Lipid Metabolism and Cancer

R.A. Towner

Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104

Who will benefit from this information?

Those that will benefit from this talk will include cancer biologists and MR spectroscopists in basic research, as well as oncologists and radiologists in clinical research and diagnostics.

How was a problem determined?

Assessment of tumor lipid metabolites in situ for disease diagnosis and response to therapy requires the use of an in vivo spectroscopic technique.

Examples of how this issue has been addressed.

In addition to MRI, MRS is an ideal method for assessing tumor growth and response to therapeutic agents. Metabolic information can be obtained by monitoring tumor metabolites by magnetic resonance (MR) spectroscopy (MRS), or variations thereof, such as MR spectroscopic imaging (MRSI) or chemical shift imaging (CSI). Magnetic resonance spectroscopy (MRS) is an MR method that allows regional metabolite levels to be measured in tumors compared to surrounding non-tumor tissue, as well as assess therapeutic response. Important lipid and lipid-associated metabolites that can be assessed by ^{1}H-MRS in tumors including choline (Cho)-containing metabolites and mobile lipids including unsaturated lipids. Mobile lipids are lipids (composed of triglycerides and cholesterol esters that accumulate in neutral lipid droplets) that are observable with the use of proton MRS in cells and tissues [1].

Specifically, MRS can be used to follow both mitotic activity and necrosis. Metabolites measured by MRS can provide information on choline-containing compounds (Choline and total choline compounds, tCho), which are involved in membrane synthesis or cell membrane turnover, and associated with cellular proliferation in tumors [2,3], and mobile lipids resulting from intracellular lipid droplets and necrosis [2]. Metabolite levels can be quantified as metabolite ratios or absolute concentrations, or analyzed using pattern recognition [2].

There is ample evidence of elevated choline-related metabolism in breast cancer, which has helped with disease diagnosis and therapeutic evaluations. For instance, variations in the concentrations of choline-based cellular metabolites have been found to be associated with malignant transformation in breast cancer tissues [4-7]. In a similar fashion, tCho has been found to be increased in malignant gliomas [8,9]. tCho is also associated with membrane degradation, and therefore processes that either promote cellular proliferation or induce cell death have an increased tCho MR spectral peak [10,11]. It has also been reported that elevated tCho/tCr ratios are commonly observed in grade IV GBM [12-14]. An increased tCho/tCr ratio is widely recognized to be associated with cellular proliferation and mitotic activity, and has been useful to differentiate between grade II and grade III tumors [14,15]. In addition to increased

tCho, increased mobile lipids are also found in brain cancers, aiding in the diagnosis of these tumors. It is well known that brain metastases and primary brain tumors such as gliomas have characteristic increased mobile lipid signals [16,17], as well as decreased tCho [16], compared to surrounding normal brain tissue. Mobile lipids (observed through their saturated methylene and methyl groups) are also monitored in brain tumors, and increased levels are thought to occur with increasing necrosis [18]. For instance, GBM all have high levels of mobile lipids [15,18,19], and these tumors also usually have elevated necrosis [12,13,20]. A multicenter patient study showed that mobile lipids occurred in 41% of high-grade tumors with higher amounts found in GBM [21]. In an another study of grading for newly diagnosed gliomas, lipids were found to be significantly increased in GBM [22]. NMR-visible mobile lipid signals observed at ~1.3 and 0.9 ppm) appear to be an inherent feature of brain tumors, and have been considered an important factor in the grading astrocytomas [23-26]. It is thought that mobile lipids originate from degraded membrane phospholipids during membrane breakdown and necrosis [27,28], and may be composed of triglycerides and/or neutral lipids [29] and phosphatidylcholine [30]. It has also been observed that lipid resonances at 5.3 ppm, due to the presence of unsaturated acyl lipd hydrogens (-C**H**=C**H**-), are elevated in a rat glioma model [29]. Spectroscopic evidence has shown that visible lipids correspond to lipid droplets in necrotic and perinecrotic tumor regions in animal studies [26]. In a transgenic mouse model for hepatocellular carcinomas (HCC) an elevated lip5.3 peak in tumor-bearing animals was also detected [31]. A ratio of the Lip2.8 (bis-allyl acyl lipid hydrogens; -CH=CH-C$\mathbf{H_2}$-CH=CH-) to the lip5.3 spectral peak areas was used to measure the degree of unsaturation in unsaturated acyl containing phospholipids, and it was determined that during tumor formation there was an increase in oleyl-containing phospholipids [31]. Lipid levels have been previously demonstrated to be not only a marker of tumor malignancy, but also an indication of response to treatment [32, 33].

What will learners be able to do differently because of this information?

Attendees of the talk will be able to gain an understanding regarding the detection and role of choline-containing compounds and mobile lipids in specific cancers (e.g. breast cancer and brain tumors) as useful markers for diagnosis and assessing therapeutic response.

References:

1. Delikatny EJ, Chawla S, Leung DJ, Poptani H (2011) MR-visible lipids and the tumor microenvironment. *NMR Biomed* 24: 592-611.
2. Waldman AD, Jackson A, Price SJ, Clark CA, Booth TC, Auer DP, Tofts PS, Collins DJ, Leach MO, Rees JH (2009) Quantitative imaging biomarkers in neuro-oncology. *Nature Reviews Clin Oncol* 6(8): 445-454.
3. Dowling C, Bollen AW, Noworolski SM, McDermott MW, Barbaro NM, Day MR, Henry RG, Chang SM, Dillon WP, Nelson SJ, Vigneron DB (2001) Preoperative Proton MR Spectroscopic Imaging of Brain Tumors: Correlation with Histopathologic Analysis of Resection Specimens. *AJNR Am J Neuroradiol* 22: 604-612.

4. Glunde K, Jiang L, Moestue SA, Gribbestad IS (2011) MRS and MRSI guidance in molecular medicine: targeting and monitoring of choline and glucose metabolism in cancer. NMR Biomed 24: 673-90.
5. Glunde K, Bhujwalla ZM, Ronen SM (2011) Choline metabolism in malignant transformation. Nat Rev Cancer 11: 835-48.
6. Sharma U, Baek HM, Su MY, Jagannathan NR (2011) In vivo 1H MRS in the assessment of the therapeutic response of breast cancer patients. NMR Biomed 24: 700-11.
7. Begley JK, Redpath TW, Bolan PJ, Gilbert FJ (2012) In vivo proton magnetic resonance spectroscopy of breast cancer: a review of the literature. Breast Cancer Res 14: 207.
8. Negendank W, Sauter R (1996) Intratumoral lipids in ^{1}H MRS *in vivo* in brain tumors: experience of the Siemens cooperative clinical trial. *Anticancer Res* 16: 1533-38.
9. Rémy C, Arús C, Ziegler A, Lai ES, Moreno A, Le Fur Y, Décorps M (1994) *In vivo*, *ex vivo*, and *in vitro* one- and two-dimensional nuclear magnetic resonance spectroscopy of an intracerebral glioma in rat brain: assignment of resonances. *J Neurochem* 62: 166-179.
10. Young GS (2007) Advanced MRI of adult brain tumors. *Neurologic Clinics* 25: 947-973, viii.
11. Sibtain NA, Howe FA, Saunders DE (2007) The clinical value of proton magnetic resonance spectroscopy in adult brain tumours. *Clin Radiol* 62: 109-119.
12. Oshiro S, Tsugu H, Komatsu F, Abe H, Onishi H, Ohmura T, Iwaasa M, Sakamoto S, Fukushima T (2007) Quantitative assessment of gliomas by proton magnetic resonance spectroscopy. *Anticancer Res* 27: 3757-3763.
13. Catalaa I, Henry R, Dillon WP, Graves EE, McKnight TR, Lu Y, Vigneron DB, Nelson SJ (2006) Perfusion, diffusion and spectroscopy values in newly diagnosed cerebral gliomas. *NMR Biomed* 19: 463-475.
14. Chen J, Huang SL, Li T, Chen XL (2006). *In vivo* research in astrocytoma cell proliferation with ^{1}H-magnetic resonance spectroscopy: correlation with histopathology and immunohistochemistry. *Neuroradiology* 48: 312-318.
15. Fan G, Sun B, Wu Z, Guo Q, Guo Y (2004) *In vivo* single-voxel proton MR spectroscopy in the differentiation of high-grade gliomas and solitary metastases. *Clin Radiol* 59: 77-85.
16. McLean MA, Sun A, Bradstreet TE, Schaeffer AK, Liu H, Iannone R, Herman G, Railkar RA, Joubert I, Gillard JH, Price SJ, Griffiths JR (2012) Repeatability of edited lactate and other metabolites in astrocytoma at 3T. J Magn Reson Imaging 36: 468-75.
17. Sjøbakk TE, Vettukatti R, Gulati M, Gulati S, Lundgren S, Gribbestad IS, Torp SH, Bathen TF (2013) Metabolic profiles of brain metastases. Int J Mol Sci 14: 2104-18.
18. Kuesel AC, Sutherland GR, Halliday W, Smith IC (1994). ^{1}H MRS of high grade astrocytomas: mobile lipid accumulation in necrotic tissue. *NMR Biomed* 7: 149-155.
19. Gotsis ED, Fountas K, Kapsalaki E, Toulas P, Peristeris G, Papadakis N (1996) *In vivo* proton MR spectroscopy: the diagnostic possibilities of lipid resonances in brain tumors. *Anticancer Res* 6: 1565-1567.

20. Li X, Vigneron DB, Cha S, Graves EE, Crawford F, Chang SM, Nelson SJ (2005) Relationship of MR-derived lactate, mobile lipids, and relative blood volume for gliomas *in vivo*. *AJNR Am J Neuroradiol* 26: 760-769.
21. Negendank WG, Sauter R, Brown TR, Evelhoch JL, Falini A, Gotsis ED, Heerschap A, Kamada K, Lee BC, Mengeot MM, Moser E, Padavic-Shaller KA, Sanders JA, Spraggins TA, Stillman AE, Terwey B, Vogl TJ, Wicklow K, Zimmerman RA (1996) Proton magnetic resonance spectroscopy in patients with glial tumors: a multicenter study. *J Neurosurg* 84**:**449-458.
22. Chang SM, Nelson S, Vandenberg S, Cha S, Prados M, Butowski N, McDermott M, Parsa AT, Aghi M, Clarke J, Berger M (2009) Integration of preoperative anatomic and metabolic physiologic imaging of newly diagnosed glioma. *J Neurooncol* 92**:**401-415.
23. Opstad KS, Ladroue C, Bell BA, Griffiths JR, Howe FA (2007) Linear discriminant analysis of brain tumor ^{1}H MR spectra: a comparison of classification using whole spectra versus metabolite quantification. *NMR Biomed* 20: 763-770.
24. Howe FA, Barton SJ, Cudlip SA, Stubbs M, Saunders DE, Murphy M, Wilkins P, Opstad KS, Doyle VL, McLean MA, Bell BA, Griffiths JR (2003) Metabolic profiles of human brain tumors using quantitative *in vivo* ^{1}H magnetic resonance spectroscopy. *Magn Reson Med* 49: 223-32.
25. Murphy PS, Rowland IJ, Viviers L, Brada M, Leach MO, Dzik-Jurasz AS (2003) Could assessment of glioma methylene lipid resonance by *in vivo* (1)H-MRS be of clinical value? *Br J Radiol* 76: 459-463.
26. Rémy C, Fouilhé N, Barba I, Sam-Lai E, Lahrech H, Cucurella MG, Izquierdo M, Moreno A, Ziegler A, Massarelli R, Décorps M, Arús C (1997) Evidence that mobile lipids detected in rat brain glioma by ^{1}H nuclear magnetic resonance correspond to lipid droplets. *Cancer Res* 57: 407-14.
27. Barbarella G, Ricci R, Pirini G, Tugnoli V, Tosi MR, Bertoluzza A, Calbucci F, Leonardi M, Trevisan C, Eusebi V (1998) *In vivo* single voxel ^{1}H MRS of glial brain tumors: correlation with tissue histology and *in vitro* MRS. *Int J Oncol* 12: 461-468.
28. Liimatainen T, Hakumäki JM, Kauppinen RA, Ala-Korpela M (2009) Monitoring of gliomas *in vivo* by diffusion MRI and ^{1}H MRS during gene therapy-induced apoptosis: interrationships between water diffusion and mobile lipids. *NMR Biomed* 22: 272-279.
29. Griffin JL, Lehtimäki KK, Valonen PK, Gröhn OHJ, Kettunen MI, Ylä-Herttuala S, Pitkänen A, Nicholson JK, Kauppinen RA (2003) Assignment of ^{1}H nuclear magnetic resonance visible polyunsaturated fatty acids in BT4C gliomas undergoing ganciclovir-thymidine kinase gene therapy-induced programmed cell death. *Cancer Res* 63: 3195-3201.
30. Righi V, Mucci A, Schenetti L, Bacci A, Agati R, Leonardi M, Schiavina R, Martorana G, Liguori G, Calabrese C, Boschetti E, Bonora S, Tugnoli V (2009) Identification of mobile lipids in human cancer tissues by ex vivo diffusion edited HR-MAS MRS. *Oncol Rep* 22**:**1493-1496.
31. Griffitts J, Tesiram Y, Reid GE, Saunders D, Floyd RA, Towner RA (2009) *In vivo* MRS assessment of altered fatty acyl unsaturation in liver tumor formation of a TGFα/c-myc transgenic mouse model. *J Lipid Res* 50: 611-622.

32. Hakumaki JM, Poptani H, Sandmair AM, Yla-Herttuala S, Kauppinen RA (1999) A. 1H MRS detects polyunsaturated fatty acid accumulation during gene therapy of glioma: implications for the in vivo detection of apoptosis. *Nat Med* 5**:**1323-1327.
33. Preul MC, Caramanos Z, Villemure JG, Shenouda G, LeBlanc R, Langleben A, Arnold DL (2000) Using proton magnetic resonance spectroscopic imaging to predict in vivo the response of recurrent malignant gliomas to tamoxifen chemotherapy. *Neurosurgery* 46**:**306-318.