Cancer-induced cachexia is a complex and poorly understood life-threatening syndrome that is characterized by progressive weight loss due to metabolic alterations, depletion of lipid stores, and severe loss of skeletal muscle protein. Gaining the ability to noninvasively image the presence or onset of cachexia is important to better treat this condition, to improve the design and optimization of therapeutic strategies, and to detect the responses to such treatments. In this study, we employed noninvasive magnetic resonance spectroscopic imaging (MRSI) and [18F]fluoro-2-deoxy-D-glucose (18FDG) positron emission tomography (PET) to identify metabolic signatures typical of cachectic tumors, using this information to analyze the types and extents of metabolic changes induced by the onset of cachexia in normal tissues. Cachexia was confirmed by weight loss as well as analyses of muscle tissue and serum. In vivo, cachexia-inducing murine adenocarcinoma (MAC)16 tumors were characterized by higher total choline (tCho) and higher 18FDG uptake than histologically similar noncachectic MAC13 tumors. A profound depletion of the lipid signal was observed in normal tissue of MAC16 tumor–bearing mice but not within the tumor tissue itself. High-resolution 1H magnetic resonance spectroscopy (MRS) confirmed the high tCho level observed in cachectic tumors that occurred because of an increase of free choline and phosphocholine. Higher succinate and lower creatine levels were also detected in cachectic tumors. Taken together, these findings enhance our understanding of the effect of cancer on host organs and tissues as well as promote the development of noninvasive biomarkers for the presence of cachexia and identification of new therapeutic targets. Cancer Res; 71(22): 6948–56. ©2011 AACR.
response to treatment, is central to developing new therapies. Significant abnormalities in carbohydrate, lipid, and protein metabolisms are observed with cachexia and are a major cause for the associated profound weight loss (5).

Noninvasive clinically translatable techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) with their respective metabolic-imaging capabilities provide the opportunity to investigate interactions between the tumor and the host, i.e., the "tumor macroenvironment," to identify stages in the cachexia cascade. With its clinical translatability, relatively high sensitivity, and ability to detect metabolites such as lipids, lactate, and total choline (tCho), which consists of free choline, phosphorylcholine, and glycerophosphocholine, 1H magnetic resonance spectroscopic imaging (MRSI) is ideally suited to explore the interactions between the tumor and its host in the induction and progression of cachexia. Similarly, [18F]fluoro-2-deoxy-d-glucose (18FDG) PET is frequently employed in oncological diagnosis. Here, we have identified tumor and normal tissue metabolic signatures associated with the well-established cachexia-inducing murine adenocarcinoma (MAC)16 tumor model, compared with the histologically similar but noncachectic MAC13 tumor model.

The presence of cachexia in our experimental model was confirmed by weight loss and an increase in the expression levels of 2 markers of muscle protein degradation, Atrogin-1 (mouse atrophy gene 1) and MuRF1 (muscle RING finger 1). Atrogin-1 and MuRF1 are 2 skeletal muscle–specific ubiquitin ligases required in protein breakdown (8), and the expression levels of these ligases increase with cachexia (5, 8–10). The presence of cachexia was additionally confirmed by the analysis of lipid content in serum from cachectic and noncachectic tumor–bearing mice (11, 12).

In vivo, cachectic tumors were characterized by increased tCho and 18FDG uptake compared with noncachectic ones and induced a profound depletion of triglycerides in normal tissue that was not observed with noncachectic tumors. Cachexia also resulted in increased 18FDG uptake in the brain and lung. An increase of phosphorylcholine and succinate along with a decrease of creatine were detected in high-resolution spectra of cachectic tumor extracts. The higher choline kinase mRNA levels observed in MAC16 cells and tumors were consistent with higher phosphorylcholine observed in tumor extract spectra and the increased tCho observed in vivo. These metabolic patterns may represent new noninvasive biomarkers and targets in the detection, management, and treatment of this condition.

Materials and Methods

Cell lines and tumor models

Cachectic MAC16 and noncachectic MAC13 cell lines were obtained from Dr. David Sidransky at Johns Hopkins University with Dr. Michael Tisdale’s permission. Cachectic MAC16 tumors induce significant weight loss in tumor-bearing animals, unlike MAC13 tumors, which although histologically similar, do not alter body weight (13). Cells were cultured in RPMI-1640 with 10% FBS. Tumors were generated by inoculating a cell suspension of 2 × 10⁶ cells in 0.05 mL of Hank’s balanced salt solution in the flank of severe combined immunodeficient (SCID) male mice. Tumor volumes were calculated from caliper measurements using the equation, volume = (π/6) × a × b × c, in which a, b, and c represent 3 orthogonal axes of the tumor. Because these are murine cancer cell lines, authentication with commercially available kits that are employed for human cancer cell lines is not possible. Instead, tumor-induced weight loss, expression of muscle-degrading markers, and serum lipid profiles were used to authenticate the cells.

18FDG-PET imaging

For 18FDG-PET imaging, MAC13 and MAC16 tumor–bearing mice were fasted overnight. Mice were injected intravenously with 200 μCi of FDG in a final volume of 200 μL. At 60 minutes after injection of the radiotracer, a 30-minute static whole-body image was acquired over the mouse body. Images were decay corrected and reconstructed using 2-dimensional (2D) OSEM (ordered subset expectation maximization). Data analysis were done on the basis of regions of interest (ROI) drawn over the tumor and tissues. After accounting for injected dose and body weight, all radioactivity concentration values were converted into standardized uptake values (SUV). Values shown are means of the pixel values (SUVmean). In the case of tumor, to avoid bias from the inclusion of any tumor necrotic areas in the ROI, SUVmean as well as SUVmax (single maximum pixel value within the ROI) were reported. Image analysis was done using AMIDE (a medical image data examiner) software (SourceForge).

In vivo 1H MR spectroscopic imaging

Anesthetized mice bearing tumor xenografts were imaged on a 4.7T Bruker Biospec spectrometer (Bruker Biospin Corp.). Body temperature of the animals was maintained in the magnet by a thermostat-regulated heating pad. To acquire localized proton spectra of the tumor, a homebuilt solenoid coil was placed around the tumor. Spectra from a 4-mm thick slice were acquired with a field of view of 16 mm; a matrix size of 16 × 16 × 1,024; 4 scans per phase encode step; and number of scans (NS) of 4, an echo time (TE) of 120 milliseconds, and a repetition time (TR) of 1 second, using a 2D-CSI (chemical shift imaging) sequence with VAPOR water suppression (14). Signals at approximately 3.2 ppm from tCho and at 1.3 ppm from lipids with some contribution from lactate that overlaps with the lipid signal were detected in localized proton spectra.

A homebuilt volume coil was used to acquire whole-body 1H MRSI and obtain in vivo cross-sectional images from the tCho and lactate + lipids signal of the mouse. Spectra from a 4-mm thick slice were acquired with a field of view of 32 mm; a matrix size of 32 × 32 × 1,024; 4 scans per phase encode step; and NS = 4, TE = 120 milliseconds, and TR = 1 second. Reference 2D-CSI images of the unsuppressed water signal were acquired with TE = 20 milliseconds and NS = 1, with all other parameters remaining the same.

Quantitative maps of tCho and lactate + lipids were generated from the spectroscopic images using unsuppressed water signal as an internal reference (15). Quantitative metabolic maps were generated using in-house IDL programs.
High-resolution ¹H MRS of dual-phase tissue extracts

High-resolution ¹H MRS of lipid- and water-soluble fractions of tissue extracts was done to resolve the components of the tCho signal and the lactate + lipids signal detected in vivo and further characterize the differences observed in vivo. Lipid- and water-soluble fractions were obtained from tumors and muscle tissue using a dual-phase extraction method with methanol/chloroform/water (1/1/1; ref. 16). Briefly, tissues were freeze clamped and ground to powder. Ice-cold chloroform, followed by ice-cold water, was added and the sample was kept at 4 °C overnight for phase separation. Samples were then centrifuged for 30 minutes at 15,000 × g at 4 °C to separate the phases. The water/methanol phase containing the water-soluble metabolites was treated with Chelex (Sigma Chemical Co.) for 10 minutes on ice to remove divalent cations. Methanol was then removed by rotary evaporation, and the remaining water phase was lyophilized and stored at −20 °C. The chloroform phase containing the lipids was dried in a stream of N₂ and stored at −20 °C. Water-soluble samples were dissolved in 0.5 mL of D₂O (Sigma Chemical Co.) containing 3-(trimethylsilyl) propionic-2,2,3,3,4-d acid (Sigma Chemical Co.) as an internal concentration standard (sample pH of 7.4). Lipid samples were dissolved in 0.6 mL of CDCl₃/CD₃OD (2/1) containing tetramethylsilane as an internal concentration standard (CDCl₃ and CD₃OD premixed with tetramethylsilane by the manufacturer, Cambridge Isotope Laboratories, Inc.). Fully relaxed ¹H MR spectra of the extracts were acquired on a Bruker Avance 500 spectrometer operating at 11.7 T (Bruker BioSpin Corp.) using a 5-mm HX inverse probe and the following acquisition parameters: 30-degree flip angle, 6,000 Hz sweep width, 12.7-second TR, time-domain data points of 32K, and 128 transients (16). Spectra were analyzed using Bruker XWIN-NMR 3.5 software (Bruker BioSpin Corp.). Integrals of the metabolites of interest were determined and normalized to the tumor weight. To determine concentrations, peak integration from ¹H spectra for all metabolites studied was compared with the internal standard.

Quantitative real-time PCR of cells and tumor extracts

Total RNA was extracted from MAC13 and MAC16 cells and tumors, using Qiagen easy mini kit (Qiagen) as previously described (17). cDNA was synthesized from 1 μg of total mRNA using qScript (Quanta Bioscience). Quantitative real-time PCR (qRT-PCR) was carried out using qPCR Green Supermix, gene-specific custom-made primers, and diluted cDNA (1:10) samples as template, in the iCycler detection system (Bio-Rad). The following primers were designed using Beacon Designer software 5.1 (Premier Biosoft International): mChk (NM_013490) forward 5'-CCAGTTCCACATCATGTGAT-3'; reverse 5'-CTTCGCAAGACTGAGCTCAG-3'; hypoxanthine phosphoribosyltransferase-1 (HPRT1; NM_001039048) forward 5'-CCAGTTCCACATCATGTGAT-3'; reverse 5'-CTTCGCAAGACTGAGCTCAG-3'; 5'-AAGACTGAGCTGAGTAACTG-3'; reverse 5'-TAGAGGGTGCAAAACTTTCTG-3' (annealing temperature, 56.1 °C); F-box protein 32 (Atrogin-1, NM_026346), forward 5'-GCGGAGAAAAGACATTCAAGAACA-3'; reverse 5'-TACACCTTCGATGATTCTTCC-3' (annealing temperature, 54 °C).

Protein isolation and Western blot analysis of muscle tissue

Total protein from freeze-clamped muscle tissue was extracted using radioimmunoprecipitation assay buffer fortified with protease inhibitor cocktail (1/500: Sigma Chemical Co.), dithiothreitol (1/1,000, 1 mL/L stock), phenylmethylsulfonyl fluoride (1/200, 0.2 mL/L stock), sodium orthovanadate (1/500, 0.5 mL/L stock), and sodium fluoride (1/500, 0.5 mL/L stock). About 100 μg of protein was resolved on 10% SDS-PAGE, transferred onto nitrocellulose membranes, and probed with a goat polyclonal antibody (1/1,000 in 5% nonfat dry milk) against Atrogin-1 (Everest Biotechnicals). Appropriate horseradish peroxidase–conjugated secondary antibody donkey anti-goat (Novus Biologicals) or donkey anti-rabbit (GE Healthcare Bio-Sciences) was used at 1/2,000 dilution. A mouse monoclonal antibody against glycerolaldehyde-3-phosphate dehydrogenase (Sigma Chemical Co.) at 1/1,000 was used as loading control. Immunoblots were developed using SuperSignal West Pico chemiluminescent substrate kit (Pierce Biotechnology, Inc.).

Serum analysis

Lipid analysis of serum was done by the Johns Hopkins Phenotyping and Pathology Core. Lipids measured included cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

Statistical analysis

Values displayed are mean ± SEM. Statistical significance was evaluated using the Student t test; P < 0.05 was considered significant.

Results

Confirming the presence of cachexia

Cachectic MAC16 and noncachectic MAC13 tumors displayed comparable growth rates and histology. However,
as shown in Fig. 1A, MAC16 tumors induced significant weight loss, confirming the induction of cachexia. MAC16 and MAC13 tumor–bearing mice that were imaged weighed 22.29 ± 0.89 g and 25.41 ± 0.55 g (p < 0.05), respectively. Tumor volumes at 535.8 ± 44.3 mm³ for the MAC16 and 493.8 ± 40.6 mm³ for MAC13 tumors were not significantly different. The mRNA (Fig. 1B) and protein expression levels (Fig. 1C) of MuRF1 and Atrogin-1 proteins in muscle tissue obtained from mice bearing MAC13 or MAC16 tumors. GAPDH was used as loading control (n = 3). D, lipid analysis of serum from mice bearing MAC13 or MAC16 tumors. Values represent mean ± SEM (MAC13, n = 8; MAC16, n = 7; *, P < 0.05), GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

Figure 1. A, normalized weights of MAC13 (▲) and MAC16 (■) tumor–bearing mice over time (n = 10 per group; *, p < 0.05). B, mRNA expression levels of MuRF1 and Atrogin-1 analyzed by RT-PCR in MAC13 (▲) and MAC16 (■) muscle tissue. Values represent mean ± SEM (n = 4; **, P < 0.01; ***, P < 0.005). C, representative immunoblot showing MuRF1 and Atrogin-1 proteins in muscle tissue obtained from mice bearing MAC13 or MAC16 tumors. GAPDH was used as loading control (n = 3). D, lipid analysis of serum from mice bearing MAC13 or MAC16 tumors. Values represent mean ± SEM (MAC13, n = 8; MAC16, n = 7; *, P < 0.05), GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

Cachectic tumors show higher glucose uptake than noncachectic tumor and induce increased uptake of glucose in brain and lungs

Representative images shown in Fig. 2A show the increased uptake of ¹⁸FDG in MAC16 compared with MAC13 tumors. Quantification of ¹⁸FDG uptake confirmed a significant difference between MAC13 and MAC16 tumors (Fig. 2B). ¹⁸FDG uptake in the brain (Fig. 2C) and lung (Fig. 2D), but not muscle (Fig. 2E), was significantly higher in mice bearing cachectic tumors.

Cachectic tumors have altered tCho levels in vivo

Representative high-resolution T₁-weighted images of a MAC13 (top) and MAC16 (bottom) presented in Fig. 3A show...
that the MAC16 (bottom) tumor had significantly higher tCho than the MAC13 tumor (top), as evident in the tCho maps shown in Fig. 3B. Representative lactate + lipid images from these tumors are shown in Fig. 3C and show that although the lactate + lipid content was not different between the MAC13 (top) and the MAC16 (bottom) tumor, the peripheral signal, most likely from subcutaneous lipids, was lower around the MAC16 tumor.

Quantitative tCho and lactate + lipid data acquired from multiple animals are summarized in Fig. 3D–F. A significant increase of tCho was observed in MAC16 compared with MAC13 tumors (Fig. 3D). There was no significant difference in lactate + lipids obtained from within the tumor (Fig. 3E), but a significant decrease of lactate + lipids around the tumor periphery in MAC16 compared with MAC13 tumors (Fig. 3F). The lactate + lipid signal around the periphery of the tumor was from subcutaneous fatty tissue that is found between the tumor and the fold of the skin, which decreased as the lipids decreased in normal tissue of cachectic mice, as discussed subsequently.

Cachectic tumor induces lipid depletion in normal tissue

To determine the effect of cachectic tumors on normal tissue tCho and lactate + lipids, we conducted in vivo 1H MRSI of the mouse whole body using a volume coil. Representative high-resolution T1-weighted images of a MAC13 (top) and MAC16 (bottom) are presented in Fig. 4A to identify the cross-sectional area from which the metabolite images were obtained. Representative lactate + lipid images obtained from this cross-sectional slice are shown in Fig. 4B and show the profound depletion of lactate + lipid signal in normal tissue in MAC16 tumor–bearing mice (bottom) compared with MAC13 tumor–bearing mice (top), as evident in Fig. 4C that displays the lactate + lipid signal overlaid with the spin density images.

Quantitative lactate + lipids data acquired from multiple animals are summarized in Fig. 4D. A significant decrease of lactate + lipids was observed in the normal tissue of MAC16 tumor–bearing mice compared with MAC13 tumor–bearing mice that was subsequently identified to be due to lipid depletion. No significant differences in tCho were observed in the normal tissues of MAC16 and MAC13 tumor–bearing mice.

Tumor extract studies confirmed in vivo data

To characterize better the observations made in vivo, we conducted high-resolution proton spectroscopy of water-soluble and lipid extracts of tumors. The tCho peak observed in vivo consists of free choline, phosphocholine, and glycerophosphocholine that can be identified in high-resolution spectra of water-soluble extracts. Similarly, contributions from lactate versus lipids to the lactate + lipid signal observed in vivo can be resolved because lactate is separated into the water-soluble phase and the lipids are separated into the lipid phase of the tumor extracts. Representative spectra from water-soluble tumor extracts are shown in Fig. 5A and B and show...
significantly higher phosphocholine and free choline in MAC16 (Fig. 5B) tumors than in MAC13 tumors (Fig. 5A), but no difference in lactate. Quantitative data acquired from multiple tumors are summarized in Fig. 5C and show a significant increase of free choline, phosphocholine, and tCho that confirmed the *in vivo* data.

In addition, a significant increase of succinate and a significant decrease of creatine were observed in the water-soluble tumor extracts of MAC16 compared with MAC13 tumors (Fig. 5C). There were no significant differences in phosphocreatine, alanine, or acetate (data not shown) between MAC16 and MAC13 tumors. Lipid signals in the lipid-phase extracts were not significantly different between MAC16 and MAC13 tumors again confirming the *in vivo* data (data not shown).

To identify further the molecular mechanism underlying the increase of phosphocholine, we carried out qRT-PCR of choline kinase, the enzyme that phosphorylates free choline to phosphocholine. We found a significant increase of choline kinase mRNA in MAC16 cells (Fig. 6A) and tumors (Fig. 6B).

Cachexia affects lipid content of muscle

The profound depletion of lipids in normal tissue observed *in vivo* was confirmed in high-resolution spectra of extracted muscle tissue. Representative lipid spectra from muscle tissue extract obtained from MAC13 and MAC16 tumor–bearing mice are shown in Fig. 7A and B, respectively. In the spectra, the different peaks are assigned to the protons signals of different groups of fatty acids, methyl (-CH₃, 0.9 ppm), aliphatic methylene (-CH₂, 1.3 ppm), carboxyl (-OOC-CH₂-CH₂-, 1.47 ppm; -OOC-CH₂, 2.4 ppm), allyl methylene (¼ CH-CH₂, 1.92 ppm), and vinyl (¼ CH-, 5.3 ppm; refs. 18–20). Signals from saturated lipids are visible at 1.3 and 0.9 ppm, polyunsaturated lipids at 1.92 and 5.3 ppm, and the carboxyl group attached to fatty acids at 1.47 and 2.4 ppm. Quantitative data summarized from multiple animals are shown in Fig. 7C and show the significant decrease of lipids induced in the muscle by cachexia. Signals from all of these groups, but especially the carboxyl and methyl groups, decreased in the muscle tissue extracted from cachectic mice.

Discussion

Here, we have identified, with noninvasive imaging, clinically translatable metabolic signatures in tumors and normal tissue that potentially detect the presence of cachexia. Cachectic MAC16 tumors displayed increased tCho and 18FDG uptake compared with noncachectic MAC13 tumors. A profound depletion of the lipid signal was observed in normal tissue of mice bearing cachexia-inducing MAC16 tumors, in addition to increased 18FDG uptake in the brain and lungs. High-resolution spectroscopy of tissue extracts identified additional metabolite signatures, such as increased phosphocholine and succinate and reduced creatine, which may also provide targets to reverse or inhibit the cachexia cascade.

The presence of cachexia induced by MAC16 tumors was confirmed by the significant weight loss, the increase of MuRF-1 and Atrogin-1 mRNA and protein expression in muscle tissue, and a significant decrease of triglycerides and increase of LDL in serum of MAC16 tumor-bearing mice. MuRF-1 and Atrogin-1 have been identified as muscle protein breakdown markers that increase with cachexia (10). Atrogin-1 and MuRF1 are skeletal muscle–specific ubiquitin ligases involved in the ubiquitin proteasome pathway and essential in the development of muscle atrophy (8, 9). Decreased serum triglycerides and increased LDLs have also been previously associated with cachexia (11, 12). Collectively, these data confirmed the induction of cachexia in MAC16 tumor–bearing mice.

Elevated tCho is characteristic of malignant tumors compared with normal tissue, but here, we observed a 2-fold increase of tCho in cachectic MAC16 tumors compared with noncachectic MAC13 tumors, suggesting that tumors with higher than usual tCho may pose a risk for the induction of cachexia. The increased tCho was identified to be due to...
significantly higher phosphocholine and free choline. An increase of cellular phosphocholine and choline-containing compounds has been consistently observed in cancer cells and tissue (21–23) and is closely related to malignant transformation, invasion, and metastasis (24, 25). Elevated phosphocholine and tCho have been previously detected by MRS studies in human lung, colon, prostate, and breast tumors, as well as in derived epithelial cell lines (21, 23). Phosphocholine is a precursor as well as a metabolic breakdown product of the major membrane component phosphatidylcholine. Here, we have identified a previously unknown association between choline metabolism and cachexia. We found that mRNA for choline kinase, a cytosolic enzyme that catalyzes the phosphorylation of choline to phosphocholine by ATP in the presence of magnesium, was significantly elevated in MAC16 cells and tumors, identifying it as a potential novel target to investigate in the treatment of cachexia.

Increased 18FDG uptake is used to detect metabolically active cancers. 18FDG is taken up by the cells through glucose transporters and phosphorylated by the first enzyme of glycolysis, hexokinase. 18FDG-PET can be used in vivo to identify tumor tissues because cancer cells exhibit a higher glycolytic activity, leading to a higher uptake of 18FDG (26). Here, we found that similar to tCho, 18FDG uptake was more than 2-fold higher in cachectic MAC16 tumors than in noncachectic MAC13 tumors, suggesting that exceedingly high 18FDG uptake may be another risk factor for the induction or presence of cachexia. Although high 18FDG uptake is usually associated with increased glycolytic activity (26, 27), we did not observe a significant difference in lactate levels between MAC13 and MAC16 tumors. Interestingly, we did detect a higher level of succinate in the cachectic tumors. Because succinate is produced in the tricarboxylic acid (TCA) cycle from α-ketoglutarate (28), increased flux through the TCA cycle may explain a higher uptake of glucose without an increase of lactate.

Subcutaneous lipids located around the tumor were significantly reduced in the cachectic tumor-bearing mice and lipids in surrounding normal tissue and the skeletal muscle of MAC16 tumor-bearing mice were depleted. It has been previously shown that increased adipocyte lipolysis, rather than decrease in synthesis, is responsible for the loss of fat mass with cachexia (29). Moreover, acetyl-CoA required for the TCA cycle can be obtained from degradation of lipids. The decrease in lipids observed in cachectic mice may arise from an increase in the flux through the TCA cycle, which is also consistent with the increase of succinate. Depletion of lipids in the muscle can be easily detected clinically with 1H MRS and may be of value in detecting the presence or onset of cachexia or in evaluating the effect of treatments arresting or reversing this condition.

The search for noninvasive biomarkers of cachexia has been ongoing for several years. One 1H MRS–based search for cachexia biomarkers in the sera of C26 adenocarcinoma–bearing mice identified increased levels of very low density lipoproteins along with hypoglycemia as serum markers (11). An assessment of hepatic and skeletal muscle bioenergetic status using 31P MRS showed that progressive cancer cachexia was associated with depletion of energy stores in liver and skeletal muscle (30). Increased hepatic inorganic phosphate (Pi)/ATP ratio was detected by 31P MRS and occurred early in the disease process (30). The liver is a central organ in the pathogenesis of cachexia (31). Increased Pi and a rapid removal of phosphonomonooesters were identified with 31P MRS in a rat cancer model of cachexia. Cachexia also induced enhanced hepatic gluconeogenic activity (32). Although the use of 31P MRS is less practical for clinical applications due to the poor sensitivity of detection limiting spatial localization, detection of global changes in liver metabolism with 31P MRS may provide additional specificity in detecting the onset or presence of cachexia.

In conclusion, we have, in a preclinical model, identified previously unknown clinically translatable tumor and normal tissue metabolic signatures characteristic of cachexia. The ease of translating these signatures to the clinic should facilitate validating these metabolites as potential biomarkers of cachexia. In addition, the metabolic changes identified here provide new targets to exploit in the treatment of cachexia. Future studies with noninvasive imaging will allow us to establish a sequence of events to identify the most lethal metabolic aspects of the cascade. Once critical single or multiple cachectic switches or cascades are identified, molecular-targeted image-guided approaches such as multiple siRNA targeting or pharmaceutical interventions can be designed and developed to downregulate or knockout effector molecules, pathways, or enzymes controlling the cascade.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


Metabolic Signatures Imaged in Cancer-Induced Cachexia

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