educational keynote lecture

IMAGING METABOLIC HALLMARKS AND THEIR SEQUELAE

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Evolutionary Dynamics of Carcinogenesis

Malignant cancers, whether inherited or sporadic, can be characterized by genetic instability within highly selective local microenvironments. This combination promotes somatic evolution and the emergences of clades of cells in spatially explicit micro-habitats. The rate of this evolution is predicted by Evolutionary Game Theory, and is dramatically affected by both Phenotypic (Genotypic) Diversity and Selection Pressures. From a practical standpoint, malignancy can be defined by these habitats, which increase the probability that cancers will develop therapy resistant phenotypes. The concept of somatic evolution in cancers is not new, being articulated by Nowell in 1976 (1). However, it has been gaining wider acceptance (2-5), likely based on two related observations. First, malignant cancers have a high degree of mutational heterogeneity that can be traced to common ancestors (6, 7). Indeed, histological nuclear heterogeneity across cancers has been known for years (8) and is a strong predictor of poor prognosis (9). Second, therapies that are exquisitely targeted to driver oncogene mutations usually result in benefits measured in months, not years, (10). For most advanced cancers and most patients, response to therapy is fleeting, owing to the inevitable evolution and proliferation of a resistant population (11). Because of these large scale genomic alterations and consequent diversity, the emergence of resistance is a predictable and fundamental property of carcinogenesis itself. This is commonly ignored in the design of treatment strategies(12).

The origins of cancer heterogeneity and the accumulation of metabolic hallmarks occur early during carcinogenesis. All carcinomas develop within ducts, which are avascular environments. Consequently, the peri-luminal aspects of developing cancers are poorly perfused. These perfusion deficits lead directly to a physical microenvironment that is pooly oxygenated, substrate-limited, and acidic. This niche is genotoxic and highly selective for cancer cells that are hyperglycolytic, resistant to apoptosis, chronically autophagic and resistant to acidosis. The acidic microenvironment induces local invasion, which can be inhibited with systemic buffer therapy. Once cancers locally invade, if they can recapitulate the acidic-hypoxic-limited environment, they will have an evolutionary selective advantage over the stromal cells into which they invade. It can be shown by evolutionary theory that this environment will also generate distinct “clades” of tumor cells in spatially explicit micro-habitats. From a practical standpoint, malignancy can be defined by these habitats, which increase the probability that cancers will develop therapy-resistant phenotypes.

Imaging Cancer Physiology

Because the microenvironmental factors of hypoxia, acidity and glucose limitation are present in growing solid tumors and because these factors select for malignancy, there is a compelling need to develop non-invasive methods to measure them and their spatial distribution. Such information could have profound effects on our understanding of carcinogenesis and malignancy, and also provide important information for therapy decision support. Tumor oxygenation can be imaged in vivo using either magnetic resonance or positron imaging approaches, reviewed in (13, 14). For magnetic resonance, both nuclear (NMR) and electron (EPR) imaging approaches have been used. In MRI, both 19-F of exogenous hpoxia sensitive tracers, and 1-H of endogenous indicators of biological hypoxia have been used. EPRI commonly involves a stable free radical whose linewidths are oxygen dependent (15). In PET imaging most, but not all, tracers are based on a 2-nitroimidazole center, which becomes covalently trapped in the absence of oxygen. Optical methods are also available. The most used has been phosphorescence, but this use has generally been restricted to window chamber models. A new report uses fluorescently tagged antibodies against the biological hypoxia biomarker, CA-IX to identify hypoxic volumes in vivo. In almost all cases, important controls compare signal intensities to the immunohistochemical distribution of pimonidazole.

Tumor pH can also be imaged in vivo using either magnetic resonance or nuclear imaging approaches, reviewed in (16). In MRI, a number of approaches are available, including 31-P MRS of 2-aminopropylphosphonate, 1-H MRSI of imidazoles, MR relaxometry, and chemical exchange saturation transfer (CEST) with either hydroxyl or amide-containing tracers (diaCEST) or tracers containing paramagnetic rare earths (paraCEST). Radionuclide approaches are currently lmited to the use of a low pH insertion peptide, pHLIP, which can be labeled with 64-Cu or 18-F (for PET) or 99m-Tc for SPECT. Optical methods to measure pH are highly developed and can be used in vitro and in vivo. Until recently, the concentration of glucose in tumors had to be inferred from either invasive microperfusion systems, or through reaction-diffusion modeling. However, recently there are two independent reports where CEST MRI has been used to detect and measure glucose levels in tumors (17, 18). These approaches have great potential to illuminate metabolism of cancers.

Image ‘omics

Because these microenvironmental factors are highly selective, they will amplify somatic evolution and the emergence of distinct genetically related sub-populations (clades) of cells within tumors. An emerging advance is to use profound image analysis (“radiomics”) to identify these regions of heterogeneity (19). Heterogeneity can be viewed radiographically, wherein a non-uniform pattern of enhancement or attenuation (“texture”) can be associated with poor outcome (20, 21). These radiographically visible sub-regions reflect underlying molecular and cellular alterations. In order to systematically address this issue, we have created a database structure that can be populated with images, as well as quantitative image feature data (e.g. Texture, Shape, Density features) that can be mined in combination with patient outcomes and genetic data from biopsies. This is allow real-time data analyses and association of features with prognostic, diagnostic and predictive models (22).

Current quantitative measurements are limited to dimensional measurements of tumor size via one (RECIST) or two (WHO) dimensional long axis measures (23). These measures do not reflect the complexity of tumor morphology or behavior, nor, in many cases, are changes in these measures predictive of therapeutic benefit (24). When additional quantitative measures are performed, they generally average values over an entire region of interest (ROI). In focused studies, texture features have been shown to provide significantly higher prognostic power than ROI-based methods (25-28). This is reflective of the fact that tumors are highly heterogeneous systems,

and that such heterogeneity has high prognostic power (29). Profound analyses of such image features can improve prediction of clinical CT (30), MR (31) or PET (32) images. Although paradigm-shifting, these analyses have been performed manually and the studies were underpowered. In order to qualify as a clinically useful biomarker, such studies have to be performed with larger cohorts in prospective, multi-institutional trials. In the current iteration of radiomics, image features have to be extracted automatically and with high throughput, putting a high premium on novel machine learning algorithm developments. The goal of radiomics is to convert images to mineable data, with high fidelity and high throughput. The radiomics enterprise can be divided into five processes with definable inputs and outputs, each with its own challenges that need to be overcome: (i) image acquisition and reconstruction; (ii) image segmentation and rendering; (iii) feature extraction and feature qualification (iv) databases and data sharing; and (v) ad hoc informatics analyses (19). Each of these steps must be developed de novo and, as such, poses discrete challenges that have to be met. For example, optimum protocols for image acquisition and reconstruction have to be identified and harmonized. Segmentations have to be robust and involve minimal operator input. Features have to be generated that robustly reflect the complexity of the individual volumes, but cannot be overly complex or redundant. Informatics data bases that allow incorporation of image features and image annotations, along with medical and genetic data have to be generated. Finally, the statistical approaches to analyze these data have to be optimized, as radiomics is not a mature field of study. Variation in results may come from variations in any of these individual processes. Thus, after optimization, another level of challenge is to harmonize and standardize the entire process, while still allowing for improvement and process evolution.

References

Nowell PC. The clonal evolution of tumor cell populations. Science (New York, NY. Oct 1 1976;194(4260):23-28.

Jones S, Chen WD, Parmigiani G, et al. Comparative lesion sequencing provides insights into tumor evolution. Proceedings of the National Academy of Sciences of the United States of America. Mar 18 2008;105(11):4283-4288.

Gerlinger M, Swanton C. How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. British journal of cancer. Oct 12 2010;103(8):1139-1143.

Greaves M, Maley CC. Clonal evolution in cancer. Nature. Jan 19 2012;481(7381):306-313.

Gatenby RA, Gillies RJ, Brown JS. Of cancer and cave fish. Nature reviews. Apr 2011;11(4):237-238.

Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature. Oct 28 2010;467(7319):1114-1117.

Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. The New England journal of medicine. Mar 8 2012;366(10):883-892.

Winge O. Zytologische untersuchungen uber die natur maligner tumoren. II. Teerkarzinome bei mausen. Z Zellforsch Mikrosk Anat. January 22, 1930 1930;10:683-735.

Allred DC, Wu Y, Mao S, et al. Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution. Clin Cancer Res. Jan 15 2008;14(2):370-378.

Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. Jul 1 2005;23(19):4265-4274.

Engelman JA, Settleman J. Acquired resistance to tyrosine kinase inhibitors during cancer therapy. Current opinion in genetics & development. Feb 2008;18(1):73-79.

Aktipis CA, Kwan VS, Johnson KA, Neuberg SL, Maley CC. Overlooking evolution: a systematic analysis of cancer relapse and therapeutic resistance research. PloS one. 2011;6(11):e26100.

Tatum JL, Kelloff GJ, Gillies RJ, et al. Hypoxia: importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy. International journal of radiation biology. Oct 2006;82(10):699-757.

Krohn KA, Link JM, Mason RP. Molecular imaging of hypoxia. J Nucl Med. Jun 2008;49 Suppl 2:129S-148S.

Krishna MC, Matsumoto S, Yasui H, et al. Electron paramagnetic resonance imaging of tumor pO(2). Radiation research. Apr;177(4):376-386.

Zhang X, Lin Y, Gillies RJ. Tumor pH and its measurement. J Nucl Med. Aug 2010;51(8):1167-1170.

Walker-Samuel S, Johnson P, Pedley RB, Lythgoe MF, Golay X. Assessment of tumour glucose uptake using gluco-CEST. Proc ISMRM (Montreal). 2011; http://www.ucl.ac.uk/cabi/imaging/researchareas/cancerImaging/tumourGlucose.

Chan KW, McMahon MT, Kato Y, et al. Natural D-glucose as a biodegradable MRI contrast agent for detecting cancer. Magn Reson Med. Oct 16.

Kumar V, Gu Y, Basu S, et al. Radioomics: the Process and the Challenges. Magnetic Resonance Imaging. 2012;(in press).

Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology. 2009;73:1200-1206.

Kawata Y, Niki N, Ohmatsu H, et al. Quantitative classification based on CT histogram analysis of non-small cell lung cancer: Correlation with histopathological characteristics and recurrence-free survival. Medical physics. Feb 2012;39(2):988.

Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012;doi:10.1016/j.ejca.2011.11.036.

Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. J Clin Oncol. Jul 10 2006;24(20):3245-3251.

Burton A. RECIST: right time to renovate? The Lancet Oncology. 2007;8(6):464-465.

Jackson A, O'Connor JPB, Parker GJM, Jayson GC. Imaging tumor vascular heterogeneity and angiogenesis using dynamic contrast-enhanced magnetic resonance imaging. Clinical Cancer Research. 2007;13(12):3449-3459.

Rose CJ, Mills SJ, O'Connor JPB, et al. Quantifying spatial heterogeneity in dynamic contrast-enhanced MRI parameter maps. Magnetic Resonance in Medicine. 2009;62(2):488-499.

Gibbs P, Turnbull LW. Textural analysis of contrast-enhanced MR images of the breast. Magnetic Resonance in Medicine. 2003;50(1):92-98.

Canuto HC, McLachlan C, Kettunen MI, et al. Characterization of image heterogeneity using 2D Minkowski functionals increases the sensitivity of detection of a targeted MRI contrast agent. Magnetic Resonance in Medicine. 2009;61(5):1218-1224.

Gillies RJ, Verduzco D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nature reviews. 2012;12(7):487-493.

Segal E, Sirlin CB, Ooi C, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. Nature biotechnology. 2007;25(6):675-680.

Diehn M, Nardini C, Wang DS, et al. Identification of noninvasive imaging surrogates for brain tumor gene-expression modules. Proceedings of the National Academy of Sciences. 2008;105(13):5213.

Nair VS, Gevaert O, Davidzon G, et al. Prognostic PET 18F-FDG Uptake Imaging Features Are Associated with Major Oncogenomic Alterations in Patients with Resected Non-Small Cell Lung Cancer. Cancer research. Aug 1;72(15):3725-3734.