Metabolic Imaging of Cachectic Tumors

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Introduction: ‘Cachexia’ is derived from the Greek “kakos” meaning bad and “hexis” meaning condition. Clinically, cachexia is defined as an unintentional weight loss of 5% over a 3 to 6 month period (1). Cancer patients with an involuntary weight loss of 5% have a shorter median survival rate (1); death from cachexia occurs with a weight loss of 30% (2). The ability to arrest or reverse this condition would have a tremendous impact on improving quality of life, treatment outcome, and increasing life expectancy, allowing a patient to have recourse to currently available or newly developing treatment options. Understanding the metabolism of cachexia-inducing tumors may lead to the identification of new targets to arrest or reverse the condition.

Methods: In this preclinical study, we performed 1H MRS/I of tumors derived from cachectic (MAC16) and non-cachectic (MAC13) marine colon adenocarcinoma cell lines inoculated in the flank of male SCID mice. Cachectic MAC16 tumors induce extensive weight loss in tumor-bearing animals, unlike MAC13 tumors, which although histologically similar, do not alter body weight (3). These cell lines were originally obtained from Dr. Tisdale (Birmingham, UK). In vivo localized MRSI of tumors was performed on a 4.7T Bruker Biospec spectrometer using a solenoid coil placed around the tumor. Localized spectra from a 4 mm thick slice were acquired with FOV 16 mm; 4 scans per phase encode step; TE=120 ms; TR=1 s with VAPOR water suppression. Quantitative maps of total choline and lactate/lipid were acquired using unsuppressed water signal as an internal reference, using in-house IDL programs. A dual-phase extraction method based on methanol/chloroform/water (1:1:1), was used to obtain lipid and water-soluble fractions from tumors (4). Fully relaxed 1H MR spectra of tumor extracts were acquired on an 11.7T Bruker Avance spectrometer 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. Spectra were analyzed using Bruker XWIN-NMR 3.5 software (Bruker BioSpin). Integrals of the metabolites of interest were determined and normalized to the tumor weight. Metabolite concentrations were obtained from 1H spectra using an internal standard.

Results and Discussion: Our preliminary 1H MRSI studies revealed that the cachectic MAC16 tumors had a significantly higher total choline levels compared to non-cachectic MAC13 tumors (Figures 1 and 2). From high-resolution spectra of extracts it was apparent that the increase of total choline was due to higher phosphocholine (PC) and glycerophosphocholine (GPC) (Figure 3). There was a trend towards higher levels of lipid/lactate in non-cachectic tumors, but this trend was due to increased lipids at the tumor periphery, since 1H MRS of lipid-phase extracts demonstrated that tumor lipid levels were not significantly different between cachectic and non-cachectic tumors. Since PC is a membrane precursor and GPC is a membrane breakdown product, the increase of both PC and GPC suggests a rapid synthesis and breakdown of membrane choline phospholipids in cachectic tumors.


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