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Nutritional control of HIV-AIDS- A case for Selenium

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Abstract: Selenium (Se) is a micronutrient that is incorporated into proteins. Some of the selenoenzymes such as GPXs and thioredoxin reductases exhibit glutathione peroxidase-dependent activities towards organic and inorganic peroxides. Thus, selenoenzymes play a pivotal role in mitigating oxidative stress caused by accumulation of peroxides. In this respect, selenoproteins may interfere with the transcription-driven by oxidative stress-dependent signaling mechanisms to influence the expression of redox sensitive genes, including inflammatory cytokines and HIV provirus. Several epidemiological studies support our view that Se supplementation affects transcription of HIV; however, the underlying mechanism is not elucidated. In this mini review, we consider the relationship between Se and HIV and propose possible mechanisms by which Se controls HIV transcription.

Keywords: Tat, NF- κ B, thioredoxin reductase, transcription

INTRODUCTION

Selenium nutrition and optimal health: Selenium is a nutritionally essential trace element that is important for optimal immunity^[1-4]. Several studies demonstrate that Se deficiency leads to impaired immune responsiveness, while Se-supplementation results in increased immunocompetence^[4]. Selenium deficiency has been associated with several pathological conditions, including cardiovascular diseases^[5], rheumatoid arthritis^[6], cancer^[7, 8] and the focus of this review, AIDS^[9]. Se-supplementation results in significant increases in tumor cytotoxicity of macrophages and natural killer cells^[3]. Furthermore, there is an inverse causal relationship of Se intake with cancer risk, notably in adult populations of the United Kingdom, Europe, China, and New Zealand. Even in the United States, mortality rates for cancer were found to be higher in low Se counties^[10; 11]. Based on several studies examining the correlation between Se and disease resistance, the National Academy of Sciences (USA), has recommended a daily intake of 55 μ g/day, with a tolerable upper daily intake of Se at 400 μ g^[12]. Furthermore, with changing life styles and eating habits,

plasma Se levels appear to be on a downward trend towards deficiency. In particular, cigarette smokers, breast cancer patients and HIV infected individuals, have plasma Se levels that are significantly reduced^[13-15].

Selenium regulates NF- κ B dependent pathways and the expression of pro-inflammatory genes:

Since the recent discovery of selenocysteine (SeCys) as the 21st amino acid in proteins, the field of Se biology has rapidly expanded. There are at least 30 mammalian selenoproteins that have been characterized to date, which contain SeCys incorporated in response to a specific in-frame UGA codon^[16-19]. These selenoproteins have different cellular functions, but in those selenoproteins for which the function is known, SeCys is located at the active center. The best characterized selenoenzymes belong to the families of Se-GPXs (GPX1-5) and TrxRs. The activities of these enzymes are responsible for Se action as an dietary antioxidant^[17,18,20]. Furthermore, thioredoxin (Trx) reductase (TrxR), acts as a "redox switch" to regulate the activities of cellular growth factors and signaling

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by catalyzing oxidation-reduction reactions of critical thiol groups^[8]. Se deficiency significantly decreases the expression and activities of Se-GPXs/TrxRs and a concomitant increase in ROS production^[21,22]. Furthermore, Se deficiency increases the sensitivity of cells to oxidative stress^[23]. Selenium-dependent GPX is essential for the reduction of H₂O₂ and lipid hydroperoxides as well as peroxynitrite^[24]. More importantly, GSH/Se-GPX system represents the major antioxidant enzyme mechanism to reduce H₂O₂ and fatty acid hydroperoxides in macrophages^[25].

Recent studies have established Se as a potential regulator of transcription^[26] by increasing the binding of nuclear proteins, such as NF-κB, NF-1, and OCT, to DNA regulatory elements. These transcription factors, in particular NF-κB, which has been shown to be the primary redox-sensitive transcription factor^[27-29], regulate transcription of genes associated with inflammation including COX-2, iNOS, and several other proinflammatory chemokines and cytokines such as IL-1, IL-6, MIP-2, and TNFα^[30-32] in response to oxidative stress or infection^[26] and provides one mechanism by which nutritional Se directly impacts inflammation and diseases.

The NF-κB/Rel family of transcription factors is comprised of five members, p65, RelB, c-Rel, p52 and p50. In general, these proteins are retained in the cytoplasm through their association with IκB proteins. Upon signaling, which can be initiated by cytokines, receptor engagement and stress, IκBs are degraded and NF-κB homo- and heterodimers translocate to the nucleus^[33,34]. Although progress has been made in identifying the biochemical events that regulate NF-κB activity, how signals are integrated to control the function of different Rel proteins has yet to be resolved. Recent work has demonstrated that two signaling pathways lead to NF-κB activation^[33, 34]. The classical pathway, which is associated with signaling in response to inflammation, requires activation of the IκB kinase (IKK) complex that includes IKKα, IKKβ and the regulatory subunit NEMO. Active IKK mediates serine specific phosphorylation of IκB, which triggers polyubiquitination and 26S proteasome-dependent degradation, releasing NF-κB subunits, in particular p65 and p50, to translocate to the nucleus^[33, 34]. NF-κB activity is also induced through an alternative or non-canonical pathway, which requires IKKα activation. IKKα phosphorylates serine residues in the C-terminus of p100, targeting the C-terminus for degradation and releasing the Rel subunit p52^[35-37]. p52 most commonly dimerizes with RelB and translocates to

the nucleus. It has been demonstrated that the alternative pathway is critical for the development of secondary lymphoid organs^[34] and regulating macrophage inflammatory activity^[38].

Glutathione peroxidase-1 inhibits NF-κB activation, via inhibition of IκB phosphorylation^[39]. Therefore, in a state of Se deficiency, GPX1 expression would be diminished leading to IκB phosphorylation and consequent translocation of NF-κB to the nucleus. As a result, inappropriate expression of pro-inflammatory genes and exacerbation of tissue destruction and disease is generally seen. Apart from selenoproteins, there is no evidence for any other gene that is strictly regulated by Se status. However, the accompanying oxidative stress in Se-deficiency leads to an increased expression of oxidative stress-inducible genes such as COX-2, iNOS, and TNF-α, which is commonly seen in macrophages.

ROS and macrophage function

Macrophages play a central role in immune regulation by presenting antigen to T-lymphocytes and ingestion and killing of various invading microorganisms. The cellular response to invading microorganisms is multifaceted with the recruitment and subsequent activation of inflammatory cell populations. Macrophages are critical cellular participants in this process and they are activated by diverse stimuli (like LPS), to synthesize and secrete cytokines, which initiate and control inflammatory and immune functions. Macrophages synthesize numerous substances involved in host defense and inflammation such as complement components, PGs, interleukin (IL)-1β, TNFα and other proinflammatory cytokines and chemokines^[40]. While fulfilling these functions, “activated” macrophages undergo a respiratory burst that produce ROS such as superoxide, hydrogen peroxide (H₂O₂), hydroxyl and lipid peroxyl radicals. Increases in the intracellular levels of ROS represents a potentially toxic insult, which if not counteracted, will lead to membrane dysfunction, DNA damage, and inactivation of proteins^[41]. ROS have been implicated in atherosclerosis, rheumatoid arthritis, osteoporosis, asthma, renal disease, Alzheimer’s disease, and AIDS; all diseases with a strong inflammatory component^[42, 43]. It is apparent that any condition that disrupts macrophage integrity will have consequences on immune function. Se through the action of GPXs and TrxRs would assure a balanced redox state in macrophages and act as critical

regulator of macrophage activity, inflammation and cell mediated damage. Along these lines, recent data from our laboratory indicates that there is increased activation of NF- κ B in the macrophage cell line RAW 264.7 when cultured under Se-deficient conditions compared to those cultured in the presence of Se^[44].

Macrophages are important for HIV infection and AIDS. HIV infection results in drastic depletion of CD4⁺ T cells, which is the hallmark of AIDS. However, AIDS is a multifactorial disease affecting multiple organs including the skin, lung, lymphoid tissue and brain^[45]. The widespread effects of HIV infection are partly due to a general inflammatory response where chronic immune activation leads to an increase in cytokine secretion and enhanced virus replication^[46]. These events result in tissue damage and the manifestation of several AIDS-related pathologies^[45]. Furthermore, the surrounding tissue environment and aberrant cellular activity that is triggered by HIV infection influences virus transcription, replication and alters the susceptibility of cells to HIV^[46].

The complexity and heterogeneity of AIDS underscores that multiple cell types and functions are affected by HIV infection. The primary targets for HIV infection are CD4⁺ T cells, dendritic cells and macrophages. Tissue resident macrophages, including alveolar macrophages, peritoneal macrophages, Kupffer cells and microglia cells, are productively infected^[47-51]. Unlike CD4⁺ T cells, macrophages are resistant to cytopathic effects of HIV and are potentially long-lived reservoirs for persistent infection and dissemination, especially during late stages of AIDS when CD4⁺ T cell counts are low or following withdrawal of anti-viral therapies^[52, 53]. Macrophages are a source of infectious virus in the lymph nodes and lung, and they facilitate HIV entry into many tissues, including the central nervous system^[54-57]. Furthermore, HIV infection activates macrophages, increasing the expression of TNF α , IL-1 β , IL-6 and IL-8, while decreasing production of M-CSF, G-CSF and GM-CSF^[26]. Elevated levels of IL-1 β , TNF α and IL-6 have been detected in the serum and cerebrospinal fluid of AIDS patients^[45,58]. HIV infection has also been suggested to disrupt other macrophage activities including chemotaxis, antigen presentation, phagocytosis and the production of reactive oxygen and nitrogen species^[59-63].

Transcriptional control of HIV expression by oxidative stress: HIV provirus expression is regulated at the transcriptional level. Provirus transcription is controlled by the upstream long terminal repeat (LTR), which includes *cis*-elements that recruit both cellular and

viral factors^[64, 65]. The HIV LTR is often divided into four functional units; the Tat activating region (TAR), the promoter, the enhancer, and the modulatory element. The promoter, enhancer and modulatory elements are complex transcriptional elements that bind a plethora of cellular factors; however, few of these sites have been demonstrated to be critical for HIV transcription. *Cis*-elements that are necessary for efficient HIV replication include sequences for Sp-1, NF- κ B^[66-71] and, in macrophages, C/EBP^[65, 72, 73]. It is interesting to note that NF- κ B and C/EBP β are both induced in macrophages by inflammation and oxidative stress suggesting an autocrine pathway that perpetuates macrophage activation and HIV replication.

The TAR element generates an RNA stem-loop structure that is recognized by the viral transcription factor Tat. Tat, which is required for HIV replication, increases processive transcription by recruiting P-TEFb to the LTR. In the absence of Tat transcription elongation by RNA polymerase II (Pol II) from the HIV promoter is very inefficient^[74,75]. Preliminary studies in our laboratories have demonstrated that Tat activity may be modulated by cellular Se status. Furthermore, our analysis has also revealed that several intramolecular disulfides in TAT are potential targets for TrXR. Since TrXR activity is modulated by cellular Se status, these results strongly suggest a mechanistic link between Se and HIV.

Studies on the underlying mechanism of Se in AIDS. Studies in sub-Saharan Africa have shown that Se-supplementation of AIDS patients increased CD4⁺ cell counts and decreased the viral titer^[76]. It is however not clear as to how Se influences the course of HIV infection. Although, Se deficiency may in part reflect malnutrition and poor health care that would exacerbate the progression of AIDS, we suggest that Se may directly influence HIV replication by two mechanisms (See Fig. 1). One way in which Se influences HIV replication is by its ability to modulate NF- κ B expression; low Se would increase oxidative stress, which in turn would induce NF- κ B activity and the expression of proinflammatory genes leading to a favorable microenvironment for HIV replication. However, recent data from our laboratory would suggest a second potential pathway in which Se targets Tat activity. Preliminary data have indicated that Se inhibits Tat-dependent induction of the promoter.

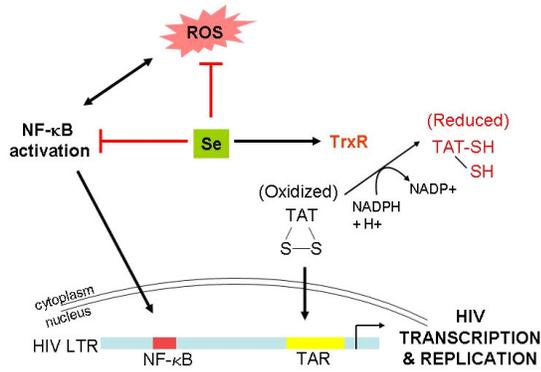


Fig. 1: Schematic representation of the anti-oxidant role of Se in HIV transcription and replication process. Selenoenzymes prevent activation of NF-κB by decreasing the oxidant species. TrxRs, in particular, may also play an important role in the redox regulation of Tat.

Furthermore, inhibiting TrxR activity enhances the ability of Tat to induce HIV promoter activity. We hypothesize that TrxR inhibits Tat by reducing active oxidized Tat. Therefore, Se by increasing TrxR activity, would inactivate Tat and block HIV replication. Further investigation of how Se regulates HIV expression is required, but these initial observations would suggest that dietary supplementation of Se could complement other anti-viral strategies to effectively manage HIV infection and AIDS.

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