EDITORIAL

Total Choline at 1H-MRS and [18F]-Fluoromethylcholine Uptake at PET

Sandi Kwee,¹ Thomas Ernst²

¹Clinical Sciences Program, University of Hawaii, Cancer Research Center of Hawaii, Honolulu, Hawaii

²Division of Neurology, Department of Medicine, University of Hawaii, John A Burns School of Medicine, Honolulu, Hawaii

The use of *in vivo* imaging techniques for assessing choline metabolism to detect cancer is supported by studies showing increased choline kinase and transporter gene expression, transmembrane choline transport, and tissue choline metabolite concentration in a number of malignancies [1, 2]. Early clinical studies employing techniques for *in vivo* imaging of choline metabolism looked promising, with early PET studies demonstrating increased choline tracer uptake in a variety of tumors, and independently, studies employing proton magnetic resonance spectroscopy (1H-MRS) demonstrating increased tissue levels of choline metabolites in several malignancies [2–5]. However, the use of these two very different *in vivo* methods to study choline metabolism have raised questions as to how their measurements interrelate; and there have been instances where choline tracer uptake on PET fails to correlate well with the tissue measurements of choline provided by 1H-MRS [6].

To address these questions, Rommel et al., in their study titled “Rodent Rhabdomyosarcoma: Comparison Between Total Choline Concentration at 1H-MRS and [18F]-fluoromethylcholine (FCH) Uptake at PET Using Accurate Methods for Collecting Data”, employed methods for achieving highly accurate spatial correspondence between small-animal PET and MRI to study the relationship between FCH uptake and spectroscopic measurement of tissue choline metabolites in a rhabdomyosarcoma animal model. Their study did not confirm a quantitative relationship between tumor FCH uptake and measures of choline concentration obtained with 1H-MRS in their experimental model. The authors offered several biological hypotheses to explain the lack of correlation between FCH uptake and choline metabolite concentration: one involving the presence of a negative feed-back mechanism of elevated levels of intracellular choline compounds on FCH uptake; another involving the rapid transport and incorporation of choline into membrane phosphatidylcholine (which is not detectable by 1H-MRS) to explain increases in FCH uptake without corresponding increases in total choline metabolite concentration on 1H-MRS.

In addition to these biological hypotheses, the limited ability of *in vivo* 1H-MRS to discriminate specific choline metabolites may also be worth considering as a potential explanation for their observations. Specifically, the “choline peak” at 3.2 ppm that is often used for *in vivo* 1H-MRS studies is known to actually reflect a number of important choline metabolites [7]. *Ex vivo* and *in vitro* NMR can readily differentiate several of these metabolites bearing the choline moiety. They include free choline, phosphocholine (PC; at 3.23 ppm), and glycerophosphocholine (GPC; at 3.24 ppm) [8, 9]. However, due to their spectral proximity it has proven difficult to resolve these compounds *in vivo* [2]. PC is a predominant biosynthetic product whose concentrations in malignancy can increase as a result of choline kinase upregulation [1]. GPC, on the other hand, is primarily a product of phospholipase activation [10, 11]. In the study by Rommel et al., the inability to separate the spectral contributions of these biochemically distinct compounds should raise the question of whether FCH uptake is actually being compared to the net result of several anabolic and catabolic processes in the CDP-choline pathway. Such a situation could potentially explain the lack of correlation observed between total choline concentration and FCH uptake.

Work by DeGrado et al. has suggested FCH to be a marker of biosynthetic PC metabolism with specificity for the transmembrane choline transporter and choline kinase [12, 13]. Consequently, the tissue concentration of PC, rather than total choline, may correlate best with FCH uptake. The relationship between PC and GPC metabolism under some tumor conditions has been studied. For example, activation of phospholipase can decrease PC and increase GPC levels in breast and prostate cancer cells, potentially leading to a less aggressive phenotype [11, 14]. Exposure to chemotherapeutic agents can also decrease tissue levels of PC while increasing the levels of GPC [15, 16]. These results suggest the possibility of assessing tumor therapeutic response through specific measurement of PC or GPC metabolism. We look forward to future studies comparing FCH PET to other methods for measuring PC metabolism *in vivo*.

References

1. Eliyahu G, Kreizman T, Degani H (2007) Phosphocholine as a biomarker of breast cancer: molecular and biochemical studies. *Int J Cancer* 120(8):1721–1730
2. Glunde K, Jacobs MA, Bhujwala ZM (2006) Choline metabolism in cancer: implications for diagnosis and therapy. *Expert Rev Mol Diagn* 6(6):821–829
3. Kwee SA, DeGrado TR, Talbot JN, Gutman F, Coel MN (2007) Cancer imaging with fluorine-18-labeled choline derivatives. *Semin Nucl Med* 37(6):420–428
4. Chang L, McBride D, Miller BL, Cornford M, Booth RA, Buchthal SD et al (1995) Localized *in vivo* 1H magnetic resonance spectroscopy and *in vitro* analyses of heterogeneous brain tumors. *J Neuroimaging* 5(3):157–163
5. Kurhanewicz J, Vigneron DB, Hricak H, Narayan P, Carroll P, Nelson SJ (1996) Three-dimensional H-1 MR spectroscopic imaging of the *in situ* human prostate with high (0.24–0.7-cm³) spatial resolution. *Radiology* 198(3):795–805
6. Kwee SA, Coel MN, Lim J, Ko JP (2004) Combined use of F-18 fluorocholine positron emission tomography and magnetic resonance spectroscopy for brain tumor evaluation. *J Neuroimaging* 14(3):285–289
7. Miller BL, Chang L, Booth R, Ernst T, Cornford M, Nikas D et al (1996) *In vivo* 1H MRS choline: correlation with *in vitro* chemistry/histology. *Life Sci* 58(22):1929–1935
8. Loening NM, Chamberlin AM, Zepeda AG, Gonzalez RG, Cheng LL (2005) Quantification of phosphocholine and glycerophosphocholine with 31P edited 1H NMR spectroscopy. *NMR Biomed* 18(7):413–420
9. Ackerstaff E, Pflug BR, Nelson JB, Bhujwala ZM (2001) Detection of increased choline compounds with proton nuclear magnetic resonance spectroscopy subsequent to malignant transformation of human prostatic epithelial cells. *Cancer Res* 61(9):3599–3603
10. Podo F (1999) Tumour phospholipid metabolism. *NMR Biomed* 12(7):413–439
11. Milkevitch M, Shim H, Pilatus U, Pickup S, Wehrle JP, Samid D et al (2005) Increases in NMR-visible lipid and glycerophosphocholine during phenylbutyrate-induced apoptosis in human prostate cancer cells. *Biochim Biophys Acta* 1734(1):1–12
12. Bansal A, Shuyan W, Hara T, Harris RA, Degrado TR (2008) Biodisposition and metabolism of [(18F)]fluorocholine in 9L glioma cells and 9L glioma-bearing fisher rats. *Eur J Nucl Med Mol Imaging* 35(6):1192–1203
13. DeGrado TR, Baldwin SW, Wang S, Orr MD, Liao RP, Friedman HS et al (2001) Synthesis and evaluation of (18F)-labeled choline analogs as oncologic PET tracers. *J Nucl Med* 42(12):1805–1814
14. Glunde K, Jie C, Bhujwala ZM (2006) Mechanisms of indomethacin-induced alterations in the choline phospholipid metabolism of breast cancer cells. *Neoplasia* 8(9):758–771
15. Morse DL, Raghunand N, Sadarangani P, Murthi S, Job C, Day S et al (2007) Response of choline metabolites to docetaxel therapy is quantified *in vivo* by localized (31P) MRS of human breast cancer xenografts and *in vitro* by high-resolution (31P) NMR spectroscopy of cell extracts. *Magn Reson Med* 58(2):270–280
16. Sterin M, Cohen JS, Mardor Y, Berman E, Ringel I (2001) Levels of phospholipid metabolites in breast cancer cells treated with antimetabolic drugs: a 31P-magnetic resonance spectroscopy study. *Cancer Res* 61(20):7536–7543