REVIEW

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Mechanisms by which selenium influences immune responses

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Abstract

Selenium (Se) is an essential dietary trace element that influences immune responses through its incorporation into selenoproteins as the amino acid selenocysteine. This review summarizes data available to date regarding the mechanisms by which Se exerts its effects on inflammation and immune responses. This includes the effects of Se on phagocytes as well as effects on lymphocyte activation, proliferation, and differentiation. Also examined are the known functions of individual selenoproteins for regulating reactive oxygen species and redox potential in leukocytes. Overall, determining how Se contributes to optimal immune responses will depend on a better understanding of the mechanisms by which the selenoproteins, individually and collectively, shape inflammation and immune responses.

Key words: selenium, selenoproteins, immune responses, inflammation, oxidative stress.

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THE INFLUENCE OF SELENIUM ON THE IMMUNE SYSTEM

Selenium (Se) is an essential dietary trace element required for many aspects of human health, including an optimally functioning immune system [26, 33, 65]. One of the first clues that Se is involved in immune responses was uncovered in 1959 by McConnell [56], who injected ^{75}Se into dogs and demonstrated isotope incorporation into leukocytes. Since those early experiments, Se has been shown to be utilized by nearly all tissues and cell types, including those involved in innate and adaptive immune responses [4, 14, 58, 60]. Agricultural animal studies have provided insight into the effects of Se deficiency or Se supplementation on immune responses to a wide variety of vaccines (reviewed in [78]). In general, these studies have demonstrated an enhancement of both cell-mediated and humoral immune responses by increasing levels of Se intake. In experimental animal studies, Se deficiency has been shown to result in less robust immune responses to viruses, tumors, and allergens compared with Se-adequate controls [8, 37, 60, 63, 68]. However, the results are less clear regarding the benefits of Se supplementation above adequate levels in conferring additional immunological protection.

Studies in humans have mainly been descriptive in design, making it difficult to draw conclusions as to the role that Se plays in "boosting" the immune system [17, 27]. Perhaps the most compelling data come from studies involving Keshan disease, a cardiomyopathy that affects residents in regions of China with Se-deficient soils [12]. Se supplementation of individuals completely prevented the development of Keshan disease. The etiology of Keshan disease has been attributed in part to an endemic coxsackievirus (CVB3) and Se supplementation acts not only to elevate antiviral immunity, but also to prevent genetic adaptations in the viral genomic RNA that lead to increased virulence and cardiac pathology [11]. Thus, even in the case of Keshan disease the mechanism by which Se affects the immune system is less clear than how Se affects the virus itself. In fact, there are no obvious immune-related diseases associated with Se deficiency. The effects of Se on immune responses are likely to be less overt, leading to increased susceptibility to common immune-driven disorders such as allergic asthma, chronic inflammation, infectious diseases, and cancers. To better understand the relationship between Se and susceptibility to these disorders, it is imperative that the mechanisms by which Se carries out its effects on immune responses be determined.

INCORPORATION OF Se INTO SELENOPROTEINS

Se exerts its biological effects through its incorporation into selenoproteins as the amino acid selenocysteine (Sec), which is often referred to as the 21st amino acid. Sec is cotranslationally inserted into the active site of all selenoproteins by a mechanism that requires translational recoding of one or more UGA codons within the mRNA from a stop signal to a Sec-insertion signal. Factors directly involved in this process include specific secondary structures in the mRNA (SECIS elements), a unique tRNA (Sec-tRNA), RNA binding proteins (SBP2, L30, SECp43, and soluble liver antigen), and a specialized elongation factor (EFsec) [18, 36, 88]. The presence of a dedicated system for carrying out the recoding process highlights the biological importance of this unique family of proteins. This is supported by the fact that genetic deletion of the gene (*trsp*) encoding Sec-tRNA, which is required for translation of all selenoproteins, is embryonic lethal in mice [15]. Twenty-five selenoproteins have been identified in humans, all but one of which exist as Sec-containing proteins in mice and rats [50]. The functions of members of the selenoprotein family elucidated to date include regulation of thyroid hormone metabolism, intra- and extra-cellular antioxidation, redox regulation, and sperm maturation/protection. Interestingly, functions for a majority of the selenoproteins have yet to be identified.

One group of selenoproteins that has been functionally characterized is the glutathione peroxidase (GPX) enzymes. These enzymes use glutathione (GSH) to detoxify hydroperoxides in intracellular and extracellular spaces as well as lipid peroxides in cellular membranes. In humans there are five Sec-containing GPX enzymes: cytosolic GPX (GPX1), phospholipid hydroperoxide GPX (GPX4), plasma GPX (GPX3), gastrointestinal GPX (GPX2), and an enzyme restricted to the olfactory system (GPX6) [31]. These proteins are also Sec-containing enzymes in mice, except for murine GPX6, which contains cysteine in place of Sec. GPX1 was the first mammalian selenoprotein to be identified and is a ubiquitously expressed enzyme that is particularly important in regulating reactive oxygen species (ROS) within cells. However, GPX1 is apparently not essential for development because GPX1-knockout mice have no phenotype unless challenged with oxidative stress [19, 20]. In contrast, genetic deletion of GPX4 is embryonic lethal, suggesting an essential role of this enzyme in maintaining lipid membrane integrity [89].

Another selenoprotein subfamily is the group of Sec-containing thioredoxin reductases (TR-1, -2, and 3). These enzymes regenerate reduced thioredoxin (TRX), which is used for regenerating cellular antioxidant systems, activating signaling molecules, reducing ribonucleotides to deoxyribonucleotides for synthesis of DNA, and regulating the activity of transcription factors [1]. The different TR enzymes have different localizations, including the cytoplasm and nucleus (TR-1), mitochondria (TR-2), and sperm (TR-3) [2, 61]. Both TR-1 and -2 are widely distributed throughout tissues and each of the knockouts in mice are embryonic lethal, emphasizing their essential biological role [23, 44].

A recent study by the Gladyshev laboratory defined and characterized a new subfamily of selenoproteins, designated Rdx, that contain primary sequence motifs and a TRX-like fold that reflect a possible redox function [25]. This subfamily includes SelW, SelV, SelT, and SelH, as well as cysteine-containing proteins of unknown function (Rdx12). Two other partially characterized selenoproteins include SelM and the distantly related 15-kDa selenoprotein (Sep15). The structures of SelM and Sep15 have recently been solved, establishing these proteins as endoplasmic reticulum-resident redox proteins [28, 49]. Finally, SelR has been characterized as a methionine sulfoxidase enzyme that reduces proteins that have been reversibly oxidated on methionine groups, and Sel R appears to be widely distributed throughout tissue and cell types [46].

GPX ENZYMES CONTROL OXIDATIVE STRESS IN PHAGOCYTES

Oxidative stress occurs in all respiring cells and involves elevated levels of ROS such as superoxide, hydrogen peroxide, and hydroxyl free radicals. Upon activation, phagocytic leukocytes such as macrophages and neutrophils exhibit a relatively rapid increase in ROS, i.e. oxidative burst [29]. ROS at high levels are considered noxious, cytotoxic by-products capable of damaging lipids, proteins, and nucleic acids. However, when properly regulated, ROS in phagocytes play critical roles in microbiocidal activity, intracellular signaling for proper activation and differentiation and for cell-to-cell communication [57]. In the form of selenoproteins, Se plays an essential regulatory role in phagocytes by maintaining a proper balance between the positive and negative effects of ROS. Thus, insufficient levels of selenoproteins such as GPXs, TRs, and others that regulate the ROS and redox state of these cells may cause oxidation-induced death of phagocytes. Alternatively, overexpression or unregulated activity of redox-regulating selenoproteins may lead to insufficient oxidative burst necessary for proper phagocytic functions.

An abundance of *in vitro* studies have demonstrated important effects of Se on phagocytes. For example, Se-deficient J774.1 murine macrophages stimulated with mitogens, including PMA and LPS, demonstrated decreased phagocytic activity, superoxide production, and cytokine secretion compared with Se-adequate controls [71]. Another study examined J774.1 cells cultured in Se-adequate media supplemented with increasing doses of Se and found that increased Se led to reduced induction of H_2O_2 by LPS treatment [47]. In contrast, neutrophils from rats fed Se-deficient diets were not significantly different from Se-sufficient controls in their ability to phagocytose or degranulate, the latter of which

was measured by the release of β-glucuronidase [6]. However, neutrophils from Se-deficient rats demonstrated reduced oxidative burst when incubated for prolonged periods with stimulants such as PMA or opsonized zymosan [5]. The mechanism of this suppressed oxidative burst was due to inadequate metabolism of H_2O_2, which led to loss of activity of the membrane-bound NADPH-dependent superoxide-generating system. The Se-replete J774.1 cells and granulocytes from these experiments exhibited higher GPX-1 activity, which would provide added protection against H_2O_2 formed from dismutation of the increased superoxide. Thus, proper levels of GPX1 are necessary for the regulation of H_2O_2, which is needed in appropriate levels for the activation of the phagocytes.

In addition to GPX1, which acts directly on H_2O_2, GPX4 has also been demonstrated to be involved in the activation of phagocytes. Hattori et al. [34] showed that stimulation of human neutrophils with tumor necrosis factor (TNF)-α upregulated the expression of GPX4 mRNA. Both mRNA and protein expression of GPX4 was similarly induced with TNF-α treatment in an ROS-dependent manner in HL-60 cells differentiated into neutrophil-like cells. This suggests that GPX4 is important for protecting neutrophils against lipid peroxidation during activation. However, the story may be more complex, as suggested by studies in which overexpression of GPX4 inhibited activation and nuclear translocation of nuclear factor (NF)-κB [16, 86]. Because activation of NF-κB in leukocytes leads to a multitude of pro-inflammatory transcriptional and signaling events as well as release of soluble mediators, this suggests that GPX4 expression may be induced in activated leukocytes for the purposes of both protecting against lipid peroxidation and modulating the activation state of the cell after release of soluble mediators. In fact, overexpression of GPX4 in RBL2H3 cells decreased the production of leukotriene C4, leukotriene B4 (LTB4), and prostaglandin D_2 compared with controls [40]. These effects were reversed upon depletion of glutathione in the GPX4-overepressing cells with diethyl malate or buthionine sulfoximine. This suggests GPX4 and/or GPX1 were responsible for the reduced leukotriene production, most likely through reduced ROS-dependent activation of NF-κB. In contrast to these findings, peritoneal macrophages from rats fed Se-deficient diets secreted lower levels of LTB4 when activated with opsonized zymosan compared with controls [30]. Thus the results based on overexpression studies need to be confirmed using physiological conditions and expanded to include other phagocytic and non-phagocytic leukocytes.

A key downstream event resulting from increased ROS-induction of NF-κB activation is increased iNOS transcription [3, 45]. Upregulation of iNOS expression in turn produces increased NO, which further regulates cellular function of phagocytes [22]. *In vitro* experiments with RAW 264.7 murine macrophages have shown that increases in Se lead to decreased mRNA and protein levels of iNOS and subsequent decreases in NO production [64]. Providing Se supplementation above adequate levels to J774A.1 murine macrophages was shown to effectively inhibit LPS-induced NO production in a mechanism that was dependent on both NF-κB and p38 mitogen-activated protein kinase [47]. In this manner, increasing levels of Se from low to medium to high levels may lead to a biphasic response of phagocytic cells that depend on ROS for activation, with optimal phagocyte function occurring at medium levels of Se intake.

There is surprisingly little information available concerning the role of selenoproteins in the function of another phagocytic cell, the dendritic cell (DC). Matsue et al. [54] have used an organic Se-containing compound, ebselen, to inhibit the TRX/TR system and raise intracellular oxidation states in DCs to study the effects of antigen presentation. Their findings suggest antigen presentation and bi-directional DC-T cell communication are disrupted using ebselen. Repeating these experiments with other methods of redox manipulation would assist in determining how Se affects DC maturation, migration, and antigen presentation. Given the central role that DCs play in initializing and maintaining immune responses and the role that ROS and redox play in their ability to mature into effective antigen-presenting cells, it seems this topic is in need of focused research.

TRX REDUCTASE BALANCES REDOX AND INFLAMMATION

As described above, TR-1 and -2 perform an essential role in the regeneration of reduced TRX, which provides reducing capacity in the intracellular space for a balanced redox state. Dietary Se levels have been shown to affect TR-1 activity and TRX levels in a wide range of tissues [32]. Several experiments have utilized a mouse model involving a transgenic mouse overexpressing human TRX (TRX-Tg) or treatment with recombinant TRX to show that increased abundance of this important reducing compound is effective in reducing inflammation during a wide range of immunological processes, including experimental colitis, LPS-induced bronchoalveolar neutrophil infiltration, myosin-induced autoimmune myocarditis, mast cell degranulation, and asthma development [39, 53, 77, 80, 81]. Part of the mechanism by which TRX carries out anti-inflammatory effects is through altered levels of certain cytokines and eicosinoids. For example, the production of the pro-inflammatory cytokine macrophage migratory inhibitory factor (MIF) was decreased by overexpression of TRX or treatment with recombinant human TRX by murine monocytes or human monocytes, respectively [80]. These studies also demonstrated an increase in TRX and MIF levels with disease activity in patients with inflammatory bowel disease. However, it was unclear whether the increased TRX was promoting inflammation or induced to ameliorate the inflammation occurring in the patients.

Overall, the studies with the TRX-overexpressing mice suggest that, at endogenously high levels or over-

active states that produce abundant TRX, TR enzymes may contribute to the modulation of inflammation and immune responses most likely by shifting redox away from oxidative stress levels in immune cells and local tissue cells. However, under conditions involving physiological levels of TRX, the actions of TR-1 appear to be mainly pro-inflammatory. Using TRX and NADPH, TR-1 has been shown to activate NF-κB by reduction of a disulfide bond involving cysteine 62, which in turn leads to stimulated DNA binding of NF-κB [55]. Inhibition of TR-1 with 1-chloro-2,4-dinitrobenzene was shown to result in reduced LPS-mediated NF-κB DNA binding and NO production by RAW 264.7 mouse macrophages [35]. In addition to TR-1 in the cytoplasm, TR-2 in the mitochondria has been shown to play a role in TNF-α-induced activation of NF-κB in HeLa cells, suggesting that TR-2 must also be included when considering mechanisms by which Se affects NF-κB-dependent activation of immune cells.

In addition to phagocytes, studies by Ueno et al. [82] used transgenic mice overexpressing human TRX described above (TRX-Tg) and revealed a role for TR in mitogenic responses by T cells. In brief, Con A--induced proliferation of wild-type murine splenic T cells was enhanced by Se supplementation in a NF-κB--dependent manner. However, splenic T cells from TRX--Tg mice did not exhibit similar enhancement at similar levels of Se supplementation. Also, higher levels of Se supplementation augmented TR activity, but not GPX-1 activity, in the TRX-overexpressing cells. These results suggest that the stimulation of T cell mitogenic responses by physiological levels of available Se is predominantly caused by increased TR activity, which may lead to a NF-κB-dependent reduction of TRX. Other studies have demonstrated the importance of thiol-based reducing capacity in enabling human T cells to progress through cell cycle and proliferation [43, 85]. This suggests a crucial role for TR enzyme(s) and roles for other selenoproteins with TRX-like structure (TR-2, Sep15, and Sel M) in T cell responses may yet be uncovered.

Upregulation of TR-1 activity and/or TRX levels as a means of controlling inflammation and immune responses must be considered with the caveat that increased TR-1 has been associated with tumor progression [83]. Conversely, treating cancers by inhibiting the TRX/TR system may have a suppressive effect on certain leukocytes' ability to become activated. Finally, TRX has been shown to be involved in the activation of the small G protein Ras in myocardiocytes through oxidation of thiol groups on Ras [51], and it may be worth investigating how Se levels may affect immune cells during activation events that depend on the Ras-Raf-MEK-ERK pathway.

MECHANISMS BY WHICH Se AFFECTS ANTIVIRAL RESPONSES

As mentioned above, infection with virulent strains of coxsackievirus B3 (CVB3) may lead to myocarditis in Se-deficient humans (Keshan disease), which can be prevented by Se supplementation. Mouse models have revealed that low Se intake or genetic deletion of GPX1 leads to viral genomic RNA mutations that increase the virulence of CVB3 [9, 11]. In a similar manner, mutations in the genomic RNA of influenza A/Bangkok/1/79 (H3N2) virus also increased along with its virulence in Se-deficient mice [62]. Viral mutations have been implicated in the severity of disease using these models, but there are some hints from these and other studies by the Beck laboratory that Se deficiency influences various components of antiviral immune responses as well. Se--deficient mice infected with influenza virus demonstrated higher numbers of total cells than Se-adequate mice lavaged from lungs after influenza infection [13]. In later stages of influenza infection, the levels of $CD8^+$ and $CD4^+$ T cells were lower in Se-deficient mice, but no changes were found in influenza-specific antibodies between Se-deficient and Se-adequate mice. This suggests that Se deficiency affects cell-mediated immunity to a greater extent than humoral immunity for anti--influenza viral responses. Se-deficient mice infected with influenza exhibited higher levels of monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1α and β, and RANTES in lung draining lymph nodes [13]. In another study, Se-deficient mice infected with a virulent, mouse-adapted strain of influenza virus mounted altered immune responses exhibiting slightly lower levels of mRNA for RANTES and MIP-1α in early stages of infection [52]. These studies differ from the earlier studies involving cytokine mRNA levels in that total RNA was extracted from lung tissue instead of draining lymph nodes. More recently, influenza infection was carried out on a transgenic mouse carrying a mutant Sec--tRNA (t-*trspi*^{6}A$^-$), which exhibits decreased selenoprotein levels in a protein- and tissue-specific manner [75]. Although GPX-1 and TR-1 activities were greatly reduced in the lungs of these mice prior to infection, the lung pathology after infection was not changed. Most cytokines were similar between the t-*trspi*^{6}A$^-$ and controls, with exceptions including higher levels of mRNA for MCP-1, MIP-1α, and IFN-γ in the lung tissue of transgenic mice. However, it is difficult to ascertain whether these altered chemokine and cytokine levels were due directly to altered selenoprotein expression or to differences in viral reproductive cycle because viral clearance was slightly lower in the transgenic animals.

Se levels have also been shown to affect HIV-1 infection at particular stages of the virus's replication cycle, but no mouse model exists to test the effects of Se on genomic RNA mutation [10, 24, 38, 73]. The relationship between Se and anti-HIV-1 immune responses differs from the previously mentioned RNA viruses in that HIV-1 infects major cells participating in the immune response against the virus, such as T cells and monocytes. Se supplementation has been shown to increase GPX-1 activity in HIV-1-infected cells, which in turn leads to lower H_2O_2 levels and decreased NF-κB activation [42, 74]. Because HIV-1 infection is activated by

ROS-dependent NF-κB activation in infected cells [41], it follows that reduction of ROS through increased selenoenzyme activity (e.g. GPX-1) may be a major mechanism by which Se mitigates HIV-1 infection. Furthermore, Richard et al. [67] reported that the expression of HIV-1 Tat protein in HeLa cells decreased the expression of GPX-1 and Sep15 and increased the expression of GPX-4. Regulation of HIV-1 infection/replication and selenoprotein expression may occur in both directions, with ROS and NF-κB serving as intermediate targets of this two-way regulation.

THE ANTI-CANCER EFFECTS OF Se

There is mounting evidence from basic and clinical studies suggesting a protective role for dietary Se in various types of cancer [59, 66, 87]. For example, the Nutritional Prevention of Cancer Trial examined the effect of high Se yeast on cancer incidence and mortality and results suggested a decrease in the risk of colorectal cancer, prostate cancer, lung cancer, and all carcinomas combined [21]. In addition, on-going prospective trials such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT) will help to clarify the role of Se in prostate cancer prevention. Potential mechanisms by which Se acts as an anti-cancer agent include antioxidant protection of DNA, enhanced carcinogen detoxification, modulation of cell cycle progression, inhibition of tumor cell invasion, and inhibition of angiogenesis [7, 59, 84]. The immune-enhancing effects of Se supplementation may also be a mechanism by which Se reduces the risk of cancer, although limited studies have been conducted directly examining Se and anti-cancer immunity. One study involved a small group of human subjects (N=33) receiving either Se supplementation (200 μg/day) or placebo and the measurement of cytotoxic T lymphocyte (CTL)-driven tumor lysis, mitogen-induced proliferation of lymphocytes, and the mixed lymphocyte reaction proliferation of lymphocytes [48]. For all three readouts, lymphocyte performance was increased with Se supplementation. However, limited data are available directly dealing with the mechanisms by which Se may enhance anti-cancer immunity, and much more information is needed regarding this important aspect of Se biology.

Se INCREASES IL-2 RECEPTOR EXPRESSION

Some of the clearest mechanistic studies of Se and lymphocyte function have been those linking Se levels and interleukin 2 receptor (IL-2R) levels. Early studies by Roy et al. [69] showed that supplementation of C57BL/6 mice with Se resulted in increased expression of both the α (CD25) and, to a lesser extent, β/γ (CD122/CD132) subunits of the IL-2R on con A-stimulated lymphocytes. This resulted in a greater number of high-affinity IL-2R per cell and enhanced proliferation and differentiation of lymphocytes. Effects of Se on IL-2R in response to allergens were similar in that increases in CD25 were found on T helper (Th) cells with increases in dietary Se, but no significant changes in CD122 expression were detected [37].

Studies in humans supported the data from mice and showed a clear correlation between Se supplementation and lymphocyte proliferation, which was preceded by enhanced expression of high-affinity IL-2R [70]. Th cells are involved in mounting effective immune responses to a wide variety of antigens and they depend on IL-2R signaling for activation, proliferation, and differentiation [90]. As described above, T cell proliferation may involve TR-1 and -2 and their effects on NF-κB activation [82], and this may also affect IL-2R expression. In addition, proliferation of human T cells in response to anti-CD3 stimulation was shown to be inhibited by depletion of GSH using buthionine-(S,R)-sulfoximine (BSO) and the proliferative response was restored with addition of exogenous GSH, but not exogenous IL-2 [79]. The inhibition of proliferation with BSO treatment was not accompanied by altered CTL capacity, suggesting a strong link between reduced intracellular environment and proliferation as opposed to differentiation [76]. These results suggest a role for GPX enzymes in promoting a proliferative response in activated T cells, perhaps through NF-κB activation or perhaps through an alternative pathway. Determining how Se intake affects IL-2R expression, what selenoproteins are involved, and how this relationship influences T cell-driven responses will provide important insight into the influence of Se levels on immune responses.

DOES Se EFFECT Th1 VS Th2 POLARIZATION?

As described above, cell-mediated immune responses against viruses were shown to be lower in Se-deficient mice. In addition, anti-cancer CTL responses may be enhanced by increased Se intake. For example, C57BL/6 mice fed increasing levels of Se in their chow exhibited an increasing ability to generate CTL and to destroy tumor cells [68]. In addition to these Th1-type responses, Th2 allergic immune responses have been studied in relation to dietary Se intake. Using an established mouse model of asthma involving sensitization/challenge with ovalbumin (OVA), our laboratory demonstrated that low Se diets led to significantly lower allergic airway inflammation compared with mice fed Se-adequate chow [37]. Interestingly, increasing the Se intake above adequate levels by feeding high-Se chow did not further increase the airway immune responses to OVA. Instead, mice fed high-Se chow had less robust asthma than the mice fed Se-adequate chow. This differs from the tumor studies in C57BL/6 mice mentioned above. In this sense, there appears to be a biphasic response to allergen challenge in the lung, with medium-Se mice displaying the strongest Th2-driven immune responses. This is in con-

trast to data from the mouse influenza model in which Se deficiency led to significantly higher IL-4 mRNA in lung tissue seven days post-infection [52].

At this point in time, there appears to be evidence that increased Se status may influence the Th1/Th2 balance of immune responses in an individual, but any polarizing effect that Se levels may have on immune responses likely depends on the type of antigen with which the animal is challenged. Results from mouse models suggest that low dietary Se results in a compromised immune system that is unable to respond to challenge with various types of antigen. This may actually be beneficial in the case of allergies or asthma, but may be devastating for viral infections or tumor progression. The benefits of Se supplementation with these models are less clear. The data from our asthma studies suggest that Se supplementation may lower the strength of allergic immune responses. However, further investigation is necessary to better characterize how Se supplementation influences immune responses to diverse antigens.

CONCLUSIONS

Overall, evidence to date suggests that Se deficiency leads to weaker immune responses against a wide variety of antigens, while questions remain concerning immune-enhancing effects provided by Se supplementation above adequate levels. Given the fact that proper regulation of ROS and redox are crucial cellular processes, it is no wonder that Se is important for optimal immune system function. Much of the current knowledge concerning the mechanisms by which Se exerts its influence over immune responses involves balanced ROS and redox by GPX and TR enzymes, respectively. With the human genome sequence completed and selenoprotein family members identified, specific lines of questioning regarding their roles in immune responses may now be taken. For example, which selenoproteins are expressed to what levels in different immune cells? How is their expression altered during different immune responses? Is the function of selenoproteins in immune cells restricted to the regulation of ROS and redox or are there other important roles for selenoproteins that affect immune responses? With answers to these questions will come a better mechanistic understanding of how Se affects immune responses.

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