Imaging the tumor macroenvironment: the effect of cachectic tumors on normal tissues

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Introduction: The two main causes of mortality from cancer are metastasis related organ failure and cachexia (1). Cachexia occurs in approximately 50% of cancer patients and accounts for at least 20% of deaths from cancer. It is characterized by progressive weight loss occurring independently of food intake, metabolic alterations, depletion of lipid stores and severe loss of skeletal muscle protein, all of which significantly impair quality of life and response to treatment (2). The complexities of cancer, and cachexia induced by cancer, dictate the necessity of studying this disease in the context of its macroenvironment as well as in the context of interactions between the tumor and the body i.e. the ‘macroenvironment’. Currently there is no known cure for cachexia, since mechanisms underlying its manifestation are not defined clearly enough to identify and design effective therapeutic strategies. Several inflammatory cytokines such as tumor necrosis factor alpha, interleukin-6 (IL-6) and IL-1β and interferon-γ, glucocorticoids, tumor-derived proteolysis-inducing factor and lipid-mobilizing factor have been shown to play a role in this condition (3). The multi-faceted nature of this condition makes it imperative that a macroenvironmental approach is used to understand the cachectic switches, and the multiple interactive networks that most likely exist between a cachexia-inducing tumor and deregulated host organ and tissue metabolism, as well as the interaction between inflammatory cytokines and metabolism. In preclinical studies we have used magnetic resonance spectroscopic imaging (MRSI) to understand the metabolic consequences of cachexia-inducing tumors on normal tissues. The noninvasive imaging indices developed here will allow us to establish a sequence of events to identify the most lethal aspects of the cachexia-cascade.

Methods: Preclinical studies were performed using cachetic (MAC16) and non-cachetic (MAC13) murine colon adenocarcinoma tumors. MAC16 tumors induce extensive weight loss in tumor-bearing animals, whereas MAC13 tumors, although histologically similar to MAC16 tumors, do not induce host weight. The MAC16 and MAC13 cell lines originally from Dr. Tisdale’s laboratory (Birmingham, UK), were obtained from Dr. Sidransky with Dr. Tisdale’s permission. Tumors were formed by inoculating 2 x 106 cells in the flank of male SCID mice. In vivo localized MRSI was performed on a 4.7T Bruker Biospec spectrometer using a volume coil. Localized spectra from a 4 mm thick slice was acquired with FOV 32 mm; 4 scans per phase encode step; TE=120 ms; TR=1 s with VAPOR water suppression. Quantitative metabolic maps are generated using in-house IDL programs were used to generate quantitative maps of total choline, creatine and lactate/lipid using unsuppressed water signal as an internal reference. Lipid and water-soluble fractions were obtained from normal tissues using a dual-vane extraction method based on methanol/chloroform/water (1:1:1) separation (4). Fully relaxed 1H MR spectra of the extracts were acquired on an 11.7T Bruker Avance spectrometer (Bruker BioSpin Corp., Billerica, MA) using a 5-mm HX inverse probe and the following acquisition parameters: 30° flip angle, 6000 Hz sweep width, 12.7 s repetition time, time-domain data points of 32K, and 128 transients. Extract spectra were analyzed using Bruker XWIN-NMR 3.5 software (Bruker BioSpin). Integrals of metabolites were determined and normalized to tissue weight and compared to an internal standard to obtain concentrations.

Results and Discussion: Lipid maps generated from MRSI data are shown in Figure 1 and demonstrate the profound depletion of the lipid signal that can be detected noninvasively in normal tissue, but not in tumor tissue, in MAC16 tumor bearing mice. Consistent with the profound depletion of lipid in normal tissue observed in vivo, there was a decrease of lipid in muscle tissue obtained from MAC16 tumor bearing mice (Figure 2).

The ability of a cachectic tumor to produce profound changes in the metabolism of normal tissue is evident from data on water-soluble muscle tissue extracts obtained from MAC16 tumor bearing mice (n=3 each). The muscle tissue extract shows a significant decrease of lipids, confirming the in vivo observations in Figure 1. The ability to non-invasively image the onset of cachexia early on with noninvasive imaging, preferably before weight loss occurs, is critically important to treat the condition, design and optimize therapeutic strategies, and detect response to such treatments.


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