. The challenge with LPS caused further increase in TNF-α and IL-1β levels, which was proportionally higher in broilers maintained in the Se-deficient diet. The morphological and biochemical markers of NET formation were increased in the Se-deficient group, with further increase after LPS administration. Silencing of SELENOS in pulmonary arterial endothelial cells increased the synthesis and secretion of pro-inflammatory cytokines. Recapitulating what was observed in vivo after Se-deficiency in broilers, the neutrophil mediated NET formation was also increased after SELENOS silencing [154].

As noted in the introduction, the association of low levels of serum Se with an increase in the severity of COVID-19 [18] can be related to a preexistence of chronic pro-inflammatory state in the patients with high-risk of developing severe COVID-19. In addition, the chronic inflammation observed in several diseases can facilitate NETs formation [155–157]. Of note, in a cohort study with 32 patients with COVID-19, Veras et al. [158] observed an increase in the concentration of NETs in the plasma of COVID-19 patients compared to the healthy control group, particularly in the tracheal aspirate and in lung tissues from 10 autopsied patients. The same authors observed that SARS-CoV-2 replication induced the release of NETs by neutrophils isolated from the blood of healthy subjects in vitro. Similarly, several biochemical markers of NETs activation (cell-free DNA, myeloperoxidase-DNA complexes and citrullinated histone H3) has been reported to be elevated in COVID-19 patients [159]. Although it has been hypothesized that disruption in the incorporation of Se into the selenocysteinyl structure may have a role in the coagulopathy problems found in severe COVID-19 [160], a causal link between low levels of Se with a predisposition to have exaggerated NETs activation has yet to be demonstrated, either by determining Se levels in patients with COVID-19 and other chronic diseases associated with inflammation and decrease in Se.

2.6. Does inflammation exacerbate Se deficiency or Se deficiency exacerbate inflammation?

Low Se plasma levels have been described in patients with pathologies associated with inflammation (Table 2). For instance, cancer, cardiovascular diseases, impaired immune function, and infertility. In contrast, there exists evidence that Se in the erythrocytes does not strongly correlate with plasma Se. Consequently, the decrease in plasma Se of patients with acute systemic inflammation could not be considered a reliable marker of the body Se burden [161]. In fact, a more refined understanding of Se status has to encompass circulating and tissue levels of Se (including intracellular Se concentration, GPX1 expression, serum SELENOP or GPX3 activity or total serum Se concentration) [161], but as can be seen in Table 2, the majority of the studies estimated the Se levels only in the plasma [122,162,163,165–167] and a few in erythrocytes and in the plasma [164,165].

Notably, increase in circulating pro-inflammatory cytokines, chronic inflammatory diseases, and systemic inflammation (inflammatory reaction triggered by infectious or non-infectious aggression) can decrease the concentration of blood Se levels and selenoprotein activity (e.g., total GPX activity) [60,164,166,167,170,171,190].

In agreement, Se levels have been reported to decrease 48 h after postoperative cardiovascular bypass (CBP) in the plasma of children [162], although GPX activity was not changed at 6, 12, and 24 h after treatment.

Table 2
Inflammation and Se-deficiency.

| Pathology                                      | Samples                             | Local of Se quantification | Observations                                                                 | Reference               |
|-----------------------------------------------|-------------------------------------|----------------------------|------------------------------------------------------------------------------|-------------------------|
| Cardiovascular diseases                        | 59 pediatric patients               | Plasma                     | Decreased plasma Se, deiodinase activity and T3 in pediatric cardiac surgery patients. | Holzer et al. [162]    |
|                                               | 858 control subjects and 606       |                           | Se-deficiency increased cardiovascular risk in the elderly and expression of inflammatory cytokines and chemokines (IL1, CCL5 e PDGF-β). | Giaconni et al. [163]  |
|                                               | cardiovascular diseases patients    |                            |                                                                               |                         |
| Connatal infection                             | 21 neonates with connatal infection and 23 neonates without infection | Plasma                     | Connatal infection increased IL-6, and decreased Se and SELENOP.              | Wiele et al. [164]     |
| Inflammatory bowel disease                     | 12 male mice                        | Plasma and leukocytes      | Decreased plasma Se and GPX. Low Se, TXNRD and GPX activity and mRNA of GPX, SELENOW, SELENOH and SELENOK. Decreased NF-κB targets gene expression. | Kipp et al. [122]      |
| Pulmonary arterial hypertension in systemic sclerosis | 30 healthy control and 66 patients with systemic sclerosis | Serum                     | Systemic sclerosis-related hypertension was associated with low serum Se, GPX3 and SELENOP. | Sun et al. [165]       |
| Respiratory failure and systemic inflammatory response | 125 critical patients               |                            | Low plasma Se, but normal plasma and erythrocyte GPX, TXNRD, TXNIP, and    | Stefanowicz et al. [166]|
|                                               |                                     |                            | decreased plasma Se and GPX. Increased oxidative stress and inflammatory biomarkers (IL-6, C-reactive protein, soluble urokinase-type plasminogen activator receptor), especially in patients with sepsis. | Mertens et al. [167]   |
| Sepsis                                        | 39 patients (20 patients with sepsis and 18 critically ill non-infected control patients) | Plasma                     | Decreased plasma Se and GPX3, increased oxidative stress and inflammatory biomarkers (IL-6, C-reactive protein, soluble urokinase-type plasminogen activator receptor), especially in patients with sepsis. | Forcille et al. [168]  |
| Septic shock                                  | 66 patients (29 in the placebo and 31 in the Se group) | Plasma                     | Continuous infusion of Se (4 mg seledine on the 1stday and 1000 mg per nine days) did not improve the clinical outcomes. | Manzanares et al. [169]|
| Systemic inflammatory response (SIRS) and multiple organ dysfunction syndrome (MODS) | 36 intensive care unit patients (without SIRS; with SIRS, with SIRS and MODS) and 23 healthy volunteer subjects | Serum                     | GPX3 and Se decreased earlier in SIRS and MODS patients compared to other groups. |                         |
surgery. CBP is normally associated with an increase in markers of inflammation and oxidative stress [6,162]. To some extent, the changes observed after CBP (elevations of parameters related to systemic inflammatory response) are also found in sepsis. However, in sepsis, the inflammatory response is always much more accentuated. Since an increased inflammatory response occurs both in CBP and sepsis, the decrease in Se in plasma, but not in erythrocytes, may indicate rapid mobilization of Se to as yet non-identified tissue (perhaps to stimulate (an autoimmune disease) has been linked with dysplasia and Beicosanoids and facilitate the exacerbation of inflammation [53,175].

The excretion of Se from the body. As already commented, decreased results [185,189,193]–193, and the effectiveness and the potential molecular mechanisms of Se in sepsis remain unclear [38].

3. Se, viral infection, and viral replication

The potential influence of Se nutritional status and selenoproteins on viral infections has been recurrently documented in the literature [16,18,19,36,38,39,41,150,167,187,188,194–201]. Studies have demonstrated that Se and selenoproteins contribute to host immunity and regulate viral pathogenesis.

For instance, the GPX1 gene ablation in mice was associated with an increase in the virulence, heart pathogenicity caused by coxsackievirus B3 (CVB3) and influenza A viruses. The immune response against the CVB3 virus (as determined by the level of neutralizing antibody titers) was markedly decreased in the GPX1 knockout mice [202]. Although the authors did not find indications of oxidative stress in the heart microsomes of infected knockout mice, the redox balance in the immune cells were not studied. Consequently, the effects of GPX1 knockout could be related to indirect change in the formation of inflammatory mediators in the immune cells mediated by GPX1 antioxidant properties (H2O2 degradation).

The knockout of SELENOK in mice led to increased mortality after West Nile virus infection, as well as higher virus titers in the brain and impaired virus elimination from the blood [150]. The results of Verma et al. [125] can be partially explained by the role played by SELENOK as a cofactor of the palmitoyl transferase activity of DHHC6. DHHC6 modulates the activity of the protein ASAP2, which is critical for proper macrophages phagocytosis. The effects of GPX1 deficiency were similar to those observed after ingestion of a Se-deficient diet and associated with hyper-inflammation [203,204]. Importantly, nutritional Se-deficiency has been commonly associated with increased incidence, virulence, and progression of some viral infections [16,35,36]. However, we have yet to understand the precise molecular roles played by Se as an antagonist of some viral infections. Furthermore, there are some contradictory studies in the literature about the potential protective effect of Se against some viruses [190–192,205]. For instance, Se-deficiency can be involved in Keshan’s disease [68,98,205–207], autoimmune thyroid disease [202–205,208], and Human Immunodeficiency Virus (HIV) infection [37,98,209–213], as discussed below.

Keshan’s disease was described around 1935 as an endemic cardiomypathy that started in Heilongjiang province, and between 1940 and 1960 it spread to 12 other provinces in China. Between 1970 and 1980, Se fertilizers were applied to the soil to supplement the population and control the disease [214]. However, Keshan’s disease appears to have a double etiology, involving both Se-deficiency and infection with coxsackievirus B3, a single-stranded RNA virus, a member of the picorna virus family [98,203,215]. This dual etiology has been described in some studies demonstrating that Se-deficiency in mice caused mutations in the RNA virus and developed virulent strains of coxsackievirus B3 [35,216,217]. Additionally, the possible mechanisms of Se in the prevention of Keshan’s disease could be modulated indirectly by Se-dependent antioxidant selenoenzymes (especially GPX4), which protect the membranes from lipid peroxidation [214].

The influenza virus consists of eight (Influenza A and B viruses) or seven (influenza C and D) viral RNA segments. Influenza subtype A is one of the most common causes of respiratory disease in humans [218]. Influenza A virus infections can progress to severe pneumonia that can result in death [219,220]. In addition, the increase in the steady-state levels of reactive species has been suggested to increase the genomic instability of Influenza A, which may facilitate the appearance of related viruses with great virulence [195,209]. Beck et al. [36] demonstrated that Se-deficient mice infected with Influenza A/Bangkok/1/79 (H3N2) exhibited an increase in the severity of lung pathology and inflammation when compared to mice with adequate Se ingestion. The hepatic and serum Se levels were decreased in Se-deficient diet as well as the total hepatic GPX activity. In contrast, the viral titers (from day 4 to day 6 after infection) and the immune response (as determined by the neutralizing antibody titers 4–21 days after infection) were similar in both Se-deficient and control mice. Another
study performed with Se-deficient mice infected with the Influenza A virus (H1N1) resulted in 75 % mortality, while the supplemented group (0.5 mg of sodium selenite per Kg of diet) had 25 % mortality [72]. In summary, the few experimental data available suggest that Se-deficiency can increase indirectly the susceptibility to Influenza viruses by disrupting the inflammatory response, but not virus replication.

HIV infection is a global disease, in which a single-stranded RNA virus infects the host’s immune cells [184]. Studies have demonstrated that Se supplementation caused symptomatic improvements and possibly disease prognosis [221,222]. It has been suggested that Se has an inhibitory effect on HIV via the antioxidant effects of GPX and other selenoproteins [189], but there is no experimental evidence supporting this assumption and mechanistic data on such hypothesis are lacking.

Se-deficiency has been invoked as an important player in the worsening of AIDS progression [83,200,223,224]. Some studies have demonstrated an association of low Se levels with a decreased total GPXs in the plasma and erythrocyte of HIV infected patients [37,83], which could be related to the development of HIV-associated cardiomyopathy [37,83,107,212] and high risk of mortality in HIV patients [225,226]. In patients with terminal HIV, it was reported a relationship between the loss of CD4+ T cells and Se depletion [83]. In addition, HIV patients supplemented with high Se yeast (200 µg/day for 9 months) had reduced HIV viral load and improved cell count of the immune system [227]. However, as discussed above for other diseases associated with inflammation and low Se status, it is not clear if the decrease in Se levels [227] is also true for HIV patients. Nevertheless, there are some clinical studies that have investigated the potential beneficial effects of Se in AIDS.

Hantaviruses are single-stranded RNA viruses that infect many species of rodents, shrews, moles, and bats. Human Hantavirus infection causes hemorrhagic fever with kidney or cardiopulmonary syndrome [228]. Hantavirus infection is estimated to affect 1500.000–200.000 people worldwide annually [229]. In China, Fang et al. [230] demonstrated that the prevalence of hemorrhagic fever with renal syndrome was about 5 times greater in Se-deficient regions and near 2 times as greater in regions with mild Se-deficiency in contrast with Se adequate areas. In short, an adequate nutritional Se status can have some beneficial effects against different types of viruses, but the discussed data are more consistent with a general modulatory role of Se (selenoproteins) in the inflammatory response and not a direct effect of Se on virus replication.

### 3.1. Se and COVID-19

Since the COVID-19 pandemic spread around the world, some studies have been published trying to link Se-deficiency with the disease severity (Table 3). The general interest in Se and COVID-19 has been attributed to its protective role against some viruses and as a modulator of the immune system and inflammatory responses [18,19,34,40,196,199,231–240]. To date, few clinical studies have indicated a possible causal relation between Se-deficiency and SARS-CoV-2 infection [241].

The first population-based retrospective analysis study was carried out by Zhang et al. [28]. The authors collected real-time data from each province, municipality, or city in China on confirmed COVID-19 cases, the number of recovered, and deaths. The authors identified an association between a higher recovery rate in patients with COVID-19 in 17 cities outside Hubei, China with the population’s Se status (hair Se concentrations). Furthermore, Liu et al. [247] observed that populations in Se-deficient areas, such as Hubei province, appear to be more susceptible to viral illnesses. The authors reported that in Chinese cities with high levels of Se in the soils (Enshi, Shiyan, and Xiangyang) the incidence of COVID-19 was 10 times lower than in cities with Se-deficient soils (Suizhou and Xiaogan). There are also some clinical studies that have investigated the potential role of Se in COVID-19.

#### Table 3

| Citation            | Aim                                                                 | Type | Population                           | Age (years) | Findings                                                                 |
|---------------------|----------------------------------------------------------------------|------|--------------------------------------|-------------|-------------------------------------------------------------------------|
| Alkattan et al. [242] | To study the association between Se levels and the severity of COVID-19. | CS   | 80 COVID-19 patients (severe — 35; non-severe — 45) | 51.54       | Se above the ideal range in severe — 160 µg/L vs non-severe cases (130 µg/L; P < 0.0001). |
| Jahromi et al. [243]  | To evaluate the correlation of serum Se and zinc with COVID-19 severity. | OB   | 84 COVID-19 patients (mild — 38; moderate — 27; severe — 19) | Mild — 51 ± 14, Moderate — 59 ± 14, Severe — 81 ± 7 | Severe (29.9 ± 11.5 µg Se/L) vs. mild (47.1 ± 20.8 µg Se/L) and moderate groups (47.4 ± 25.6 µg Se/L). |
| Majeed et al. [244]  | To study blood serum Se levels in COVID-19 and control individuals.   | EX   | 30 COVID-19 patients vs 30 healthy individuals | 18–45       | Lower blood serum Se levels in COVID-19 (69.2 ± 8.7 µg Se/L) vs. controls (79.1 ± 10.9 µg Se/L; P < 0.0003). Se correlated positively with the survival in COVID-19 patients. |
| Moughaddam et al. [18] | To test if severe Se-deficiency could be linked with poor survival in COVID-19. | CS   | 33 COVID-19 patients (survivors — 27; non-survivors — 6) | Survivors — 38–91, Non-survivors — 81–94 | Se status in survivors (53.3 ± 16.2 µg Se/L; SELENOP 3.3 ± 1.3 mg/L) higher than in non-survivors (40.8 ± 8.1 µg/L; SELENOP 2.1 ± 0.9 mg/L). |
| Muhammad et al. [44] | To examine antioxidants and oxidative stress markers in COVID-19 patients. | CS   | 50 COVID-19 vs 21 healthy individuals | COVID-19 — 43.8 ± 13.8 Healthy — 35.8 ± 6.8 | Se levels and GPX activity were lower in COVID-19 (p < 0.001) compared to healthy individuals. |
| Skalny et al. [245]  | To evaluate metal levels in COVID-19 patients with markers of lung damage. | OB   | 150 patients with COVID-19 (mild, moderate, and severe, N = 50/ group) vs 43 healthy individuals | Mild — 55.7, Moderate — 54.2, Severe — 64.5 | Se decreased by 9 % (mild), 12 % (moderate; p = 0.047) and 15 % (severe; p < 0.001) vs healthy controls. |
| Younesian et al. [246] | To study the serum Se levels in COVID-19 patients and control group. | CS   | 50 COVID-19 patients vs 50 healthy individuals | COVID-19 patients: — 56 (42–77), Survivors (N = 37) = 49 (42–66), Non-survivors (N = 13) = 72 (65–77) | Se serum levels: 77.8 ± 13.9 µg/L in COVID-19 vs 91.7 ± 16.7 µg/L in controls. |

CS, Cross-section study design; EX, Exploratory study; OB, Observational study.
are summarized below and in Table 3.

In an exploratory study, Majeed et al. [244] observed that patients with COVID-19 had lower blood serum Se levels (69.2 ± 8.7 μg Se/L) compared to the healthy control group (79.1 ± 10.9 μg/L). In addition, the authors demonstrated that Se correlated positively with the survival of patients with COVID-19 compared to non-survivors. The age of the control group (33.5 years, range 26–37 years) was different from patients with COVID-19 (40.5 years; range 37.5–43 years), which could have been an important confounding factor. In fact, age is the main risk factor of COVID-19 severity [27] and Se blood levels decrease with age (Fig. 4).

In another study, the authors took into consideration the potential confounding factors, Jahromi et al. [243] reported the Se levels (μg Se/L of blood serum) in severe (29.9 ± 11.5 μg Se/L) COVID-19 was about 40% lower than in the mild (47.1 ± 20.8 ng μg Se/L) and moderate COVID-19 groups (47.4 ± 25.6 μg Se/L). Noteworthy, the levels of Se in all groups were in the deficient range (see Fig. 4). After adjustment for potential confounding factors, including age, it was observed that the increase in Se levels was accompanied by a decrease in the level of serum CRP, but there was no association between Se levels and COVID-19 severity. Thus, the inclusion of age as a confounding factor in the analyses is critical.

In a cross-sectional study, Moghaddam et al. [18] found that serum Se and SELENOP levels of survivors (median 69 years-old and 53.3 ± 16.2 μg/L) were higher than in non-survivors (median 89 years and 40.8 ± 8.1 μg/L). However, no adjustment in relation to age was presented. In another small study, Hackler et al. [252] found a significant increase in serum Se and SELENOP levels along the days of hospitalization until the discharge SELENOP in the survivors (p < 0.001). In contrast, in non-survivor patients the Se levels did no vary and SELENOP decrease along the time of hospitalization. Though the number of patients in the non-survivor group (n = 7) was very small, the trend observed for Se and SELENOP in the 4 weeks before the death may indicate that the tendency of SELENOP to decrease during hospitalization could be a potential predictor of negative outcome in COVID-19. It is also reasonable to posit that the decrease of SELENOP might have a causal relationship with inflammation. Since SELENOP has an important role in the transport and distribution of Se to the body, its decreased levels may reflect a general disruption in the distribution of Se in COVID-19.

The potential importance of selenium and selenoprotein deficiency in post-COVID-19 infection (the long COVID pandemic), which is characterized by persistent inflammation and autoimmunity [253], should be investigated in detail. In fact, the decreased GPX4 levels can have deleterious effects in neutrophils via ferroptosis promotion in Gpx4 haploinsufficient mouse, which was associated with a lupus-like phenotype. Most importantly, the neutrophils from patients with systemic lupus erythematosus (SLE) were more prone to die from ferroptosis than neutrophils from control subjects [254]. The induction of ferroptosis in systemic lupus erythematosus patients’ neutrophils was linked to autoantibodies and interferon-α circulating in systemic lupus erythematosus patients’ blood by increasing the binding of a transcriptional repressor of the glutathione peroxidase 4 synthesis [254]. Although not frequent, during the post-COVID-19 syndrome some patients may have severe neutropenia [255], it can occur in young patients or as a consequence of tocilizumab treatment during ongoing COVID-19. In view of the potential participation of autoimmune components in the post-COVID-19, and the participation of GPX4 in the neutrophilia found in lupus erythematosus patients and rodent lupus-like phenotypes [254, 256,257], it would be important to study the levels of Se and GPX4 in the erythrocytes and blood-immune cells in patients with post-COVID-19 syndrome.

In a cross-sectional study, Younesian et al. [246] investigated the serum levels of 50 hospitalized patients with COVID-19 compared to the healthy control group. Patients with COVID-19 had a lower serum Se level (77.8 ± 13.9 μg/L) compared to the healthy control group (91.7 ± 16.7 μg/L). In contrast to previous studies cited above [241,244], there was no relationship between Se, severity, and mortality (37 survivors vs 13 non-survivors) of patients with COVID-19 [246]. As expected, the survivors were younger than the non-survivors and proportionally, the men died more than women. Although the authors stated that the control group (n = 50) were paired by age and sex, no demographical or health data were provided. It should also be noted that the levels of Se both in COVID-19 patients were in the ideal range (Fig. 2).

In a cross-sectional study, Alkattan et al. [242] reported discrepant results from the other studies cited above. The authors observed that Se levels in 80 adult patients with COVID-19 (mean age 51 years) were above the ideal Se levels (80–120 μg/L; Fig. 2). The mean of non-severe (134 μg/L) was lower than the severe patients (162 μg/L). The study had several limitations, for instance, the severe group was older than the non-severe and the percentage of hypertension was about two time higher in the severe than in non-severe group. No logistic regression analyses or confounding factors were considered. The high levels of Se in both groups, the incidence of diabetes and hypertension may indicate that high Se levels were an important factor in determining the severity of COVID-19. Although the study was with a small group of patients, it is possible that high levels of Se status (i.e., above the optimal to support adequate selenoproteins synthesis) may be a risk factor for severity of COVID-19. However, more detailed and studies large number of subjects are needed to determine the role of high Se as a detrimental agent in viral infection.

3.1.1. Se and aging: potential implication for COVID-19

The main risk factor in COVID-19 is age, followed by sex [33,258]. It has been also pointed out that the risk of death in the aging subjects with chronic age-associated diseases is increased by Se-deficiency (lower than 57 μg Se/L of serum vs greater than this value) [259,260] and Se (100 μg twice a day) + Coenzyme Q10 supplementation decreased the serum D-dimer levels and the risk of mortality in aging subjects with cardio-myopathies [261]. Of potential clinical importance, the relationship between Se levels and aging has been studied and a negative correlation of Se status and age has been reported [42,111,180,250,251], Olivieri et al. [248] investigated this relationship with 105 healthy individuals (53 women and 52 men), distributed into groups (I, 20–39 years; II, 40–59 years; III, 60–75 years; IV, > 75 years). The authors observed that Se and GPX levels decreased with aging (mainly in the older groups). In addition, multiple regression analyses revealed inverse correlations
between Se status and aging (R = −0.462, P < 0.001). A 9-year longitudi
nal study by Akbaraly et al. [249], with 1389 individuals between 60 and 71 years of age, also demonstrated that Se levels decreased with age. Following 2 years subjects had a decrease in Se of about 5 % (−0.055 μmol/L), and after 9-years of follow-up it decreased to around 9 % (−0.096 μmol/L), in both men and women. Notably, Se levels decreased with age and low Se levels were associated with high risk of mortality [11,44] (Fig. 4).

The decreased Se levels associated with age could be explained, at least in part, by the increase in chronic inflammation with ageing [262]. If the inflammation has a causal role in the decrease of Se status with ageing has yet to be further supported by large epidemiological studies. Indeed, the elucidation of how Se (and selenoproteins) participates in the increase of the chronic inflammation found along ageing and how inflammation interacts to disrupt the immunological response will require collaborative and coordinated studies. Regarding the influence of sex in Se levels, the literature data indicate small variations in the Se levels in males and females [251,263]. Several studies have shown that men with cancer had lower Se status than women with cancer [77]. In an opposing trend, levels of Se were reported to be higher in women with metabolic syndrome than in the group without metabolic syndrome. In men, Se levels were not modified by metabolic syndrome and Se levels were similar to the women without metabolic syndrome. Regarding COVID-19 patients, no significant differences in Se levels were reported between men and women [264]. In summary, the data available indicate that the Se status in men and women are similar or fluctuate little and possibly has no contribution to the increased susceptibility of male to COVID-19.

4. Conclusions

Although some evidence is consistent with a role for Se as a protective factor against some viral infection, we poorly understand the molecular mechanisms involved in the modulation of immune and inflammatory responses by selenoproteins, and occasionally, by selenide (HSe\(^-\)) metabolites. In addition to unraveling how each individual selenoprotein participates in the fine-tuning of the complex immune and inflammatory responses towards invading viruses and other microorganisms, it will be necessary to clarify several critical points. i) From the point of view of nutrition, the most critical are 1) to determine the ideal levels of ingested Se that afford optimal response efficacy of immune cells to infection; 2) how these levels of ingested Se correlate with total blood levels of Se, as well as with Se levels in each subpopulation of immune cells; 3) what should be the lowest level of serum or blood Se to be considered critical for the initiation of Se supplementation (as well as the highest to stop the supplementation)?; 4) how the chemical forms of Se supplementation interfere with immune cells function and with the selenoproteome? II) From the medical point of view, the main questions are: 1) does inflammation always has a negative impact on the general Se status or does it specifically affect to the greater extent the Se status in immune cells? 2) Could Se supplementation negatively modulate inflammation and how does it impair or enhance immune responsiveness?

The inquiry of the potential effectiveness of transitory Se supplementation as a potential enhancer of immune response is delicate, but an important question. The predominant thoughts in the literature on the role of Se as a protective agent against viruses is biased in favor of optimization of selenoproteins functioning (and even selenide metabolites [265]). This is a serious bias because we do not know what is an ideal balance between different selenoproteins synthesis to produce adequate inflammatory and immune responses against microorganisms. Furthermore, the increase in the synthesis of several specific proteins (e. g., GPX1 and SELENOP) can have detrimental roles in the development of chronic diseases, for instance, type 2 diabetes and possibly some types of cancer and neurodegenerative diseases [7,14,21–23,204,264–272]. In short, the concept of “optimization” of selenoproteins synthesis as a panacea for the prevention or cure of human diseases has to be reconsidered, because it is a vague and a potentially dangerous concept (for a recent critical review see Vinceti et al. [270]). Indeed, the chronic intake of Se supplements seems to be not appropriate in any circumstance, especially considering the narrow range between dietary deficiency and toxic levels (see Fig. 2). In contrast to what the critical review by Vinceti et al. [273] suggests, the impact of elevated Se in diabetic patients is still uncertain and debatable, as described in the systematic review by Kohler et al. [29] and in other studies (see Section 1.1). For instance, it has been hypothesized that the increase in Se in the blood of patients with diabetes can be a consequence and not the cause of type 2 diabetes [31,274]. As corollary, the increase in Se in the blood could even be a protective response to increase antioxidant selenoprotein levels to counter potentially toxic concentrations of blood glucose. However, the solid experimental data and preliminary clinical data from Japanese researchers can indicate a role for SELENOP as a causal factor in the development of diabetes type 2 [27,29,31,270–274]. In relation to virus infections and, specifically in COVID-19, the potential therapeutic efficacy of transitory supplementation with Se (either as preventive agent and remedy) will require randomized clinical trials [31].

The history of Se in human physiology has swung between an extremely toxic element to a remedy for almost all human diseases. In fact, in the last 5 decades (as a consequence of the antioxidant selenoproteins discoveries) the balance has tipped greatly towards the side of Se as a panacea. However, the slowly emerging epidemiological and experimental data have clearly indicated that Se, and, more recently, selenoproteins can also have deleterious effects on cellular biochemistry and human health at levels just above the optimal range. In short, our knowledge about the chemical physiology of selenoproteins is rudimentary, particularly, on how they modulate immune responsiveness. The scarcity of detailed studies on selenoproteins is understandable, because the concentration of the majority of them is very small and we have only a vague idea on their function. They are also highly reactive (particularly their unique selenol group(s)) and difficult to be purified for biochemical studies. In the case of the immune system, the best approach to be followed has captured in a few studies (see for instance, Norton et al. [64]; Fredericks et al. [65]) and involves the temporary or permanent interference with a single selenoprotein. The task for investigating the 25 selenoproteins individually and in combination (two by two, three by three etc.) is hard and time consuming, and will require collaborative efforts.

CRediT authorship contribution statement

Agnieli Golin: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. João Batista Teixeira da Rocha: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. Alexey A. Tinkov: Writing – review & editing. Michael Aschner: Writing – review & editing. Marcelo Farina: Writing – review & editing.

Declaration of interest

The authors declare that there are no conflicts of interest.

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