Cancer Treatment Response

Sabrina M. Ronen
Radiology and Biomedical Imaging, UCSF, San Francisco, California, USA

Traditional anticancer therapy involves treatment with radiation and DNA-damaging chemotherapies. More recently, insight into the molecular and genetic changes associated with cancer has led to a shift in anticancer drug development, and new drugs typically modulate specific molecular targets associated with onset and progression of the disease. The oncologist's armamentarium has thus expanded substantially, and anticancer therapy is becoming increasingly personalized. However, assessing response to treatment can be challenging. Response to traditional chemotherapy and radiotherapy is typically associated with eventual tumor shrinkage, but this effect is frequently delayed. Many emerging therapies lead only to tumor stasis. Noninvasive biomarkers of drug delivery and molecular drug action are therefore essential in order to assess, at the earliest possible time point, localized drug activity and thus the likelihood of clinical response. The value of magnetic resonance spectroscopy (MRS) as a method to assess response will be presented and discussed.

Response to radiotherapy and DNA-damaging chemotherapy was shown several years ago to result in ^{1}H and ^{31}P MRS-detectable metabolic changes. In particular, the phospholipid precursor phosphocholine (PC), which is elevated in tumors compared to normal tissue, drops following treatment, frequently prior to tumor shrinkage (1-3). This observation can be explained in part by inhibition in cellular proliferation (4-7). ^{1}H-MRS detectable modulation in lactate levels has also been reported as an indicator of response to treatment (8-10), consistent with a reversal of the Warburg effect. Elevation in the lipid signal, and in particular elevation in polyunsaturated fatty acids, has been observed by ^{1}H-MRS and is associated with apoptosis, the program of cell death induced in many cases by chemotherapy and radiotherapy (10-14). Apoptosis also leads to a drop in cellular NADH levels, which is required for the conversion of pyruvate into lactate (15, 16). As a result, DNA damage by chemotherapeutic agents, which leads to NADH depletion, is associated with in a reduction of the ^{13}C MRS-detectable conversion of exogenous hyperpolarized pyruvate into hyperpolarized lactate (17, 18). The conversion of fumarate into malate has been shown as another hyperpolarized ^{13}C MRS approach that can inform on response to chemotherapy via necrotic cell death (18).

MRS has also been used to monitor the metabolic consequences of treatment with targeted therapies. An overall change in the ^{1}H-MRS detectable metabolomic prolife can be detected (19). Additionally, specific metabolic changes have been investigated in detail. PC and total choline-containing metabolites (tCho) drop following treatment with inhibitors of the phosphoinositide-3-kinase (PI3K) or the mitogen-activated protein kinase (MAPK) oncogneic signaling pathways as well as inhibitors of their common downstream effector hypoxia-inducible factor 1 (HIF-1) (20-26). This effect is likely mediated by inhibition of the expression of choline kinase, the enzyme responsible for PC synthesis (7, 24, 27). Inhibition of PI3K signaling also leads to a drop in the expression of several glycolytic enzymes, including lactate dehydrogenase, resulting in a decrease in the hyperpolarized pyruvate conversion to lactate (26, 28). Interestingly, inhibition of

heat shock protein 90, either directly or via reduction of histone deacetylase activity, leads in most cases to elevation in PC levels (29-32), recently shown to result from elevation in choline transport (33). In some cases an elevation in GPC has also been reported and is due to elevated phospholipase A2 activity (33-35).

Finally, because metabolic reprogramming is likely a factor in cancer development, anti-metabolites provide anther therapeutic approach, and MRS can be used to monitor such therapies. Inhibition of choline kinase resulted in the expected drop in MRS-detected PC levels (36). Inhibition of fatty acid synthase, the enzyme responsible for lipid synthesis, also led to a drop in PC (37). More recently the effect of a lactate dehydrogenase inhibitor was monitored using hyperpolarized ^{13}C MRS of pyruvate (38).

In summary, several MRS-detectable metabolic changes have been observed following anticancer treatment. Whereas many of these are not specific to just one drug, they serve, nonetheless, as highly valuable noninvasive longitudinal biomarkers that can inform on drug delivery and drug target modulation to thus help predict response and identify resistance.

References

1.   Negendank W. Studies of human tumors by MRS: a review. NMR Biomed. 1992;5:303-24.
2.   Leach MO, Verrill M, Glaholm J, Smith TA, Collins DJ, Payne GS, et al. Measurements of human breast cancer using magnetic resonance spectroscopy: a review of clinical measurements and a report of localized 31P measurements of response to treatment. NMR Biomed. 1998;11:314-40.
3.   Gillies RJ, Morse DL. In vivo magnetic resonance spectroscopy in cancer. Annual Review of Biomedical Engineering. 2005;7:287-326.
4.   Ronen SM, Rushkin E, Degani H. Lipid metabolism in large T47D human breast cancer spheroids: 31P- and 13C-NMR studies of choline and ethanolamine uptake. Biochim Biophys Acta. 1992;1138:203-12.
5.   Smith TA, Baluch S, Titley JC, Ormerod MG, Eccles S, Tombs AJ, et al. The effect of oestrogen ablation on the phospholipid metabolite content of primary and transplanted rat mammary tumours. NMR Biomed. 1993;6:209-14.
6.   Podo F. Tumour phospholipid metabolism. NMR Biomed. 1999;12:413-39.
7.   Glunde K, Bhujwalla ZM, Ronen SM. Choline metabolism in malignant transformation. Nat Rev Cancer. 2011;11:835-48.
8.   Aboagye EO, Bhujwalla ZM, Shungu DC, Glickson JD. Detection of tumor response to chemotherapy by 1H nuclear magnetic resonance spectroscopy: effect of 5-fluorouracil on lactate levels in radiation-induced fibrosarcoma 1 tumors. Cancer Res. 1998;58:1063-7.
9.   Poptani H, Bansal N, Jenkins WT, Blessington D, Mancuso A, Nelson DS, et al. Cyclophosphamide treatment modifies tumor oxygenation and glycolytic rates of RIF-1 tumors: 13C magnetic resonance spectroscopy, Eppendorf electrode, and redox scanning. Cancer Res. 2003;63:8813-20.
10.   Lee SC, Poptani H, Pickup S, Jenkins WT, Kim S, Koch CJ, et al. Early detection of radiation therapy response in non-Hodgkin's lymphoma xenografts by in vivo 1H magnetic resonance spectroscopy and imaging. NMR Biomed. 2010;23:624-32.

11.   Blankenberg FG, Storrs RW, Naumovski L, Goralski T, Spielman D. Detection of apoptotic cell death by proton nuclear magnetic resonance spectroscopy. Blood. 1996;87:1951-6.

12.   Hakumaki JM, Poptani H, Sandmair AM, Yla-Herttuala S, Kauppinen RA. 1H MRS detects polyunsaturated fatty acid accumulation during gene therapy of glioma: implications for the in vivo detection of apoptosis. Nat Med. 1999;5:1323-7.

13.   Al-Saffar NM, Titley JC, Robertson D, Clarke PA, Jackson LE, Leach MO, et al. Apoptosis is associated with triacylglycerol accumulation in Jurkat T-cells. Br J Cancer. 2002;86:963-70.

14.   Hakumaki JM, Brindle KM. Techniques: Visualizing apoptosis using nuclear magnetic resonance. Trends Pharmacol Sci. 2003;24:146-9.

15.   Ronen SM, DiStefano F, McCoy CL, Robertson D, Smith TA, Al-Saffar NM, et al. Magnetic resonance detects metabolic changes associated with chemotherapy-induced apoptosis. Br J Cancer. 1999;80:1035-41.

16.   Williams SN, Anthony ML, Brindle KM. Induction of apoptosis in two mammalian cell lines results in increased levels of fructose-1,6-bisphosphate and CDP-choline as determined by 31P MRS. Magn Reson Med. 1998;40:411-20.

17.   Day SE, Kettunen MI, Gallagher FA, Hu DE, Lerche M, Wolber J, et al. Detecting tumor response to treatment using hyperpolarized (13)C magnetic resonance imaging and spectroscopy. Nat Med. 2007;13:1382-7.

18.   Witney TH, Kettunen MI, Hu DE, Gallagher FA, Bohndiek SE, Napolitano R, et al. Detecting treatment response in a model of human breast adenocarcinoma using hyperpolarised [1-13C]pyruvate and [1,4-13C2]fumarate. Br J Cancer. 2010;103:1400-6.

19.   Lodi A, Ronen SM. Magnetic resonance spectroscopy detectable metabolomic fingerprint of response to antineoplastic treatment. PLoS One. 2011;6:e26155.

20.   Ronen SM, Jackson LE, Beloueche M, Leach MO. Magnetic resonance detects changes in phosphocholine associated with Ras activation and inhibition in NIH 3T3 cells. Br J Cancer. 2001;84:691-6.

21.   Beloueche-Babari M, Jackson LE, Al-Saffar NMS, Workman P, Leach MO, Ronen SM. Magnetic resonance spectroscopy monitoring of mitogen-activated protein kinase signaling inhibition. Cancer Research. 2005;65:3356-63.

22.   Beloueche-Babari M, Jackson LE, Al-Saffar NM, Eccles SA, Raynaud FI, Workman P, et al. Identification of magnetic resonance detectable metabolic changes associated with inhibition of phosphoinositide 3-kinase signaling in human breast cancer cells. Mol Cancer Ther. 2006;5:187-96.

23.   Jordan BF, Black K, Robey IF, Runquist M, Powis G, Gillies RJ. Metabolite changes in HT-29 xenograft tumors following HIF-1alpha inhibition with PX-478 as studied by MR spectroscopy in vivo and ex vivo. NMR Biomed. 2005;18:430-9.

24.   Al-Saffar NM, Jackson LE, Raynaud FI, Clarke PA, Ramirez de Molina A, Lacal JC, et al. The Phosphoinositide 3-Kinase Inhibitor PI-103 Downregulates Choline Kinase {alpha} Leading to Phosphocholine and Total Choline Decrease Detected by Magnetic Resonance Spectroscopy. Cancer Res. 2010.

25.   Koul D, Shen R, Kim YW, Kondo Y, Lu Y, Bankson J, et al. Cellular and in vivo activity of a novel PI3K inhibitor, PX-866, against human glioblastoma. Neuro Oncol. 2010;12:559-69.

26.   Ward CS, Venkatesh HS, Chaumeil MM, Brandes AH, Vancriekinge M, Dafni H, et al. Noninvasive detection of target modulation following phosphatidylinositol 3-kinase inhibition using hyperpolarized 13C magnetic resonance spectroscopy. Cancer Res. 2010;70:1296-305.

27.   Glunde K, Shah T, Winnard PT, Jr., Raman V, Takagi T, Vesuna F, et al. Hypoxia regulates choline kinase expression through hypoxia-inducible factor-1 alpha signaling in a human prostate cancer model. Cancer Res. 2008;68:172-80.

28.   Dafni H, Larson PEZ, Hu S, Yoshihara HAI, Ward CS, Venkatesh HS, et al. Hyperpolarized 13C Spectroscopic Imaging Informs on Hypoxia-Inducible Factor-1 and Myc Activity Downstream of Platelet-Derived Growth Factor Receptor. Cancer Res. 2010;70:7400-10.

29.   Chung YL, Troy H, Banerji U, Jackson LE, Walton MI, Stubbs M, et al. Magnetic resonance spectroscopic pharmacodynamic markers of the heat shock protein 90 inhibitor 17-allylamino,17-demethoxygeldanamycin (17AAG) in human colon cancer models. J Natl Cancer Inst. 2003;95:1624-33.

30.   Sankaranarayanapillai M, Tong WP, Maxwell DS, Pal A, Pang J, Bornmann WG, et al. Detection of histone deacetylase inhibition by noninvasive magnetic resonance spectroscopy. Mol Cancer Ther. 2006;5:1325-34.

31.   Chung YL, Troy H, Kristeleit R, Aherne W, Jackson LE, Atadja P, et al. Noninvasive magnetic resonance spectroscopic pharmacodynamic markers of a novel histone deacetylase inhibitor, LAQ824, in human colon carcinoma cells and xenografts. Neoplasia. 2008;10:303-13.

32.   Le HC, Lupu M, Kotedia K, Rosen N, Solit D, Koutcher JA. Proton MRS detects metabolic changes in hormone sensitive and resistant human prostate cancer models CWR22 and CWR22r. Magn Reson Med. 2009;62:1112-9.

33.   Brandes AH, Ward CS, Ronen SM. 17-allyamino-17-demethoxygeldanamycin treatment results in a magnetic resonance spectroscopy-detectable elevation in choline-containing metabolites associated with increased expression of choline transporter SLC44A1 and phospholipase A2. Breast Cancer Res. 2010;12:R84.

34.   Milkevitch M, Shim H, Pilatus U, Pickup S, Wehrle JP, Samid D, et al. Increases in NMR-visible lipid and glycerophosphocholine during phenylbutyrate-induced apoptosis in human prostate cancer cells. Biochim Biophys Acta. 2005;1734:1-12.

35.   Beloueche-Babari M, Arunan V, Jackson LE, Perusinghe N, Sharp SY, Workman P, et al. Modulation of melanoma cell phospholipid metabolism in response to heat shock protein 90 inhibition. Oncotarget. 2010;1:185-97.

36.   Al-Saffar NM, Troy H, Ramirez de Molina A, Jackson LE, Madhu B, Griffiths JR, et al. Noninvasive magnetic resonance spectroscopic pharmacodynamic markers of the choline kinase inhibitor MN58b in human carcinoma models. Cancer Res. 2006;66:427-34.

37.   Ross J, Najjar AM, Sankaranarayanapillai M, Tong WP, Kaluarachchi K, Ronen SM. Fatty acid synthase inhibition results in a magnetic resonance-detectable drop in phosphocholine. Mol Cancer Ther. 2008;7:2556-65.

38.   Dutta P, Martinez G, Le A, Dang CV, Gatenby RA, Gillies RJ. 13C MRS/I of Hyperpolarized Pyruvate to Assess Xenografted Tumor Response to Therapy Based on LDH-A Inhibition. World Molecular Imaging Congress; 2012; Dublin, Ireland; 2012.