Selenium: an essential element for immune function

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The importance of selenium for optimal immune function is now apparent. Here, Rodney McKenzie and colleagues describe how selenium is involved in the function of immune cells, and the various immune deficiencies and diseases that result from inadequate dietary intake.

Sources of Se

Ultimately, the soil is the source of Se; it enters the food chain through incorporation into vegetable protein as the amino acids selenocysteine and selenomethionine. Thus, if the animal and human population eat predominately food produced locally, the Se status of the population will reflect soil levels.

In many parts of Europe Se intake is low (30–40 μg/day)3,4. The recommended dietary intake (RDI) for Se in the UK is 75 μg/day for adult males and 60 μg/day for adult females. In many parts of the USA, intake is above the RDI at 90 μg/day.

Selenoproteins and protection from oxidative damage

Selenoproteins are present in every cell type. At least 20–30 selenoproteins exist, but...
Box 1. Effects of Se on immune cell function

**Se supplementation**
- Neutrophil migration and O$_2^-$ activity (cow)
- High-affinity IL-2 receptor (mouse)
- T-cell proliferation and function following age-related decline (mouse)
- Natural killer cell activity (mouse, human)
- Cytotoxic T-cell activity (mouse)
- T-cell response to pokeweed mitogen (cow)
- Lymphokine-activated killer cell activity
- Enhanced delayed-type response due to better antigen presentation (mouse)
- Cell death following paraquat exposure (rat)
- UV-induced skin cancers and mortality (mouse)
- Erythema following UV exposure (human, mouse)
- Vaccine-induced immunity to malaria (mice)

In vitro
- HIV long-terminal-repeat activation and HIV replication in T cells (human)
- NF-$kappa$B activation (human)
- B-cell lipoxigenase activity (human)
- Antibody responses (primary and secondary) to virus (cow)
- Cell death following UV irradiation of skin cells (mouse, human)
- DNA damage and lipid peroxidation in UV-exposed skin cells (mouse, human)
- IL-6, IL-8 and TNF mRNA following UV treatment of skin cells (human)
- Cell death following paraquat exposure (human)
- Apoptosis in tumours (human, mouse)
- Apoptosis induced by UV in normal skin cells (human)
- Physiohaemagluttinin response in lymphocytes (human)
- Killing by macrophages (human)
- Target killing by cytotoxic T cells (human)

**Se deficiency**
- Platelet aggregation and leukotriene synthesis (atopic human)
- IgG and IgM titres (human)
- Antibody production by lymphocytes (mouse)
- Virulence of Coxsackievirus (mouse)
- Neutrophil migration and O$_2^-$ activity (cow)
- Neutrophil chemotaxis (goat)
- Neutrophil and leukocyte activity (pig)
- Candidal activity by neutrophils (rat)
- CD4$^+$ T cells, CD8$^+$ T cells, CD4$^+$/CD8$^+$ thymocytes (mouse)

**Abbreviations:** HIV, human immunodeficiency virus; IL, interleukin; TNF, tumour necrosis factor; UV, ultraviolet radiation; T, mouse; N, human.

Much is known about the functions of the family of GPxs. The membrane-bound phospholipid hydroperoxide GPX (PHGPX) detoxifies phospholipid hydroperoxides and, along with vitamin E, helps prevent oxidative damage to membranes. The PHGPX may be more important than the cGPX in protecting the cell from oxidative stress. Elimination of peroxides in the extracellular fluid is dealt with by the extracellular or plasma form of GPX. Peroxynitrites, products of superoxide and nitric oxide, are produced in skin cells during exposure to UV and cause single-strand DNA breaks. The synthetic Se compound ebselen functions as a GPX and prevents these breaks. Ebselen also inhibits the proinflammatory enzymes nitric oxide synthase and protein kinase C (Ref. 9). In addition, the GPxs play a vital role in the synthesis of arachidonic acid metabolites. The lipoygenase and cyclooxygenase pathways produce hydroperoxycisatoeicosanoic acids, which must be reduced for lipoxin, prostaglandin and leukotriene synthesis. Eicosanoid synthesis is depressed in Se deficiency (see Ref. 2). Furthermore, accumulation of lipoperoxides impairs prostacyclin synthesis and promotes thromboxane accumulation, which can increase platelet aggregation in cardiovascular disease.

Other selenoproteins include the iodothyronine deiodinases (types I, II and III), which regulate the metabolism of thyroid hormones in all tissues. Clear functions are still being sought for other selenoproteins such as selenoprotein P and selenoprotein W. The former may be involved in Se transport; the latter is lost in Se-deficiency-induced myopathy.

The discovery that thioredoxin reductase (TDR) is a selenoenzyme is of great interest. One of its substrates is the 12 kDa thiol-protein thioredoxin9. On which it acts as a protein disulfide reductase. TDR acting alone or in conjunction with thioredoxin can thus affect the redox regulation of a variety of key enzymes, transcription factors and receptors including ribonucleotide reductase, the glucocorticoid receptor, AP-1 and NF-$kappa$B. Thioredoxin is classified as a T-cell leukaemia survival factor because it stimulates expression of the a subunit of the interleukin 2 (IL-2) receptor. In addition to...
**Box 2. Human diseases affected by Se or correlated with Se status**

**Se deficiency**
Keshan disease (endemic cardiomyopathy)
Atopic asthma – low platelet glutathione peroxidase
Kashin-Beck disease (endemic deforming arthritis)
Coronary heart disease – correlates directly with low serum Se
AIDS – low serum Se correlated with rapid disease progression
Spontaneous abortion – correlates with low Se status
Psoriasis – severity and duration of disease correlated directly with decreased blood Se levels
Skin cancers – abnormally low serum Se in T-cell lymphoma and malignant melanoma
Mycosporaneous candidosis – low serum Se

**Se supplementation**
Reduction in gastrointestinal, prostate and lung cancers (Se-replete population)
Depressed neutrophil activity and increased monocyte chemoattractant protein in the elderly
Protection against hepatitis B-induced hepatitis
Improved sperm motility in subfertile men
Decrease in lipid peroxidation following UV exposure

For abbreviations, see Box 1.

**Selenium and viral diseases**
In mice, the coxsackievirus mutates to a virulent cardiotoxic form when it is passaged through Se-deficient hosts14, possibly because the host immune system is weakened. The fact that human Keshan disease is seen in Se-deficient areas of China led to the hypothesis that it may be caused by a coxsackievirus B virus that mutates to a cardiotoxic form in Se-deficient hosts. This disease responds to Se-dietary supplementation. Similarly, in China, the incidence of hepatitis B-induced hepatoma fell after Se supplementation15. In AIDS patients, Se status is predictive of survival times16. There is also the intriguing observation that virulent strains of influenza virus evolve in Se-deficient areas of China and the suggestion that human immunodeficiency virus (HIV) may have crossed the species barrier into man in Se-deficient areas of Africa. Selenium also seems to protect mouse cells in culture from the transforming effects of murine mammary tumour virus. Interestingly, several viruses (melanoma contagiosum, HIV-1, coxsackie B and EBoola) contain sequences with homology to GPX (Ref. 17); perhaps these viral GPXs might be involved in protecting the virus from host-cell-derived peroxides.

**Se and protection from UV-induced damage and cancer**
UV is the most ubiquitous environmental carcinogen. Skin exposure leads to DNA, lipid and protein damage by direct and free-radical-mediated effects. In mice, dietary Se supplementation reduces incidence of and mortality from UV-induced non-melanoma skin cancers. Se supplementation prevents DNA adduct accumulation, cell death, lipid peroxidation and inflammatory cytokine induction in skin cells in culture following UV irradiation18. Transfection with a viral GPX also improves keratinocyte survival following UV exposure19.

An exciting finding is that doses of 200 μg/day selenomethionine reduce the overall incidence of prostate, lung and gastrointestinal cancers by 39% (Ref. 20). These effects may result from a number of mechanisms including preventing oxidative damage to DNA, maintaining effective immune defences and inhibiting tumour proliferation.

**Conclusion**
In conclusion, adequate Se is essential for immune function and can protect the immune system from oxidative damage. Dietary Se supplements hold promise as a means of treating inflammatory conditions and rejuvenating the ageing immune system, and in protection from carcinogenesis.

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**References**
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