Commentary

Could zinc dipicolinate be used to “smuggle” zinc into prostate cancer cells?

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How to cite this article: McCarty MF, Iloki-Assanga S, Lujan LL. Could zinc dipicolinate be used to “smuggle” zinc into prostate cancer cells? J Cancer Metastasis Treat 2020;6:20. http://dx.doi.org/10.20517/2394-4722.2020.47

Received: 17 May 2020  First Decision: 24 Jun 2020  Revised: 24 Jun 2020  Accepted: 6 Jul 2020  Published: 19 Jul 2020

Academic Editor: Rafat A. Siddiqui  Copy Editor: Cai-Hong Wang  Production Editor: Jing Yu

Abstract

Although prostate epithelium concentrates zinc for the purpose of promoting citrate secretion, it loses its capacity to import zinc while undergoing malignant transformation. This exclusion of zinc may be necessary for the viability of prostate cancer, as measures which increase the intracellular zinc content of prostate cancers lead to cell death, oxidative stress, and a marked reduction in ATP, suggestive of mitochondrial damage. The anti-fungal drug clioquinol, which can act as a zinc ionophore, can markedly slow the growth of human prostate cancer in nude mice, and has been proposed as a clinical therapy for prostate cancer. However, clioquinol is currently only available as a topical agent, as it was linked to subacute myelo-optic neuropathy with oral use. A more practical option for promoting zinc transport may be offered by the nutraceutical zinc dipicolinate, a stable chelate in which four coordination positions of zinc are occupied by two molecules of the tryptophan metabolite picolinic acid. Zinc dipicolinate is a highly effective supplemental source of zinc that has been shown to be more potent than soluble zinc salts for alleviating the symptoms of acrodermatitis enteropathica, a genetic zinc deficiency disorder reflecting homozygous loss of functional ZIP4 zinc importers in enterocytes. This suggests that the zinc dipicolinate complex is sufficiently stable and lipophilic to transfer zinc across cellular membranes. If so, it may have potential for “smuggling” zinc into prostate cancer cells. Hence, cell culture and rodent studies to evaluate the impact of zinc dipicolinate on human prostate cancer are warranted.

Keywords: Prostate cancer, zinc, clioquinol, picolinic acid, ZIP4
VIABILITY OF PROSTATE CANCER MAY REQUIRE EXCLUSION OF ZINC

Prostate epithelium is characterized by high intracellular levels of zinc, particularly within the mitochondria\(^1\). This intra-mitochondrial zinc is believed to promote the proper function of prostate epithelium by inhibiting aconitase activity, thereby causing an accumulation of citrate in the Krebs cycle\(^2,3\). Much of this citrate is exported into the seminal fluid, where it serves as an energy substrate for spermatozoa.

However, malignantly transformed prostate epithelium is far lower in intracellular zinc, reflected greatly diminished expression or activity of transporter proteins - ZIP1, ZIP2, and ZIP3 - that import zinc\(^4-8\). This loss of intracellular zinc appears to be essential to the viability of the transformed cells, as measures which restore high intracellular zinc levels - exposure to high extracellular zinc, or treatment with zinc ionophores such as pyrithione or clioquinol - slows their proliferation and up-regulates cell death\(^8-11\). *In vivo*, continual intravenous infusion of zinc, injection of zinc acetate directly into tumors, or parenteral administration of the zinc ionophore clioquinol has notably slowed the growth of human prostate cancers in nude mice\(^12-14\).

In particular, administration of clioquinol was associated with an 85% growth retardation of a ZIP-1-deficient human prostate cancer\(^14\).

In a range of human prostate cancer cells lines, increasing intracellular zinc with zinc pyrithione led to necrotic cell death associated with plummeting ATP levels, oxidative stress, and activation of ERK and PKC\(^10\). The antioxidants N-acetylcysteine (NAC) and trolox protected against cell death in this system; NAC, but not trolox, likewise blunted the decline in ATP. Since prostate epithelium tends to concentrate zinc in mitochondria, it would be of interest to know whether excessive zinc uptake by mitochondria mediates the oxidative stress and reduction in ATP seen after prostate cancer cells are exposed to zinc pyrithione. In addition to inhibiting aconitase activity, zinc is also capable of inhibiting complex III of the respiratory chain, with a \(K_i\) of about 100 nmol/L\(^15-18\).

Could malignant transformation of prostate epithelium somehow sensitize their mitochondria to the toxic impact of excessive zinc? The mitochondria of cancer cells are prone to structural abnormalities - possibly reflecting mutations in mitochondrial or nuclear DNA - which increase their propensity to produce superoxide\(^16,20\). Defects of the mitochondrial respiratory chain or of ATP synthase activity that moderately boost mitochondrial superoxide generation can be expected to promote cellular proliferation, angiogenesis, and mutagenesis; hence, they may act as tumor promoters, in which case these defects would be selected for\(^20-23\). The exceptionally high mitochondrial zinc levels of prostate epithelium presumably reflect increased expression or activity not only of ZIP1, but also of one or more zinc transporters -possibly ZnT2 - which import zinc into the mitochondrial inner matrix\(^24\). In mammary epithelial cells, ZnT2 transports zinc into mitochondria, and over-expression of this protein lowers cellular ATP levels and oxygen consumption, and promotes apoptosis; oxidant production was not measured in this study\(^24\).

If this increased intramitochondrial transport of zinc is maintained in transformed prostatic epithelial cells, then high mitochondrial zinc levels might interact with the mitochondrial abnormalities typical of cancer to induce severe dysfunction: excessive production of superoxide, decreased production of ATP, and further mitochondrial structural damage. This sequence of events could evidently be prevented by down-regulation of ZIP1 - which is what in fact is observed in transformed prostate epithelium.

In light of the utility of parenteral clioquinol for controlling growth of a prostate cancer in nude mice, it has been suggested that oral clioquinol could have potential as a therapeutic alternative for prostate cancer control. While it might indeed be the case that some sufficiently modest dose of clioquinol could prove useful in this regard, past clinical experience with oral administration of clioquinol as a fungicide or as a treatment for acrodermatitis enteropathica has been complicated by its association with subacute myelo-
optic neuropathy, characterized by peripheral neuropathy and blindness[^25,26]. Ten thousand patients in Japan were afflicted with this syndrome until oral use of clioquinol was discontinued in Japan. Hence, clioquinol is now available solely for topical use. The zinc-clioquinol chelate has been shown to lead to rapid mitochondrial damage and loss of mitochondrial membrane potential in a melanoma-derived cell line, possibly explaining the clinical toxicity of clioquinol[^27].

**ZINC DIPICOLINATE MAY ACT AS A ZINC TRANSPORTER**

However, an alternative strategy for boosting the intracellular zinc levels of clinical prostate cancer may be at hand. Zinc dipicolinate is a readily-available nutraceutical, originally patented by the U.S. Department of Agriculture, in which zinc is chelated by two molecules of the natural tryptophan metabolite picolinic acid; 4 coordination positions of zinc are occupied by picolinic acid in this complex. There is reason to suspect that, at least at neutral pH, zinc dipicolinate is sufficiently stable to carry zinc across bilipid layers. When children with acrodermatitis enteropathica (AE) were treated with either zinc dipicolinate or zinc sulfate, the dose of zinc required to prevent exacerbations of this disorder was found to be one-third as high with zinc dipicolinate, as opposed to zinc sulfate[^28]. AE is a hereditary zinc deficiency syndrome in which those afflicted are heterozygous for loss of function of ZIP4, the chief zinc importer expressed by the apical membranes of enterocytes[^29,30]. The superior utility of zinc dipicolinate in this syndrome, as opposed to forms of zinc that ionize readily (such as zinc sulfate), seems likely to reflect the ability of the zinc dipicolinate chelate to carry zinc across enterocyte membranes in the absence of zinc transporter proteins. Furthermore, in healthy human subjects, when zinc was administered at 50 mg daily as either zinc dipicolinate, zinc citrate, or zinc gluconate, zinc dipicolinate was shown to have a significantly greater impact on zinc levels in erythrocytes, hair, and urine[^31]. When nursing rat mothers were fed zinc as either dipicolinate or acetate, the zinc content of the kidney or liver of nursing pups was higher after the dipicolinate supplement[^32].

If zinc dipicolinate is sufficiently stable and lipophilic to “smuggle” zinc into enterocytes lacking ZIP4, might it not also be able to transport zinc into prostate cancer cells lacking ZIP1 activity? This possibility could be readily tested in prostate cancer cell cultures and, if preliminary results are promising, in nude mice xenografted with human prostate cancer. The possibility that zinc dipicolinate supplementation might also have potential for prevention of prostate cancer might also be envisioned, as reduction in intracellular zinc is believed to arise at an early stage of prostate cancer evolution[^33].

While therapies which boost intracellular zinc in prostate cancer might at best be expected to slow prostate cancer progression, the fact that such therapy might boost oxidative stress and lower ATP levels in prostate cancer cells raises the possibility that preceding zinc therapy might render prostate cancer more sensitive to hyperthermia and/or high-dose intravenous ascorbate[^34]. The selective susceptibility of cancer cells to high extracellular levels of ascorbate - which generate a high flux of hydrogen peroxide into the these cells - may reflect increased cancer production of superoxide, which can interact with hydrogen peroxide in a transition metal-catalyzed reaction to generate deadly hydroxyl radicals[^34,35]. And the lethality of whole body-tolerable hyperthermia (42 °C) to cancer cells may be potentiated by hydrogen peroxide; conversely, overexpression of mitochondrial superoxide dismutase protects a prostate cancer cell line from 43 °C hyperthermia[^36-39]. Mitochondrial superoxide production by zinc-treated cancer cells might be potentiated by concurrent treatment with dichloroacetate, which can increase the availability of pyruvate to mitochondria by inhibiting pyruvate dehydrogenase kinase; the latter is highly active in many cancers owing to up-regulated hypoxia-inducible factor-1 activity[^34,40,41].

**DECLARATIONS**

**Authors’ contributions**

Conceived and wrote the first draft: McCarty MF
Provided suggestions that were incorporated into the final manuscript: Iloki-Assanga S, Lujan LL
Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there is no conflict of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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REFERENCES
34. McCarty MF, Contreras F. Increasing superoxide production and the labile iron pool in tumor cells may sensitize them to extracellular ascorbate. Front Oncol 2014;4:249.