

Role of Zinc in the Pathogenesis of Prostate Cancer

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It has been well documented that prostate epithelial cells contain high concentration of zinc and these levels are significantly decreased in prostate carcinoma relative to normal prostate tissue and are increased in benign prostatic hyperplastic (BHP tissue) (1-2). Although zinc is essential for proper maintenance of all cells, it is particularly important in the prostate which secretes high levels of citrate and proteins that contains zinc (reviewed in 3-4). There is compelling evidence that zinc is involved in the pathogenesis of prostate cancer (3-5). Of note, the prostate gland in a human male is divided into three zones: the peripheral zone (PZ) covers about 70% of the gland, whereas the central zone (CZ) is comprised of 25% and the transition zone (TZ) covers the remainder of the 5%. Most interestingly, the majority of the prostate cancer occurs in the PZ and this area essentially loses its ability to retain zinc in the cancerous epithelial cells (3-4). On the other hand, zinc is significantly increased in the BPH area (located in the CZ) and that portion of the glands rarely develops carcinoma (3-4). A major function of the PZ epithelium is to secrete an extraordinary amount of citrate and the same zone accumulates about 10-fold more zinc than the rest of the gland (3-5). Importantly, the decrease in zinc and in citrate occurs early in malignancy, before any histopathological changes can be discerned under the microscope (6-7). Zinc depletion proceeds decreased citrate production (6-7). The question that begs the answer is, “why the PZ epithelia of the prostate gland would accumulate such high zinc levels, particularly when it is well documented that high zinc levels can have adverse consequences at the molecular and cellular levels (8-10)?” And, curiously, why the same cells that contain such a high zinc level also produce an enormous amount of citrate (5)? It has been established that the accumulation of mitochondrial zinc inhibits m-aconitase activity and citrate oxidation (5). Is it citrate that protects the prostate epithelial cells in PZ from the toxic effect of zinc? In this issue Costello et al (11), explore the effects of zinc on mitochondrial terminal oxidation. They provide excellent documentation through a series of well-designed experiments that free zinc ions would inhibit cellular respiration and terminal oxidation, and hence, a high intracellular mitochondria level of zinc in the PZ prostate cells is essential for the normal physiology of these cells (5). The cytoplasmic zinc is transported to mitochondria via one or more intermediary molecules that subsequently inhibit the terminal step in the electron transport system. Such an inhibition significantly reduces the total energy output at the cellular levels, forcing the cells to rely on aerobic oxidation of glucose. A decrease in the zinc uptake and accumulation results in citrate oxidation and production of more energy, allowing cells to go malignant (after certain neoplastic mutations to take place). The authors hypothesize that more energy efficient specialized citrate producing epithelial cells of the PZ of the prostate may be an essential step towards conversion from normal to malignancy step (5,11-12).

Even though, there are still many questions that remain to be answered, the current observations reported by Costello et al are highly relevant in the understanding of the molecular pathogenesis of prostate cancer.

The most important issues that needs to be resolved in the area of prostate cancer are that:

- 1) Unlike other malignant tumors that are monoclonal in nature, prostate cancer is multi-focal (reviewed in 13). Does the lost ability of PZ cells to accumulate zinc initiate the malignancy process? One can imagine that the lost ability to take in zinc would arise at multiple loci in the PZ! If so, then what are the events at the molecular levels?
- 2) The significant clues regarding the uptake of zinc are already accumulating with a great speed. It is now known that there are several zinc transporters that work in concert to regulate zinc uptake. ZIP transporters, hZIP1 to hZIP4, are plasma membrane proteins that belong to the superfamily of Zrt/rt-like proteins and are involved in the uptake of zinc from the extracellular environment (reviewed in 15-17).
- 3) Several hormones are known to up-regulate ZIP transporters, including prolactin and androgens (1, 17).
- 4) Various ZIPs are differentially expressed in human prostate cells (18-19). The factors that govern the differential expressions of these transporters may add in the therapy and prevention of prostate cancer.
- 5) There is evidence that genetic factors also play an important role in the degree of expression of ZIP1 and ZIP2 transporters. These two transporters are down-regulated in malignant areas of the PZ as compared to surrounding normal cells. Most importantly, expressions of both of these zinc transporters are significantly more down-regulated in African Americans as compared to age and Gleason score-matched white men (19). Of note, African Americans have twice as much incidence of prostate cancer than whites (20).

Answers to these questions may help us conquer this illness that takes millions of lives annually worldwide.

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