Lipid Metabolism and Cancer
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Who will benefit from this information?
Those that will benefit from this talk will include cancer biologists and MR spectroscopists in basic research, as well as oncologists and radiologists in clinical research and diagnostics.

How was a problem determined?
Assessment of tumor lipid metabolites in situ for disease diagnosis and response to therapy requires the use of an in vivo spectroscopic technique.

Examples of how this issue has been addressed.
In addition to MRI, MRS is an ideal method for assessing tumor growth and response to therapeutic agents. Metabolic information can be obtained by monitoring tumor metabolites by magnetic resonance (MR) spectroscopy (MRS), or variations thereof, such as MR spectroscopic imaging (MRSI) or chemical shift imaging (CSI). Magnetic resonance spectroscopy (MRS) is an MR method that allows regional metabolite levels to be measured in tumors compared to surrounding non-tumor tissue, as well as assess therapeutic response. Important lipid and lipid-associated metabolites that can be assessed by 1H-MRS in tumors including choline (Cho)-containing metabolites and mobile lipids including unsaturated lipids. Mobile lipids are lipids (composed of triglycerides and cholesterol esters that accumulate in neutral lipid droplets) that are observable with the use of proton MRS in cells and tissues [1].

Specifically, MRS can be used to follow both mitotic activity and necrosis. Metabolites measured by MRS can provide information on choline-containing compounds (Choline and total choline compounds, tCho), which are involved in membrane synthesis or cell membrane turnover, and associated with cellular proliferation in tumors [2,3], and mobile lipids resulting from intracellular lipid droplets and necrosis [2]. Metabolite levels can be quantified as metabolite ratios or absolute concentrations, or analyzed using pattern recognition [2].

There is ample evidence of elevated choline-related metabolism in breast cancer, which has helped with disease diagnosis and therapeutic evaluations. For instance, variations in the concentrations of choline-based cellular metabolites have been found to be associated with malignant transformation in breast cancer tissues [4-7]. In a similar fashion, tCho has been found to be increased in malignant gliomas [8,9]. tCho is also associated with membrane degradation, and therefore processes that either promote cellular proliferation or induce cell death have an increased tCho MR spectral peak [10,11]. It has also been reported that elevated tCho/tCr ratios are commonly observed in grade IV GBM [12-14]. An increased tCho/tCr ratio is widely recognized to be associated with cellular proliferation and mitotic activity, and has been useful to differentiate between grade II and grade III tumors [14,15]. In addition to increased
tCho, increased mobile lipids are also found in brain cancers, aiding in the diagnosis of these tumors. It is well known that brain metastases and primary brain tumors such as gliomas have characteristic increased mobile lipid signals [16,17], as well as decreased tCho [16], compared to surrounding normal brain tissue. Mobile lipids (observed through their saturated methylene and methyl groups) are also monitored in brain tumors, and increased levels are thought to occur with increasing necrosis [18]. For instance, GBM all have high levels of mobile lipids [15,18,19], and these tumors also usually have elevated necrosis [12,13,20]. A multicenter patient study showed that mobile lipids occurred in 41% of high-grade tumors with higher amounts found in GBM [21]. In another study of grading for newly diagnosed gliomas, lipids were found to be significantly increased in GBM [22]. NMR-visible mobile lipid signals observed at ~1.3 and 0.9 ppm) appear to be an inherent feature of brain tumors, and have been considered an important factor in the grading astrocytomas [23-26]. It is thought that mobile lipids originate from degraded membrane phospholipids during membrane breakdown and necrosis [27,28], and may be composed of triglycerides and/or neutral lipids [29] and phosphatidylcholine [30]. It has also been observed that lipid resonances at 5.3 ppm, due to the presence of unsaturated acyl lipid hydrogens (-CH=CH-), are elevated in a rat glioma model [29]. Spectroscopic evidence has shown that visible lipids correspond to lipid droplets in necrotic and perinecrotic tumor regions in animal studies [26]. In a transgenic mouse model for hepatocellular carcinomas (HCC) an elevated lip5.3 peak in tumor-bearing animals was also detected [31]. A ratio of the Lip2.8 (bis-allyl acyl lipid hydrogens; -CH=CH-CH=CH-) to the lip5.3 spectral peak areas was used to measure the degree of unsaturation in unsaturated acyl containing phospholipids, and it was determined that during tumor formation there was an increase in oleyl-containing phospholipids [31]. Lipid levels have been previously demonstrated to be not only a marker of tumor malignancy, but also an indication of response to treatment [32, 33].

What will learners be able to do differently because of this information?

Attendees of the talk will be able to gain an understanding regarding the detection and role of choline-containing compounds and mobile lipids in specific cancers (e.g. breast cancer and brain tumors) as useful markers for diagnosis and assessing therapeutic response.

References:


