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Review Article

Multinuclear magnetic resonance evaluation of tumor tissue

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ABSTRACT

Current biomedical research requires quantitative and qualitative studies of tissue metabolites. In this review, we discuss recent advances in multinuclear magnetic resonance (MR) technology that enhance biomedical research. The advances presented herein clearly show that MR is a diagnostic tool for the study of tumor tissue metabolism associated with changes in small molecule concentrations. Biomedical MR offers a non-invasive view of cancer cell metabolism by detection of resonance nuclei such as hydrogen-1, carbon-13, phosphorus-31 and fluorine-19. Due to current progress in MR technology, it is now possible to monitor changes in cancer cell metabolism before and after therapy.

Our criteria for the selection of research papers for this review were focused on those that show progress in biomedicine achieved by using MR. Our review demonstrates that small molecule detection in cancer tissue by MR has advanced biomedical research allowing for significant improvements in tumor detection and treatment.

Introduction

Recent advances in magnetic resonance (MR) technologies have provided medical researchers the ability to analyze metabolic profiles of tumor tissue. Tumor cellular metabolism is associated with increased glycolysis, cataplerosis, anaplerosis, abnormal membrane and energy metabolism needed to deliver substrates required for rapid tumor growth. MR has already been used to obtain metabolic profiles of malignant and non-malignant tissue in humans. The MR profile provides information for identifying specific metabolites which act as diagnostic biomarkers of cancer (Robinson et al., 1996). The ultimate goal of most MR based metabolomic cancer studies is to discover cancer-specific diagnostic biomarkers that will indicate risk of disease occurrence, progression and response to treatment. MR allows detection and spatial localization of hydrogen-1 (^{1}H), phosphorus-31 (^{31}P), carbon-13 (^{13}C) and fluorine-19 (^{19}F) nucleus in cancer tissue. To date ^{1}H MR is the most popular non-invasive method to study cancer metabolites, however, the detection of nuclei different than ^{1}H may have the advantage of high signal-to-noise ratios (SNR). In addition, MR spectroscopy (MRS) is recognized as an analytical tool employed by biomedical researchers to investigate the physiology, pharmacology and biochemistry of cancer tissue. MRS provides spectral information on small molecule

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metabolites participating in various metabolic pathways (Von Brand et al., 2009). MRS imaging (MRSI) is defined as a non-invasive imaging method that provides information about cellular activity and metabolic information. This makes it possible to generate images by deciphering emitted frequencies according to the spatial locations of nuclei and translating the concentration of nuclei contributing to each frequency to proportional image intensities for each unit of the image (Bernstein et al., 2004). MRSI is based on chemical shifts that occur when the resonance frequency of a nucleus is modified by its surrounding chemical environment. By measuring the distribution of chemical shifts from a sample, it is possible to identify a particular molecule. MRS data can be acquired either from a single volume of interest (VOI) or region of interest (ROI), which is often referred to as a voxel. It can also be acquired from multiple voxels by the techniques commonly referred to as either chemical shift imaging (CSI) or MRSI (Maudsley et al., 2009). This review provides an overview of applications of multinuclear MRS to the identification of biochemical characteristics, e.g. key biomarkers, of breast cancer during growth and post-administration of anticancer drugs. CSI is a technique based on imaging sequences, but with the modification that during data acquisition the read out gradient is omitted to conserve chemical shift information. From this multi-dimensional spectral data array, the chemical shift can be visualized from multiple small voxels located within a large examined area, and the registered signal forms a map of spatial distribution of the metabolites being studied (Heywang et al., 1986; Li et al., 2002). MR of nuclei such as ^{1}H, ^{31}P and ^{19}F have the potential for use in detection of drug concentration and toxicity at the site of action. Moreover, MRS localized to the tumor has potential for use in early detection and provide useful information about tumor phenotype (Negendank, 1992). All three ^{1}H MR approaches such as ^{1}H MRS, ^{1}H MRI and ^{1}H MRSI have been used to evaluate tumor metabolomics. The MR challenges include combined studies conducted with immunotherapy (Chen et al., 2014), chemoradiotherapy (Meng et al., 2014), photothermal/radiotherapy (Wang et al., 2013), simultaneous MRI and Positron Emission Tomography (PET) (Thompson et al., 2014), MRI and Transrectal Ultrasound (TRUS) (Gomez-Iturriaga et al., 2014), PET/MRI and computed tomography (CT) fusion (Miwa et al., 2014). Another aspect in metabolomics is application of ^{13}C and ^{19}F MR in research focused on labeling substrates (e.g. drugs, metabolites) with ^{13}C or ^{19}F nuclei. The labeling of substrates with MR active isotopes provides quick and non-invasive methods to access metabolite fluxes or drug response. MR does not discriminate between endogenous metabolites and endogenous administered substances.

^{1}H magnetic resonance

Most of the pathophysiological processes in tissue can be noninvasively monitored by using ^{1}H MR. The ^{1}H isotope is found in almost 100% natural abundance and is ubiquitous in biological compounds. ^{1}H MR is used to investigate a number of diseases and most extensively, cancer in the human body. The first *in vivo* MRI of a tumor in an animal was obtained in 1974 (Lauterbur, 1974). The high water content of the body provides an appreciable number of ^{1}H nuclei for analysis. However, in terms of spectroscopy, those same water molecules with their corresponding ^{1}H nuclei that serve to enhance imaging techniques unfortunately lead to significant spectral interference, particularly when attempting to observe protons of small organic metabolites and other key biomarkers for illness. Three years later in 1977, the first human MRI studies were published (Damadian et al., 1977). Some of the earliest work on ^{1}H nuclear MR (NMR) spectroscopy of mammary tumor extracts was conducted by Gribbestad and coworkers in 1993. Results indicated that tumor tissue contain elevated levels of lactate, succinate, Cho and PCho. In contrast, healthy breast tissue contains higher levels of glucose and inositol when compared with tumor tissue (Gribbestad et al., 1993). Metabolic ratios of glycerophosphocholine (GPCho), phosphocholine/creatine (Pcho/Cr), myo-inositol/scyllo-inositol, choline/creatine (Cho/Cr) and other ratios were found to correlate with the number of tumor cells, tumor cell proliferation, and (for non-malignant tissue) the distance to the nearest tumor (Cheng et al., 2005). ^{1}H MR has been used to study the metabolic status of human tumors with examples that include brain (McKnight, 2004a,b), gastric (Jung et al., 2014), rectal (Wang et al., 2013), renal (Süllentrop et al., 2012), lung (Chen et al., 2011), bladder (Srivastava et al., 2010), ovarian (McLean et al., 2009), breast (Haddadin et al., 2009), cervix (Mahon et al., 2004), kidney (Tate et al., 2000), adipose tissue (Chen et al., 2002) and other types of tissues (Tugnoli et al., 2006). ^{1}H MRS can have a clinical impact providing detailed information on changes in all observed tissue metabolites simultaneously. The ultimate goal for the use of ^{1}H MRS on brain tumor specimens is to improve the accuracy of diagnosis, characterization and evaluation of tumor progression and treatment response. ^{1}H MRS taken from gliomas and meningiomas revealed 37 and 44 different metabolites, respectively (Sze et al., 1998; Martinez-Bisbal et al., 2004). MR analysis of prostate cancer detected higher levels of polyamines and citrate metabolites, as well as lower levels of Cho containing compounds such as Cho, PCho and GPCho (Swanson et al., 2003). Cho and Cho metabolites are increased together during breast tumor growth (Mackinnon et al., 1997a,b; Leach et al., 1998; Aboagye and Bhujwalla, 1999; Yeung et al., 2002; Gillies and Morse, 2005; Morse et al., 2005). ^{1}H MRS identifying the Cho peak with a SNR greater than 2 is consider to be highly sensitive and specific for the detection of malignancy (Mackinnon et al., 1997a,b; Bartella et al., 2007). Research has also shown that the Cho/Cr ratio can provide a distinction between benign and malignant disease with an accuracy of 96% (Mountford et al., 2004). The Cho peak in the ^{1}H spectrum could be used to distinguish between benign and malignant tumors with relatively high sensitivity and specificity (Mackinnon et al., 1997a,b; Mountford et al., 2004). The major contributors to the Cho peaks are PCho, GPCho, phosphoethanolamine (PEth) and taurine (Gribbestad et al., 1999; Beckonert et al., 2003). Often, results of ^{1}H MRSI of tumors demonstrate high Cho content, low levels of glucose and increased levels of lactate (Gribbestad et al., 1994; Cecil et al., 2001; Jagannathan et al., 2001; Morse and Gillies, 2005). Many authors suggested that the presence of Cho compounds appears to be an indicator for malignant breast tissue (Cheng et al., 1998; Perou et al., 2000). We summarize types of cancer metabolites identified by ^{1}H MR in Fig. 1. Cancer tissue metabolomics is a tool which is still new to the clinic,