Selenium and Vitamin E Status: Impact on Viral Pathogenicity 1–3

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Abstract
Selenium (Se), an essential trace element, and vitamin E, a lipid soluble antioxidant, are important mediators for protection against oxidative stress. Recent work has demonstrated that deficiencies in either Se or vitamin E result in increased viral pathogenicity and altered immune responses. Furthermore, deficiencies in either Se or vitamin E results in specific viral mutations, changing relatively benign viruses into virulent ones. Thus, host nutritional status should be considered a driving force for the emergence of new viral strains or newly pathogenic strains of known viruses. J. Nutr. 137: 1338–1340, 2007.

Selenium and Vitamin E
Selenium (Se), an essential nutrient, has been the subject of intense research over the past 50 y. In the early 1970s Se was found to be an essential cofactor of glutathione peroxidase, an antioxidant enzyme (1). Ten years following this discovery, selenoprotein P was identified as an Se-containing protein (2,3) and, shortly thereafter, other selenoproteins were identified (4,5). To date, there are ~2 dozen mammalian selenoproteins identified, although not all have described functions (6). Se is incorporated into proteins as selenocysteine via a specific selenocysteine tRNA that reads the stop codon UGA as an insertion site. Thus, selenocysteine is considered to be the 21st amino acid (7).

Se deficiency is associated with Keshan disease, a primarily childhood cardiomyopathy (8). Keshan disease is found in areas of China with very low Se in the food supply, due to raising crops in Se-poor soils. Once Se deficiency was identified as a major factor for the development of Keshan disease, widespread Se supplementation of the at-risk populations succeeded in reducing the incidence of Keshan disease. However, the annual and seasonal incidence of the disease suggested that an infectious cofactor, along with a deficiency in Se, may play a role in the development of the disease. Indeed, scientists in China were able to isolate coxsackieviruses from the blood and tissues of Keshan disease patients (9). This finding led to the suggestion that host Se status may influence a viral infection.

Vitamin E consists of 8 forms: 4 tocopherols and 4 tocotrienols. However, α-tocopherol is found in the greatest amounts in blood and tissues of humans. Vitamin E functions as a lipid soluble antioxidant. The correction of vitamin E deficiency in rats and chicks could be achieved with Se, demonstrating that, in some cases, vitamin E and Se could spare one another’s activities through their common action as antioxidants (with Se working through antioxidant selenoproteins) (10).

Se and viral interaction
The association of Keshan disease with a possible coinfection of coxsackievirus led to the development of an animal model to mimic Keshan disease. Mice were fed a diet deficient in Se for 4 wk, at which time they were inoculated with coxsackievirus B3/0, an amyocarditic strain of coxsackievirus. This strain of CVB3 has been shown previously to be amyocarditic in mice, even though the virus is able to replicate in the heart tissue. As expected, mice that were fed a diet with sufficient Se did not develop myocarditis. However, mice that were fed a diet deficient in Se developed moderate to severe myocarditis (11).

Previous studies have demonstrated that a deficiency in Se can lead to immune dysfunction (12). Indeed, spleen cells from CVB3-infected, Se-deficient mice had an impaired proliferative response to both mitogen and antigen stimulation (13). Natural killer cell activity, however, was not affected. The ability of the Se-deficient host to secrete virus-specific neutralizing antibody was also not altered. Chemokines are an important component of the immune response to coxsackievirus. In the infected Se-deficient mice, monocyte chemotactic protein 1 and macrophage inhibitory protein-1α were elevated in the hearts compared with infected Se-adequate mice. Because these chemokines are...
important mediators of the inflammatory response, elevated levels of these chemokines may be a cause for the increased inflammation seen in the hearts of the Se-deficient mice.

Although the Se-deficient mice clearly had immune dysfunction, an unexpected finding was that the viral genome itself was changed. Six nucleotides of the CVB3/0 genome were mutated to nucleotides found in myocarditic strains (14). Thus, the benign viral genome was altered in the Se-deficient host to a myocarditic strain. Once these mutations occurred, even mice with normal Se status were susceptible to the newly pathogenic strain. This was the first evidence presented, to our knowledge, which demonstrated that host nutritional status could influence a viral genome.

One function of Se is as a cofactor for the antioxidant enzyme, glutathione peroxidase. A deficiency in Se leads to decreased glutathione peroxidase activity. However, Se is also an important component of other Se-containing proteins, including thioredoxin reductase and thyroid hormone deiodinase. To determine whether the increased pathology and altered viral genome found in the CVB3-infected Se-deficient mice was due to a reduction in glutathione peroxidase activity, mice with a disrupted glutathione peroxidase 1 gene were utilized. Gpx-1 knockout (KO) mice were infected with CVB3/0 and killed at various times postinfection for study.

As for Se-deficient mice, CVB3/0-infected Gpx-1 KO mice developed myocarditis, whereas the wild-type mice did not (15). In contrast to Se-deficient mice, Gpx-1 KO mice had a deficient antibody response, although their spleen cell proliferative responses to both mitogen and viral antigen were normal. Chemokine responses in the Gpx-1 KO mice were similar to the wild-type mice, although delayed. Thus, the wild-type mice had peak chemokine responses at 5 d postinfection, whereas the peak response in the KO mice occurred at d 10 postinfection. Of particular note, virus that replicated in the Gpx-1 KO mice that developed pathology had 7 nucleotide changes, 6 of which were identical to those found in the Se-deficient mice. These results suggest that the increased pathogenesis and viral mutations that occurred in the Se-deficient mice were due to a decrease in glutathione peroxidase activity, leading to increased host oxidative stress.

In a model of murine acquired immunodeficiency, Sepulveda et al. (16) found that coinfection of a normally coxsackievirus-resistant strain of mouse with LP-BM5 retrovirus and CVB3 resulted in myocarditis. However, supplementation of the mice with Se during the retrovirus infection significantly increased the survival and diminished the heart pathology of the dual-infected mice.

A very interesting study in a human population demonstrated that adults in the United Kingdom with low Se status (not deficient) had a decreased immune response to live poliovirus vaccination. Of particular interest was the finding that individuals with low Se status had increased shedding of vaccine strain mutations (17). Supplementation to increase Se status diminished the development of these variants.

A deficiency in Se can also affect influenza virus infection. Infection of Se-deficient mice with a mild strain of nonmouse-adapted influenza A, Influenza A/Bangkok/1/79, induces severe pneumonitis but only mild lung pathology in Se-adequate mice (18). Immune function was also altered in the Se-deficient mice. Analysis of mRNA for cytokines and chemokines in the lungs of infected mice demonstrated that influenza-infected, Se-deficient mice had increased levels of IL-4, IL-5, IL-10, and IL-13 and decreased levels of IL-2 and γ-IFN compared with Se-adequate mice. This pattern suggests a skewing of the immune response away from a Th1 response (which is typical for influenza infection) and toward a Th2 response. Chemokine responses were also altered in the Se-deficient mice with an overexpression of a number of chemokines, including macrophage inhibitory protein-1α, RANTES, and monocyte chemotactic protein 1. Taken together, the immune data suggest a more heightened inflammatory response in the Se-deficient influenza-infected mice, leading to the increased lung pathology. For infection of Se-deficient mice with coxsackievirus, the influenza virus genome was altered in the Se-deficient animals (19).

In contrast to infection of Se-deficient mice with the Bangkok strain of influenza virus, infection of Se-deficient mice with a mouse-adapted, highly virulent strain of influenza virus, Influenza A/Puerto Rico/8/34 (PR8), leads to increased survival compared with Se-adequate mice. The PR8 strain of virus, in contrast to the Bangkok strain described above, is a human influenza strain that has been adapted to grow efficiently in mice. In normal mice, the PR8 strain induces severe pathology in contrast to the Bangkok strain, which induces a much milder lung pathology. The finding of enhanced survival of Se-deficient mice infected with PR8 may be related to the fact that much of the lung pathology of influenza-infected mice is due to the inflammation that occurs in response to the lung infection. Thus, a reduction in inflammation as a consequence of Se-deficiency may have led to the increased survival in the Se-deficient, PR8-infected mice. Therefore, it is important to keep in mind that the effects of Se deficiency on a viral-infected host may depend on the type of pathology induced. A reduction in inflammation may be beneficial under some conditions.

Vitamin E and viral infection

Many of the Keshan disease patients were of marginal vitamin E status in addition to being deficient in Se. Because both Se and vitamin E work as antioxidants, the idea that vitamin E deficiency may also influence the host response to viral infection was tested. Vitamin E-deficient mice infected with the myocarditic strain of coxsackievirus B3 developed moderate to severe myocarditis, whereas vitamin E-replete mice did not develop myocarditis (20). Genetic sequencing of virus isolated from the deficient mice demonstrated 6 nucleotide changes that were identical to those found in the virus isolated from Se-deficient hosts.

To further investigate the link between vitamin E and antioxidant protection, mice were fed a diet deficient in vitamin E with or without N’N’-diphenyl-p-phenylenediamine, a synthetic antioxidant that is structurally unrelated to vitamin E yet mimics its antioxidant activity. Vitamin E-deficient mice infected with CVB3/0 developed myocarditis; however, the deficient mice supplemented with N’N’-diphenyl-p-phenylenediamine did not develop myocarditis, thus demonstrating that antioxidant protection is important for limiting viral damage.

Excess iron in the diet is seen as a pro-oxidant stimulator. When mice were fed a diet containing excess iron, increased heart pathology occurred with CVB3 infection. The most severe pathology occurred in mice fed a diet deficient in vitamin E with excess iron (21).

Antioxidant nutrient deficiency as a driving force for viral mutations

Although there are a number of reasons for increased viral mutations and emergence of new and/or old pathogens with new pathogenic properties, nutrient status of the host is often not considered. Work in several laboratories clearly demonstrates a role for nutrient status as a driving force for the emergence of
viral mutations. Although the mechanisms for the increased viral mutations are not currently understood, most likely there is an interplay between host nutrient immune dysfunction, which may allow for selection of viral variants, and direct oxidative damage of viral genes, resulting in an increased mutation rate. The standard model for understanding the effect of host nutrition on viral disease presumes a linear relation between increased oxidative stress, immune dysfunction, and increased viral pathogenicity (Fig. 1). Recent work suggests that a revised model, which takes into account the ability of the virus to mutate under conditions of oxidative stress, should be considered. Clearly, more work needs to be done to further understand this phenomenon.

**Literature Cited**

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