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Abt. Gastroenterologie und Hepatologie, USZ

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Selenium and RNA viruses: an update for HIV, SARS, hepatitis and flaviviruses

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Selenium and RNA viruses: an update for HIV, SARS, hepatitis and flaviviruses

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Since the pioneering work of Gerhard Schrauzer in the late 1970s showing that selenium inhibits mouse mammary tumors induced by the retrovirus MMTV, an impressive body of evidence has accumulated for the antiviral effects of dietary Se. The possibility that coxsackievirus is a cofactor for the classical Se-deficiency disease, Keshan disease, is supported by a body of work by Beck and her collaborators. Since the mid-1980's, evidence has accrued of a progressive decline in serum Se in AIDS patients. A number of studies have confirmed that Se status predicts outcome in HIV infection, i.e., disease progression and mortality are strongly correlated with Se deficiency. Unfortunately, these and other data have sometimes been overinterpreted as justification for taking Se supplements in excessive doses that, if sustained, may actually do more harm than good.

In 1994, based on a theoretical analysis of the HIV-1 RNA, I showed that HIV-1 potentially encodes several selenoprotein genes, the expression of which could compete for limited intracellular pools of selenocysteine (Sec). My research group has now cloned several of those genes for in vitro studies. One was shown to be a viral homologue of glutathione peroxidase (GPx), active in enzyme assays (Zhao et al., PNAS, 2000), and capable of protecting transfected cells against oxidant-induced apoptosis (Cohen et al., Apoptosis, 2004). We find that the expression of the HIV GPx via a –1 frameshift is enhanced during arginine deficiency, which has been correlated with increased oxidative stress. We have demonstrated an identical heptameric –1 frameshift sequence in the SARS coronavirus, associated with potential Sec codons in the overlapping reading frame, encoding a peptide with significant homology to a family of Se binding proteins. Significantly, serum Se abnormalities have been observed in SARS patients.

Another novel HIV-1 protein that we call pro-fs, encoded overlapping the protease gene, appears to be a viral mimic of the transcription factor NF-kB, a known cellular activator of HIV gene expression. We have demonstrated that recombinant pro-fs is a potent activator of the HIV promoter in vitro, and binds to thioredoxin, an essential bioreductant for NF-kB activation.

These results, along with the strong clinical correlations between Se status and disease outcome, provide the basis for a Se depletion model for HIV pathogenesis. One site in HIV-1 where Se incorporation may occur lies in the nef gene, which is known to be a major contributor to the pathogenic effects of HIV (nef gene deletion is the basis of "attenuated" HIV vaccines). By this model, the detrimental effects of HIV-1 on the host may be significantly decreased and delayed if optimal Se and sulfur status (cysteine and glutathione) is maintained. This theory of HIV pathogenesis can also explain why various cofactors such as drug abuse, coinfections and malnutrition accelerate the disease, because all of them increase oxidative stress.

Various studies have linked Se deficiency to enhanced progression of viral hepatitis associated with HBV and HCV. We have also identified potential GPx-related sequences in some subtypes of the latter. In a similar genomic location, the related flaviviruses dengue virus and Japanese encephalitis virus encode a related hypothetical selenoprotein gene with homology to ferredoxin (Zhong and Taylor, J. Mol. Graphics & Modelling 2004).

Significantly, some scientists believe that during the last 50 years or more, there has been an ongoing global decline of Se in the food chain, due in part to fossil fuel burning and acid rain. This could contribute to an apparent recent increase in virulence of HIV and other viruses. Because the virus-host interaction, not just viral load per se, is the determinant of outcome in viral infections, a realistic goal is to try to establish homeostasis between the virus and host. Current evidence suggests that optimizing dietary antioxidant status will be essential to achieving that outcome.