

ZINC DEFICIENCY

Cancer Association

Tumor Suppressor Genes

**Many diseases, especially cancer, are associated with defects in tumor suppressor genes (or transcription factors) that are involved in the metabolic pathways regulating apoptosis (cell death) and cell proliferation (Hamatake M, 2000, Rezvani M, 2000). When tumor suppressor genes are functioning correctly, they have the power to arrest cell division and suppress uncontrolled cell proliferation (tumor growth). Gene p53, the most frequently mutated gene in human cancer, requires zinc fingers in its configuration. If any are missing the gene becomes mutated, resulting in its inactivation or suppression (Robert V 2000, Kihara C, 2000, Werner H, 1996). Dysfunction of or alterations in the p53 gene have been particularly documented in head and neck (eg: esophageal), and gynecological (eg: breast) cancers (Ishiji T, 2000, Kihara C, 2000, Zachos G, 1998, Borresen AL, 1995). Dietary zinc deficiency has also been found frequently in these patients, especially those with esophageal cancer. Both correlate significantly with poorer tumor prognosis and treatment outcome. Researchers have also discovered that not only do many esophageal cancer patients harbor p53 mutations and acquire dietary zinc deficiency, but they also have suppressed immune systems, demonstrated by a disturbance in cytokine balance—there was a notable premature shift from Th-1 cytokines to Th-2 cytokines with an accompanying poor T-cell function. The zinc-dependent hormone, thymulin, activates T-cell proliferation and function, and this same premature shift and T-cell dysfunction occurs with zinc deficiency (Doerr TD, 1998 Prasad AS, 1998). In a recent cell study, researchers demonstrated the existence of a direct relationship between cellular zinc concentrations and p53 activity. When zinc concentrations were low, tumor suppressor gene p53 activity was also low, but when zinc levels were high, p53 activity was also high (Reaves SK, 2000). Wilm's tumor is found in association with defects in the WT-1 transcription factor which has four zinc fingers (Hata J, 2000). WT-1 may be deleted completely or missing a zinc finger on chromosome 11 at band p13. One or more of these mutations may result in urogenital malformations early in childhood, and/or fast growing "Wilm's" tumor of the kidney. WT-1 mutations have also been associated with leukemia (Hirose M 1999, Pritchard-Jones K, 1994).*

Tumor Suppressor Gene Candidates

**A newly discovered and widely expressed zinc finger protein, hZAC, has recently been shown to share the same antiproliferative properties as gene p53. This zinc finger gene is located on the long arm of chromosome 6, a section that is often missing in many types of cancer. Chromosome 6 is the fourth most common rearranged chromosome in human tumors, being reported in gastric, pancreatic, breast, renal cell, and ovarian cancers, and certain lymphomas, etc. (Varrault A, 1998). Another zinc finger, Zac1, which is expressed in the pituitary gland and brain, has also been found to regulate both apoptosis and cell cycle arrest (Spengler D, 1997). RIZ (retinoblastoma protein interacting zinc finger) has strong tumor suppressor gene activity. It is found mutated on a section of a chromosome (1p36) which is often altered in cancers of the pancreas, stomach, and colorectum (Sakurada K, 2001, Chadwick RB, 2000, Huang S, 1999). 1p36 is almost always altered in breast cancer (Bieche I, 1999, He L, 2000). RIZ has also been found mutated, deleted, or under-expressed in cancers of the liver and endometrium (Fang W, 2000, Piao Z, 2000). HKR3 (human kruppel-related 3), another novel zinc finger suppressor gene, is also located on chromosome 1p36, which is usually rearranged or deleted in neuroblastomas (Maris JM, 1997). Myeloid leukemia has recently been linked to a newly discovered zinc-dependent tumor suppressor gene candidate, 5qNCA, which functions on a section of chromosome 5. This gene is frequently deleted or partially lost in Myeloid leukemia (Westbrook CA, 2000). In-vitro zinc ions in themselves have been shown to suppress or kill cultured human malignant cells of the prostate, colon, and lung, as well as melanomas (Chai F, 2000, Borovansky J, 1997).*

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HPV/Cervical Lesions

**High plasma zinc levels provide a protective effect against HPV-16, a strain of HPV strongly associated with cervical cancer (Liu T, 1995). Recent studies have shown HPV often inserts itself on chromosome 10 when there is a disruption in zinc finger transcription factors (Cottage A, 2001). HPV oncoproteins, E6 and E7, are known to deactivate gene p53, stimulating cell proliferation and HPV, but not unless other conditions exist (eg: poor immune functioning) (Cardillo M, 2001, Ishiji T, 2000). As mentioned, p53 requires zinc fingers to keep it from mutating. Perhaps only when zinc ions (and certain other micronutrients such as folic acid and retinoic acid) are unavailable will p53 be rendered functionless by E6 and E7, allowing HPV to manifest. A recent study of cultured normal and cervical cancer cells found the human gene, APM-1 ("affected by papillomavirus DNA integration in ME180 cells"), located on chromosome 18, acted as a tumor suppressor gene in the normal cervical cells but not in the cervical cancer cell line (Reuter S, 1998).*

Prostate Neoplasms

**Prostatic neoplasms are the most common tumors in men. Normal secretory prostatic gland cells function to synthesize, accumulate, and secrete extraordinary amounts of citrate. Citrate production is regulated by prolactin in men (Costello LC, 1994). Prostate cells are said to contain more zinc than all other human cells. Zinc is stored in the mitochondria and regulated by testosterone and prolactin, which act to increase levels in normal cells (Untergasser G, 2000, Liu Y, 1997). Zinc protects and maintains high citrate levels by preventing citrate from being oxidized via inhibition of the enzyme, m-aconitase (Costello LC, 1998). Prostatic gland cells that cannot accumulate high levels of zinc have altered ATP production, and are transformed from citrate-producing to citrate-oxidizing cells which appear abnormal or malignant (Costello LC, 2000, & 1994). In addition, zinc within the prostate helps the DNA regulating enzyme, PARP [(poly(ADP)-ribose polymerase], stimulate apoptosis (independent of p53) to guard against uncontrolled cell growth and enforce normal cell division and maturation (Feng P, 2000, Untergasser G, 2000).*

Leukoplakia

**Leukoplakia of the mouth is associated with tobacco use and oral cancer, as well as low zinc levels (Kleier C, 1998). Low levels may reduce production of the zinc-dependent saliva enzyme, carbonic anhydrase, which quenches free radicals and toxins produced and found in tobacco smoke, explaining its association with oral cancer.*

Other Associations

**Endothelial cell damage induced by inflammatory cytokines and certain lipids may occur with zinc deficiency, increasing the risks of atherosclerosis (Meerarani P, 2000, Hennig B, 1999, Connell P, 1997). Luekocytospermia, oligospermia, and poor sperm morphology are associated with reduced antioxidant levels and a disturbance in T-helper 1 cytokines (Omu AE, 1999). Sperm cell membrane and nuclei damage, and infections in seminal fluid have been associated with zinc deficiency and infertility. Zinc deficiency is common in patients with SCD (Sickle Cell Disease) due to increased urinary excretion and rupturing of RBC's, which adversely affects T-helper cell activity and cytokine production. Zinc therapy in SCD patients has been shown to improve T cell function and reduce infections (Prasad AS, 1999). A deficiency is frequent in diabetes mellitus, where supplementation has proven to reduce complications by improving Th1/Th2 balance, and activating the enzyme, sorbitol dehydrogenase (Sprietsma JE, 1999, Blostein-Fujii A, 1997).*