Biology and Pathology

Cancer Biology

Tumor Metabolomics

John Kurhanewicz
Radiology and Biomedical Imaging, Urology and Pharmaceutical Chemistry, University of California San Francisco, San Francisco, California, USA

Learning objectives:

- Understanding important metabolic changes that occur in cancer and their cause.
- Awareness of the NMR and mass spectrometry-based metabolomics approaches and pre-clinical model systems used to identify metabolic targets for patient imaging studies.
- Awareness of the clinical imaging methods that can be used to assess tumor metabolism and the types of clinical questions that can be addressed.

Cancer metabolism can be viewed as the sum of a large but finite number of interdependent biochemical pathways, each of which provides a specific function for the survival and growth of the malignant cell (1). Metabolic shifts in cancer are too numerous to describe in full within this lecture, but include [1] an increase choline metabolism, [2] an increase in both oxidative phosphorylation and aerobic glycolysis, [3] increased consumption of glutamine and [3] redox adaptation, whereby cancer cells accumulate intracellular antioxidants (2). These metabolic shifts are enforced by oncogenes (most notably PI3K/AKT, MYC, and HIF-1) and the loss of tumor suppressor genes such as P53. Due to the short-comings of single time point biopsies and histopathology which is the current clinical standard for cancer diagnosis and therapeutic follow-up, there is intense interest in metabolic imaging techniques that can non-invasively monitor metabolism from the whole tumor and surrounding tissues thereby over-coming issues with tumor heterogeneity and providing information concerning the interplay between metabolism and tumor micro-environment. This lecture will focus on metabolic imaging methods that are widely used in clinical practice, positron emission tomography (PET) and proton magnetic resonance spectroscopic imaging (¹H MRSI). Additionally, we will discuss a new metabolic imaging approach, magnetic resonance spectroscopic imaging of hyperpolarized ¹³C labeled biomolecules. The development of hyperpolarized ¹³C MRSI, and its recent application to prostate cancer patients (3), have significantly expanded the metabolic targets for imaging. The identification of appropriate metabolic targets for patient studies has required extensive NMR and mass spectrometry-based metabolomics studies using a combination of pre-clinical cell and tissue culture and murine models with associated correlative pathologic and molecular studies (4). This lecture will describe these pre-clinical studies and provide several examples of how cancer metabolism can be exploited using metabolic imaging techniques. Specifically, the metabolic phenotype associated with aggressive prostate cancer, the key clinical question at diagnosis, will be discussed. The metabolic phenotype associated with recurrent cancer after radiation therapy, the mainstay of focal therapy, and with the development of resistance to prolonged androgen deprivation therapy, the primary therapy used for the treatment of metastatic prostate cancer, will also be described.

References:

1. Kaelin WG, Thompson CB. Nature, 465(7298):562-564 (2010)
2. Coller, et al. Am. J. Pathol. 184(1): 4-17 (2014)

3. Nelson, SJ, et al. Science Translation Medicine, 5(198):198ra108 (2013)
4. Keshari, K. The Prostate, 73(11):1171-81 (2013)

Acknowledgements: Support from the NIH, DOD, GE Healthcare and UC Discovery grants.