Mol. Nutr. Food Res. 2008, *52*, 1273 – 1280 DOI 10.1002/mnfr.200700330

Review

The influence of selenium on immune responses

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Selenium (Se) is a potent nutritional antioxidant that carries out biological effects through its incorporation into selenoproteins. Given the crucial roles that selenoproteins play in regulating reactive oxygen species (ROS) and redox status in nearly all tissues, it is not surprising that dietary Se strongly influences inflammation and immune responses. The notion that Se "boosts" the immune system has been supported by studies involving aging immunity or protection against certain pathogens. However, studies examining the effects of Se status on other types of immunity such as antiparasitic responses or allergic asthma have suggested more Se may not always be beneficial. In this review, we summarize and compare the available data regarding how the levels of Se affect different types of immunity. Overall, determining how Se intake differentially affects various types of immune responses and dissecting the mechanisms by which this occurs will lead to a better utilization of Se-supplementation for human diseases involving the immune system.

Keywords: Immune responses / Inflammation / Oxidative stress / Selenium / Selenoproteins

Received: August 22, 2007; revised: October 1, 2007; accepted: October 6, 2007

1 Introduction

Dietary selenium (Se) is an essential micronutrient that affects various aspects of human health, including optimal immune responses. Through its incorporation into selenoproteins, Se is involved in regulating oxidative stress, redox, and other crucial cellular processes in nearly all tissues and cell types, including those involved in innate and adaptive immune responses [1 – 3]. A number of studies in agricultural animals have provided insight into the effects of Se-deficiency or Se-supplementation on immune responses (reviewed in [4]). In most cases, 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 to Se-adequate controls. However, the results are less clear regarding the benefits of Se-supplementation above adequate levels in conferring additional immunological protection. Limited data from studies in humans suggest that Se-supplementation may enhance immunity, including both humoral and cell-mediated responses [5]. However, it remains unclear whether all types of immune responses are "boosted" by increasing Se intake. In this review, we will summarize and compare results from a wide variety of studies involving Se levels and different facets of immunity.

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Abbreviations: GPX, glutathione peroxidase; **HIV-1,** human immunodeficiency virus-1; **MCP-1,** monocyte chemoattractic protein-1; **MIP,** macrophage inflammatory protein; **NK,** natural killer; **ROS,** reactive oxygen species; **OVA,** ovalbumin

2 Viral infections

Perhaps the most compelling data regarding detrimental effects of Se-deficiency come from studies involving Keshan disease, a cardiomyopathy that affects residents the in regions of (China) with Se-deficient soils [6]. Se-supplementation of individuals completely prevents 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 to prevent genetic adaptations in the viral genomic RNA that lead to increased virulence and cardiac pathology [7]. In fact, the data are much clearer regarding how Se levels affect CVB3 itself than how low Se affects the host's immune responses to the virus.

Studies by the Beck laboratory involving mouse models of infection with another RNA virus, influenza A, have

revealed that this virus also undergoes increased mutational alterations in genomic RNA resulting from Se-deficiency [8]. In addition, a great deal of information regarding how Se-deficiency alters immune responses to this viral infection has been obtained using this model. Compared to Se-adequate mice, Se-deficient mice infected with influenza virus demonstrated higher numbers of total cells lavaged from lungs, suggesting Se-deficiency may result in elevated inflammation perhaps due to higher levels of oxidative stress [9]. Early in infection, a higher percentage of macrophages are found in the Se-deficient lungs. In later stages of influenza infection, the levels of macrophages, $CD8^+$ and $CD4^+$ T cells were lower in Se-deficient mice, but no changes were found in levels of influenza-specific antibodies between Se-deficient and -adequate mice. This suggests that Se-deficiency affects cell-mediated immunity to a greater extent than humoral immunity for antiinfluenza viral responses in this model.

Se-deficient mice infected with influenza virus exhibited higher levels of monocyte chemoattractic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α and β, and RANTES in lung draining lymph nodes [9]. In another study, Se-deficient mice infected with a virulent, mouse-adapted strain of influenza virus mounted altered immune responses characterized by slightly lower levels of mRNA for RANTES and MIP-1α in early stages of infection [10]. In addition to the strain of virus used, these studies differed from the earlier studies involving chemokine mRNA levels in that total RNA was extracted from lung tissue instead of draining lymph nodes.

More recently, influenza infection studies were carried out on a transgenic mouse carrying a mutant Sec-tRNA (t-*trsp*i^6A^-) [11], which is characterized by overall decreased selenoprotein levels in most tissues with subsets of selenoproteins differentially affected in each tissue [12]. The authors were examining various tissues using ^{75}Se incorporation to determine if differences in isoforms of Sec-tRNA available in the mice during infection would result in altered patterns of selenoprotein expression compared to wild-type mice, but no changes were found. The main difference between the transgenic and wild-type mice was an overall decreased selenoprotein expression as is found in uninfected mice. Examination of mRNA levels for cytokines and chemokines showed that IFNα, IFNβ, TNFα, and IL-6 were similar between the t-*trsp*i^6A^- and controls, but significantly higher levels of mRNA for MCP-1, MIP-1α, and IFNγ were found in the lung tissue of transgenic mice. Thus, the reduced selenoprotein expression that accompanies the transgenic phenotype caused an altered pattern of certain cytokines and chemokines, but no change in lung pathology. These data are interesting, but do not specifically address the relative importance of selenoprotein expression levels in the lung *versus* immune cells responding to influenza virus, which would require more tissue-specific models.

In a related study by Jaspers *et al.* [13] *in vitro* influenza infection of differentiated human bronchial epithelial cells (BECs) in Se-deficient *versus* -sufficient conditions demonstrated that low Se resulted in an altered phenotype with reduced antioxidant enzymatic activity and increased IL-6 production. These data emphasize the role that Se status plays in regulating oxidative stress of nonleukocytic tissue cells, which may lead to altered secretion of important proinflammatory cytokines during influenza infection.

Human immunodeficiency virus-1 (HIV-1) is another RNA viral infection affected by host Se status. Deficiencies in micronutrients such as Se present a problem among HIV-1-seropositive individuals, particularly in regions of the world where resources for fighting HIV-1 infection are limited. Among HIV-1-infected individuals, lower serum Se concentrations have been associated with lower $CD4^+$ T cell counts, greater HIV-1 disease progression, and higher HIV-1 related mortality [14 – 17]. In addition, risk of developing mycobacterial infection in HIV-1-infected individuals was found to be higher in those individuals with serum Se lower than 135 μg/L [18]. However, whether Se status is directly related to the ability of the immune system to fight infection or whether serum Se concentration is an indicator of overall nutritional or metabolic status has not been firmly established [19]. Daily Se-supplementation has been shown to correlate with slower progression of HIV-1 viral burden and improved $CD4^+$ T cell count [20], but data revealing the role Se-supplementation plays in boosting anti-HIV-1 immunity are limited.

One study suggested that low Se levels were associated with a reduced natural killer (NK) cell-mediated cytotoxicity in HIV-1-infected individuals [21]. Several *in vitro* studies have provided support for the anti-HIV-1 effects of Se-supplementation. For example, Hori *et al.* [22] demonstrated that Se-supplementation for 3 days prior to exposure to TNFα partially suppressed the induction of HIV-1 replication in both chronically infected T lymphocytic and monocytic cell lines. HIV-1 replication stimulated by TNFα in acutely infected human monocytes, but not in T lymphocytes, was suppressed by Se-supplementation. In acute HIV-1 infection of T lymphocytes and monocytes in the absence of exogenous TNFα, the suppressive effect of Se-supplementation was not observed.

Another antiviral immune response affected by host Se status is that against poliovirus. In particular, Broome *et al.* [23] used an oral live attenuated poliomyelitis vaccine to show that Se-supplementation in human subjects with low Se status resulted in increased production of IFNγ and IL-10, an earlier peak T cell proliferation, and increased percent of T cells that were of the T helper phenotype ($CD4^+$) in response to the vaccine. Se-supplemented subjects also showed more rapid clearance of the poliovirus, and the poliovirus RT-PCR products recovered from the feces of the supplemented subjects contained a lower number of mutations. Certain parameters of immune responses to poliovi-

rus were unaffected by Se-supplementation, including numbers of B or NK cells, antibody titers, or NK cell-mediated cytotoxicity. For this particular vaccine, as perhaps with other vaccines involving viral antigens, the Th1 immune responses were more robust with Se-supplementation.

3 Immunity to nonviral pathogens

While higher levels of Se have generally been shown to provide protection against viruses, the relationship between host Se status and immunity to nonviral pathogens is not so one-sided. Most of the available data suggest the influence of Se status on resistance to infections with bacteria, parasites, and fungi, depends on the microorganism involved. For example, an early study involving *Candida albicans* infection in mice showed that Se-deficiency resulted in higher susceptibility to this pathogen [24]. The authors demonstrated an impaired ability of Se-deficient, glycogen-elicited peritoneal neutrophils to kill *C. albicans in vitro*, which was repeated in other experiments and shown to be due to reduced superoxide production, oxygen consumption, and glucose utilization [25]. In contrast, killing of *Salmonella typhimurium* and *Staphylococcus aureus* by neutrophils was unaffected by Se-deficiency [24]. Se-deficient rats demonstrated increased mortality after i.p. injection of *S. aureus*, although injection of low doses of organisms ($<8 \times 10^7$) did not result in mortality differences when comparing Se-deficient and -sufficient rats. In contrast, Se-deficiency was shown to increase survival of rats infected with pathogens such as *S. typhimurium*, *Plasmodium bergeii*, or *Listeria monocytogenes* [26, 27].

In a more recent study, Se-deficient mice infected with *Trypanosoma musculi*, a protozoan parasite specific to mouse, cleared the pathogen whereas mice fed Se-sufficient or -supplemented chow exhibited sustained parasitemia [28]. A possible explanation was offered by the observation that trypanosomes lack sufficient capacity to reduce oxidative stress because the parasites do not have the classical glutathione peroxidase (GPX)/GR enzymatic system [29], thus making them reliant on Se-sufficient host antioxidants for survival. Regarding the immune response, the Se-deficient mice exhibited lower antibody responses against *T. musculi*, which suggests that persistant infection and/or Se-sufficiency are required for proper antibody production against such parasitic pathogens.

Studies in mice infected with *T. cruzi* demonstrated that Se-deficiency in the murine host increased the severity of *T. cruzi* -induced chronic inflammatory myopathy [30]. Infection with this parasite requires adequate antibody production for an effective immune response, although it remains secondary in importance to cellular immune responses [31]. It would be of interest to measure levels of lytic antibodies or antigen-specific CTLs in this model to determine how Se-deficiency affects either. Overall, it is difficult to determine whether the increased lesions in muscle tissue found in this study were due to inadequate immune responses or increased oxidative stress and inflammation in these tissues.

A study in mice involving Se-deficiency and the gastrointestinal nematode parasite, *Heligmosomoides polygyrus*, showed that low dietary Se resulted in decreased resistance to the nematodes upon secondary infection [32]. The lowered resistance did not appear to involve IL-4, as Se-deficiency had no effect on circulating levels of this key cytokine involved in host protection. However, a combined deficiency of Se and vitamin E produced lower IL-4 levels and even lower levels of resistance, suggesting synergistic effects of these two antioxidant nutrients in clearance of this parasite.

Overall, the relationship between host Se status and resistance to infections with nonviral pathogens may involve effects of Se availability on pathogen viability as well as on the host immune system. In this sense, these infections are similar to certain viral infections, which are directly affected by Se status as well as by the immune competence of the host. Finally, one must consider the levels of oxidative stress in the infected tissues and how that limits or enhances the infection and its related pathology.

4 Allergies and asthma

Oxidative stress plays an important role in the pathogenesis of asthma such as enhancing airway hyperreactivity (AHR), mucus secretion, and bronchoconstriction [33]. For this reason, antioxidants have received a great deal of recent attention for their potential in lowering susceptibility or severity of allergies and allergic asthma [34]. Se is a particularly potent antioxidant that has been proposed as an inexpensive prevention or treatment modality for asthma. However, the role of Se in reducing oxidative stress in the lower airways during asthma must take into consideration the immune enhancing effects of Se on the immune responses that drive asthma. This dual role of Se may explain conflicting data from studies in humans, with some data suggesting that dietary Se may play an important role in reducing the onset or severity of asthma [35 – 37], while other studies have failed to verify such correlations [38 – 40].

These discordant findings led our research group to carry out studies in mice using varying levels of dietary Se and a standard model of asthma involving sensitization and challenges with ovalbumin (OVA) [41]. Results from this study suggested that diets moderately deficient in Se (0.08 ppm) led to lower susceptibility to asthma, while Se-adequate diets (0.25 ppm) resulted in high levels of asthma. The mice fed highly supplemented levels of Se (2.7 ppm) tended to have slightly lower levels of asthma in response to OVA challenge, but for most parameters measured, the differences between Se-adequate and Se-supplemented animals

were not statistically significant. Thus, diets prevalent in most of the developed world that include adequate levels of Se may actually cause the highest levels of susceptibility to asthma in humans. These results may help explain some of the conflicting findings of Se-supplementation in humans. That is, providing Se-supplementation to an individual with preexisting, moderately low Se status may increase asthma susceptibility, while supplementing an individual with preexisting adequate Se status may slightly lower their susceptibility. In our study, the observed effects of high Se status on slightly lowering asthma responses may be in part due to skewing of immune responses toward Th1, as our studies showed that the Th2 marker, phosphorylated-STAT6, was significantly reduced in the lung of OVA-challenged mice fed high Se compared to those fed adequate levels of Se. Investigations are underway in our laboratory to determine the mechanisms by which Se may influence differentiation of Th cells and potentially polarize responses to different antigens.

5 Cancer immunity

There is mounting evidence from basic and clinical studies in humans suggesting a protective role for dietary Se in various types of cancer [42 – 44]. 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 [45, 46]. In follow-up analyses to this study, Se-supplementation was found to be associated with reduced risk of colorectal adenomas, particularly among subjects with either a low baseline Se level or among current smokers [47]. 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 anticancer agent include antioxidant protection of DNA, enhanced carcinogen detoxification, modulation of cell cycle progression, inhibition of tumor cell invasion and inhibition of angiogenesis [42, 48, 49]. 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 anticancer immunity. One study focusing on the effect of Se on antitumor immunity was conducted by Kiremidjian-Schumacher and Roy [50]. This 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 mixed lymphocyte reaction (MLR) proliferation of lymphocytes. For all three readouts, lymphocyte performance was increased with Se-supplementation.

Roth *et al.* [51] conducted a study to determine whether nutrient supplements containing a combination of Se (50 μg), β-carotene (15 mg), and α-tocopherol (30 mg) would correlate with both enhanced immune responses and lowered cancer incidence. The nutrient supplement was associated with significantly increased T-lymphocyte mitogenic responsiveness. However, multivariate analyses showed no significant associations between phytohemagglutinin-M, concanavalin-A, or anti-CD3 stimulation indices and subsequent cancer incidence or total mortality. This implies that immune competence, as measured by these stimulation indices, was not associated with incident cancer or total mortality in the study population. Se used in the daily supplement was lower than those conventionally used for supplementation studies and other supplements were involved, making it difficult to draw conclusions about the effects of Se on immune-driven reduction in cancer incidence. Overall, there is a paucity of data to directly support or reject the notion that Se increases immune responses to cancer, thus there is much to be gained by including immune response parameters in future studies focusing on Se and cancer.

6 The aging immune system

Aging leads to a progressive decline in multiple physiological processes, including immune responses [52, 53]. Nutritional status holds particular sway on immune function in the elderly [54] and contributing to waning immunity in this population is the cumulative oxidative damage to protein, lipid, and nucleic acid macromolecules that steadily lead to cellular dysfunction [55, 56]. Over time, a progressively pro-oxidative shift arises due to an increased imbalance between the rate of generation of oxidant compounds, such as reactive oxygen species (ROS), and their rate of clearance by the antioxidant systems. Se is incorporated into crucial antioxidant selenoenzymes such as the GPXs, which provide protection against ROS. In addition, selenoproteins such as the thioredoxin reductases, methionine sulfoxide reductase (Sel R), and perhaps others play key roles in reversing oxidative damage inflicted upon macromolecules. Leukocytes are dependent on both oxidant and proinflammatory compounds to carry out functions such as activation, proliferation, differentiation, and phagocytosis [57]. Over time, leukocytes may suffer oxidative damage resulting from required production of ROS [58]. This makes proper levels of Se and other antioxidants available to these cells especially important for maintaining proper immune responses in aging individuals.

In vitro studies have shown that peripheral blood mononuclear cells (PBMC) from elderly patients exhibit increased production of MCP-1-induced chemotaxis of monocytes when cultured in media supplemented with both vitamin E and Se [59]. Polymorphonuclear leukocytes

(PMN) from these same subjects cultured in the same supplemented media showed improved chemotactic and phagocytic functions. In one study, a mouse model of premature aging was used to determine the effects of a multinutrient supplement on leukocyte functions [60]. The method of supplementation involved a standard diet at 95 or 80% plus 5 or 20% w/w, respectively, of biscuits enriched with nutritional doses of the antioxidants vitamins C and E, β-carotene, zinc, and Se. The effect of supplementation on GPX activity was profound in the premature aging mice, suggesting that the Se component of the supplement was utilized by these mice. The multinutrient supplementation significantly increased several parameters of leukocyte function including phagocytosis, lymphoproliferation, NK cytotoxic activity, and IL-2 release. However, it is difficult to determine the contribution of Se in relation to the other nutrients in boosting these immune cell functions.

In one study involving healthy aged humans (57–84 years of age), the effects of supplementation with β-carotene (45 mg/day), and/or Se (400 μg/day) for 6 months and after 2 months of discontinuation was evaluated [61]. Plasma Se concentration was increased by 20% in the group receiving Se plus β-carotene, while there was only a 10% increase in the Se alone group during the 6 months of supplementation. Oddly, Se-supplementation alone, but not in combination with β-carotene (which caused larger increases in plasma Se), caused an increase greater than 50% in percentage of T cells, particularly $CD4^+$ T cells, in peripheral blood at 6 months from pretreatment levels. This increase persisted 2 months after supplementation was discontinued. No differences were found in complete blood cell (CBC) or white blood cell (WBC) counts with any of the supplements nor were any differences found in percentage of B lymphocytes in the blood. Interestingly, there was an increase in NK cell percentage in blood during the supplementation period with the combination of β-carotene and Se, but not with either individually, and the percentage returned to pretreatment levels by 2 months postsupplementation. Somewhat paradoxically, NK cell-mediated cytotoxicity was enhanced after 3 months of Se-supplementation yet decreased after 6 months and then slightly increased again after supplementation was discontinued. It seems difficult to reconcile the opposing effects of these supplements on NK cell percentage and NK cell function, but one may consider the increase in NK cell function a better readout of protection against pathogens or cancer in aging subjects.

Other studies in humans have also attempted to measure potential correlations between Se status and immune cell types in elderly subjects. For example, Ravaglia *et al.* [62] found that serum Se concentration was positively associated with peripheral $CD16^+$ NK cells. However, functional capacity of these NK cells, *e.g.*, cytotoxicity, was not determined. Thus, in this study that did not directly utilize Se-supplementation there was an association between Se status and NK cell number, but in the study mentioned above Se-supplementation seemed to affect NK cell function rather than cell number in aged subjects. Another study involving participants in the Women's Health and Aging Study I evaluated these subjects for antioxidants and serum levels of the proinflammatory cytokine, IL-6 [63]. Results from this study indicated that subjects with the lowest levels of Se were significantly less likely to be in the highest tertile of serum IL-6 and those with the lowest Se levels had a significantly higher risk of total mortality over a period of 5 years. While these results are not definitive, they suggest a relationship between Se status in the elderly and inflammatory processes mediated by IL-6, a cytokine that has been associated with poor health outcome in this subpopulation [64]. Another study involving supplementation with Se and vitamin E in aged mice showed that the supplementation slightly increased plasma IL-6 concentrations in response to LPS challenge [65]. The increased IL-6 was evident when comparing low Se to adequate Se diets, but not adequate Se to high Se diets.

Overall, Se status is generally perceived as an important factor for maintaining health in the elderly [66, 67]. However, there is a need for more details regarding mechanisms by which Se-supplementation may improve immune responses in aged individuals.

7 Summary

We have provided a summary of findings from the wide variety of studies involving Se and immunity (Table 1). Overall, there is considerable evidence strengthening the notion that Se affects different types of immune responses in different ways. The influence of Se-supplementation on enhancing immunity depends on what type of antigens and tissues are involved. For example, Se-supplementation may enhance Th1-type immune responses to a greater extent than Th2-type responses, and certain infectious agents may actually benefit from the added levels of Se by utilizing it for their own antioxidant enzymes. Importantly, when comparing various studies it is apparent that the starting Se status of the individual is an important factor when considering Se-supplementation. Much of the available evidence suggests that boosting Se levels in moderately low Se individuals may have more immune enhancing effects than supplementing a Se adequate individual. Of course, there are some disorders such as cancer for which Se-supplementation of Se adequate individuals may be beneficial due to antidisease effects of increased Se levels that fall outside the realm of the immune system.

The relationship between Se status and immunity is turning out to be more complex than the simplified notion of Se being in general an immunity "booster," which highlights the critical need for determining the mechanisms by which Se affects the immune system. Ultimately, mechanistic

Table 1. Summary of relevant studies

Topic	Conclusions	References
Review of experimental and agricultural animal studies	Se enhances cell-mediated and humoral immunity in many cases. Results depend on the type of organism or vaccine involved.	4
Se-supplementation in humans	Se-supplementation produces increased lymphocyte counts and mitogenic responses.	6, 23
Viral infections	Se-deficiency leads to increased host-susceptibility in most cases. High Se levels may be beneficial to host, particularly for HIV-1, which itself appears to affect host Se status.	7 – 23
Nonviral infections	The effects of host Se status on the pathology of infection depend on the micro-organism involved.	24 – 32
Allergies and asthma	Descriptive studies in humans are conflicting. Animal studies suggest Th2-immune responses like asthma may actually decrease with se-deficiency. Se-supplementation only slightly decreases pathology.	35 – 41
Cancer immunity	Se-supplementation may lower risk of several types of cancer, particularly colorectal cancers. Whether this involves enhanced anticancer immunity is unclear.	42 – 51
Aging immunity	Results are encouraging, but not conclusive. Most evidence suggests that Se-supplementation may benefit aging immunity.	59 – 64

studies will need to involve specific selenoproteins and the roles they play during inflammation and immune responses. Many selenoproteins play critical roles in reducing oxidative stress and balancing redox in a wide variety of tissues and cell types, including those involved in innate and adaptive immune responses. However, functions for many selenoproteins remain unknown. By identifying roles of selenoproteins and relating those roles to inflammation and immune responses, greater insight may be gained into the mechanisms by which Se affects immunity and the use of Se-supplementation may be more optimally utilized.

The authors have declared no conflict of interest.

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