Imaging Cancer

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Cancer has recently been described in terms of six key hallmarks and four emerging and enabling characteristics (1, 2). These include sustained proliferative growth, evasion of growth suppressors, replicative immortality, invasion and metastasis, induction of angiogenesis, resistance to cell death, deregulated cellular metabolism, avoidance of immune destruction, enhanced tumor-promoting inflammation, and genome instability. Importantly, many of these characteristics of cancer can be readily imaged using a range of magnetic resonance-based approaches. The presentation will focus on the most established methods used in preclinical studies of cancer models.

The ability of cancer cells to sustain proliferative growth, evade growth suppressors, and achieve replicative immortality, are all associated with multiple oncogenic mutations that ultimately enable sustained tumor growth. This growth can be monitored in a nonspecific manner using standard MR imaging sequences (T2-weighted, T1-weighted, contrast–enhanced T1-weighted) that simply inform on anatomical structure and thus on tumor volume and tumor growth (3, 4). In addition, spectroscopy has been useful in detecting metabolic alterations that are directly associated with some specific oncogenic events that drive tumor development, and, as such, can serve as indirect biomarkers of those oncogenic drivers (5-12).

Tumor angiogenesis, or the development of new vasculature, is essential to nourish the developing tumor and enhance its growth and metastasis. A major regulator of this process is vascular endothelial growth factor (VEGF also called vascular permeability factor), and one of the early responses to VEGF stimulation is an increase in vascular permeability. Enhanced permeability can be imaged using dynamic contrast enhanced (DCE) MRI and is likely one of the most frequently imaged hallmark of cancer. In the clinical setting, DCE MRI using low molecular weight contrast agents such as GdDTPA is most common, providing information not only on tumor angiogenesis, but also on response to inhibitors of the angiogenic process (13). Preclinically, the use of macromolecular contrast agents provides a more specific measure of vascular permeability, and has been used in animal studies to probe the modulation of permeability with onset of cancer and in response to therapy (7, 14-16).

Tumor cells are often resistant to programs of cell death, or apoptosis, and such programs can be activated by anticancer therapies. MR imaging of apoptosis has been achieved using both MRS and MRI approaches. Specifically, induction of apoptosis is associated with a detectable increase in the signal of mobile lipid droplets that is detectable in the ^{1}H MRS spectrum at 0.9 and 1.3 ppm. In addition, an increase in the signal of polyunsatureated fatty acids has been reported during cell death (17, 18). Some contrast agents that specifically target apoptosis-associated cellular changes have also been reported (19, 20). Finally, downstream changes in diffusion have been useful in assessing cell death (21, 22).

Deregulated cellular energetics, and more broadly the metabolic reprogramming that occurs in cancer cells as part of their transformation, are detectable by MRS. Increases in choline-containing metabolites, and most notably in PC, are readily detectable by ^{1}H and ^{31}P MRS (8). Increased glycolysis and its inhibition following therapy can be probed using ^{13}C MRS to assess the fate of ^{13}C-labeled pyruvate (7, 10, 23-25), and more generally cancer cell metabolism can be investigated by monitoring the fate of specific ^{13}C-labeled metabolic precursors (26-29).

In summary, a range of MR-based imaging methods can be used to probe the anatomic, functional, and metabolic alterations that are associated with tumor development and progression.

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57-70.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646-74.
3. Gore JC, Manning HC, Quarles CC, Waddell KW, Yankeelov TE. Magnetic resonance in the era of molecular imaging of cancer. Magn Reson Imaging. 2011;29:587-600.
4. Borges AR, Lopez-Larrubia P, Marques JB, Cerdan SG. MR imaging features of high-grade gliomas in murine models: how they compare with human disease, reflect tumor biology, and play a role in preclinical trials. AJNR Am J Neuroradiol. 2012;33:24-36.
5. 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.
6. Beloueche-Babari M, Jackson LE, Al-Saffar NM, Workman P, Leach MO, Ronen SM. Magnetic resonance spectroscopy monitoring of mitogen-activated protein kinase signaling inhibition. Cancer Res. 2005;65:3356-63.
7. Dafni H, Larson PE, Hu S, Yoshihara HA, 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.
8. Glunde K, Bhujwalla ZM, Ronen SM. Choline metabolism in malignant transformation. Nat Rev Cancer. 2011;11:835-48.
9. Park I, Bok R, Ozawa T, Phillips JJ, James CD, Vigneron DB, et al. Detection of early response to temozolomide treatment in brain tumors using hyperpolarized (13) C MR metabolic imaging. J Magn Reson Imaging. 2011;33:1284-90.
10. 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.
11. Mori N, Delsite R, Natarajan K, Kulawiec M, Bhujwalla ZM, Singh KK. Loss of p53 function in colon cancer cells results in increased phosphocholine and total choline. Mol Imaging. 2004;3:319-23.

12. Hu S, Balakrishnan A, Bok RA, Anderton B, Larson PE, Nelson SJ, et al. 13C-pyruvate imaging reveals alterations in glycolysis that precede c-Myc-induced tumor formation and regression. Cell Metab. 2011;14:131-42.
13. Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, et al. Assessment of antiangiogenic and antivascular therapeutics using MRI: recommendations for appropriate methodology for clinical trials. Br J Radiol. 2003;76 Spec No 1:S87-91.
14. Bhujwalla ZM, Artemov D, Glockner J. Tumor angiogenesis, vascularization, and contrast-enhanced magnetic resonance imaging. Topics in magnetic resonance imaging : TMRI. 1999;10:92-103.
15. Neeman M, Dafni H. Structural, functional, and molecular MR imaging of the microvasculature. Annu Rev Biomed Eng. 2003;5:29-56.
16. Dafni H, Israely T, Bhujwalla ZM, Benjamin LE, Neeman M. Overexpression of vascular endothelial growth factor 165 drives peritumor interstitial convection and induces lymphatic drain: magnetic resonance imaging, confocal microscopy, and histological tracking of triple-labeled albumin. Cancer Res. 2002;62:6731-9.
17. 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.
18. Hakumaki JM, Brindle KM. Techniques: Visualizing apoptosis using nuclear magnetic resonance. Trends Pharmacol Sci. 2003;24:146-9.
19. Krishnan AS, Neves AA, de Backer MM, Hu DE, Davletov B, Kettunen MI, et al. Detection of cell death in tumors by using MR imaging and a gadolinium-based targeted contrast agent. Radiology. 2008;246:854-62.
20. Ye D, Shuhendler AJ, Pandit P, Brewer KD, Tee SS, Cui L, et al. Caspase-responsive smart gadolinium-based contrast agent for magnetic resonance imaging of drug-induced apoptosis. Chemical science. 2014;4:3845-52.
21. Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, et al. Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst. 2000;92:2029-36.
22. Thoeny HC, Ross BD. Predicting and monitoring cancer treatment response with diffusion-weighted MRI. J Magn Reson Imaging. 2010;32:2-16.
23. Golman K, Zandt RI, Lerche M, Pehrson R, Ardenkjaer-Larsen JH. Metabolic imaging by hyperpolarized 13C magnetic resonance imaging for in vivo tumor diagnosis. Cancer Res. 2006;66:10855-60.
24. Chaumeil MM, Ozawa T, Park I, Scott K, James CD, Nelson SJ, et al. Hyperpolarized 13C MR spectroscopic imaging can be used to monitor Everolimus treatment in vivo in an orthotopic rodent model of glioblastoma. Neuroimage. 2012;59:193-201.
25. Park I, J. M, M. I, M.M. C, L.E. J, K. G, et al. Changes in pyruvate metabolism detected by magnetic resonance imaging are linked to DNA damage and serve as a sensor of temozolomide response in glioblastoma cells. Cancer res. 2014;*Minor Revision*.
26. Chaumeil MM, Larson PE, Woods SM, Cai L, Eriksson P, Robinson AE, et al. Hyperpolarized [1-13C] Glutamate: A Metabolic Imaging Biomarker of IDH1 Mutational Status in Glioma. Cancer Res. 2014.

27. Chaumeil MM, Larson PE, Yoshihara HA, Danforth OM, Vigneron DB, Nelson SJ, et al. Non-invasive in vivo assessment of IDH1 mutational status in glioma. Nat Commun. 2013;4:2429.
28. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci U S A. 2007;104:19345-50.
29. Marin-Valencia I, Yang C, Mashimo T, Cho S, Baek H, Yang XL, et al. Analysis of tumor metabolism reveals mitochondrial glucose oxidation in genetically diverse human glioblastomas in the mouse brain in vivo. Cell Metab. 2012;15:827-37.