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Editorial

Positron Emission Tomography of Altered Copper Metabolism for Metabolic Imaging and Personalized Therapy of Prostate Cancer

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EDITORIAL

Malignant transformation of prostate epithelial cells is associated with metabolic changes, including alteration of copper metabolism. Preclinical studies demonstrated that human prostate cancer xenografts with increased ^{64}Cu radioactivity could be visualized in vivo by positron emission tomography after intravenous injection of copper-64 chloride ($^{64}CuCl_2$) as a radiotracer. Altered copper metabolism holds potential as an imaging biomarker for metabolic imaging and personalized anti-copper therapy of prostate cancer.

Prostate cancer is the second most common cause of cancer death, after lung cancer, for men in the United States [1]. Malignant transformation of prostate epithelial cells is associated with change of metabolism, leading to the development of multiple radiotracers for positron emission tomography (PET) of prostate cancer targeting the altered metabolism [2,3]. These include F-18 FDG [4] for PET of glucose metabolism, C-11 choline [5] and F-18 choline [6], F-18 Fluoroethylcholine [7] for phospholipids synthesis, C-11 acetate [8] for lipid synthesis, F-18 FMAU [9] for DNA synthesis, and C-11 methionine [10] for protein synthesis. Prostate cancer is a complex, heterogeneous disease [11,12], there are continuous efforts to develop new radiotracers for PET of other various metabolic changes in prostate cancer.

Copper is an essential nutrient required for cell proliferation, and higher quantities of copper ions were detected in prostate cancer tissue compared with those present in normal tissues [13,14]. Human prostate cancer xenografts with increased ^{64}Cu radioactivity in mice were visualized by PET at 24 hours post injection of copper-64 chloride ($^{64}CuCl_2$) as a radiotracer [15]. The molecular mechanism of increased copper uptake by PC-3 human prostate cancer xenografts remains to be elucidated, which may be mediated by influx copper transporter activity of human copper transporter 1 (hCtr1) detected by immunohistochemistry analysis [15]. Copper is required for normal function of many molecules in signal transduction pathway regulating cell proliferation, but excess copper is cytotoxic. Increased copper uptake by prostate cancer cells may reflex increased demand for more copper ions due to oxidative stress related to uncontrolled growth of cancer cells. In addition to hCtr1, analysis of changes of other copper transporters, chaperons, and other molecules related to maintenance of copper homeostasis may provide useful information for further investigation of the role of altered copper metabolism in oncogenesis of prostate cancer.

Positron emitting ^{64}Cu radionuclide has a half-life of 12.7 hours, making it desirable for PET of copper metabolism in vivo. Copper-64 chloride ($^{64}CuCl_2$) was used as a tracer for assessment of copper metabolism disorders in normal human subjects and patients with Wilson's disease by ex vivo radioactivity assay of body fluids or scintiscans [16,17]. Recently, preclinical radiation dosimetry of $^{64}CuCl_2$ using *Atp7b* $^{-/-}$ knockout mouse model of Wilson's disease provided additional evidence to support use of $^{64}CuCl_2$ as a radiotracer for PET of altered copper metabolism in humans [18,19]. It remains to be determined whether PET/CT using $^{64}CuCl_2$ as a radiotracer ($^{64}CuCl_2$ –PET/CT) can be used for early diagnosis of prostate cancer. It is likely that $^{64}CuCl_2$ –PET/CT may be useful for detection of local recurrence and/or metastasis of prostate cancer if it is found, in future studies, that most of recurrent or metastatic prostate cancer are copper hypermetabolic and has increased uptake of ^{64}Cu in vivo. Based on recent findings that copper may promote invasion of prostate cancer cells [20], copper hypermetabolism holds potential as a prognostic imaging biomarker for prediction of metastasis in the patients diagnosed with prostate cancer. Copper chelators were tested for anti-copper therapy of prostate cancer with variable response [21,22]. Selection of patients with copper hypermetabolic prostate cancer by $^{64}CuCl_2$-PET/CT may be helpful to improve efficacy of anti-copper cancer therapy and

realize personalized prostate cancer therapy targeting copper metabolism.

CONCLUSION

Altered copper metabolism holds potential as a metabolic imaging biomarker in prostate cancer. $^{64}CuCl_2$-PET/CT may be used for detection of recurrent and/or metastatic prostate cancer with increased copper uptake, and selection of patients with copper hypermetabolic tumors for personalized anti-copper therapy of prostate cancer.

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