



Tissue Microenvironment MRI

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Conflicts of Interest

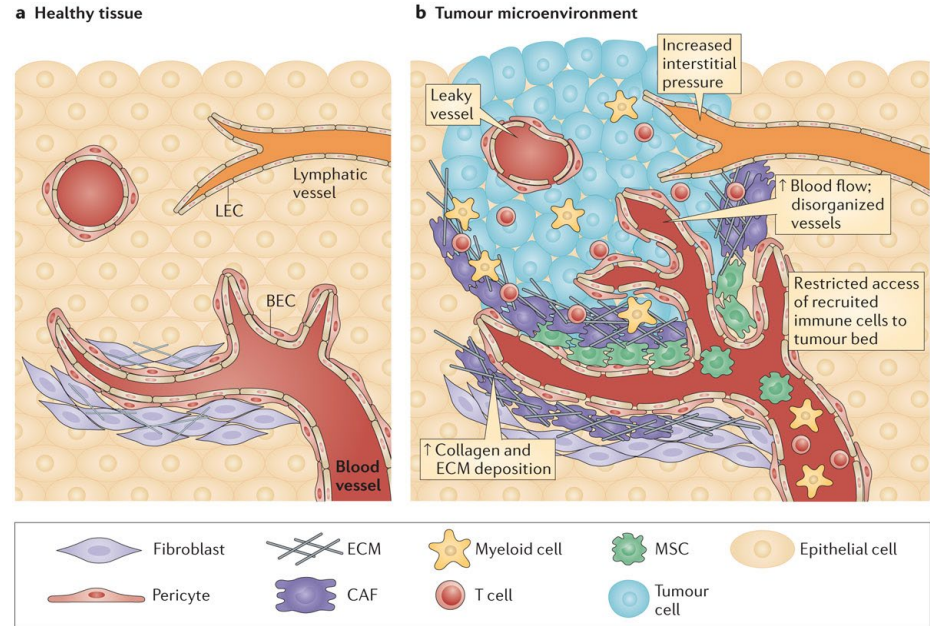
- None

Objectives

- Understand the motivations of investigating tumor microenvironment.
- Comprehend the non-invasive MRI methods (MRS & CEST) that can be used to probe tumor microenvironment information.
 - MRS – Magnetic Resonance Spectroscopy
 - CEST – Chemical Exchange Saturation Transfer

Motivations

- Tumor microenvironment differs significantly from that in normal tissues.
 - Poor vascular perfusion
 - Regional hypoxia
 - High glucose metabolism
 - Extracellular acidosis

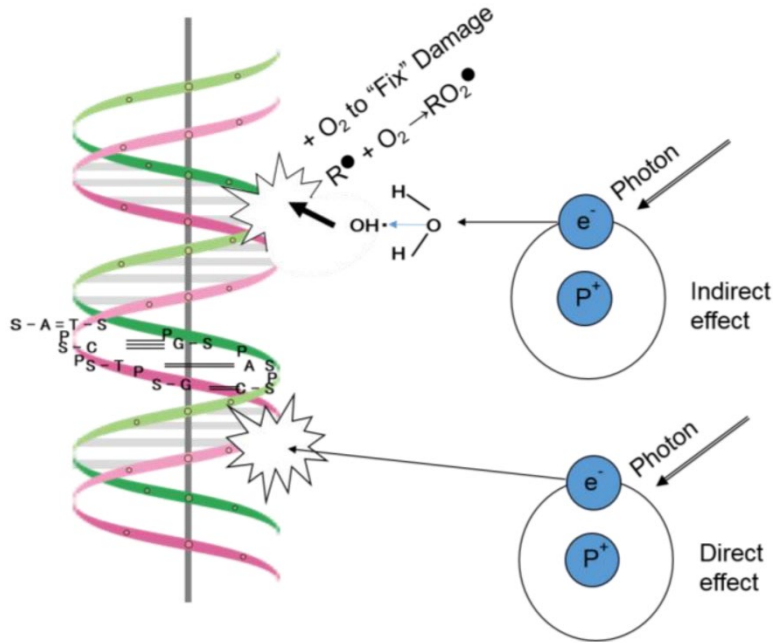


Turley S, et al. *Nat Rev Immunol* 15, 669–682 (2015).

Motivations

- In radiation oncology, the interest in tumor microenvironment comes from a desire to overcome the challenge of tumor radio-resistance.
- There are evidences that the hypoxic and acidic microenvironment in tumors significantly affect the progression and treatment of cancer.

Motivations



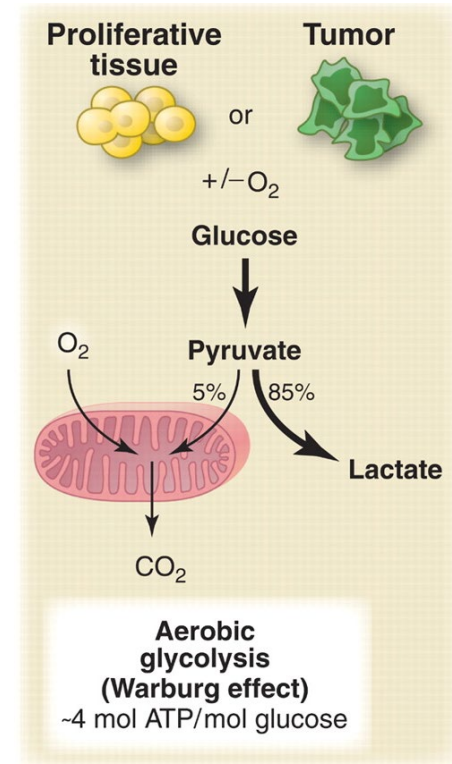
Ogawa Y. Cancers (Basel). 2016 Feb 25;8(3):28.

- Tumors often outgrow the blood supply and have hypoxia regions.
- Oxygen can enhance the radiation induced damage.
- At $pO_2 < 10$ mm Hg, tumors become resistant to radiation therapy.

Motivations

- Cancer cells generate large amount of lactate regardless of the availability of oxygen.
- This is often referred to as aerobic glycolysis.
- It leads to a significant increase in production and release of acidic metabolites into the extracellular space which decreases its pH.
- Acidic microenvironment is associated with increased metastatic potential and resistance to chemo- and radiotherapy.

Vander Heiden MG, et al. *Science*. 2009 May 22;324(5930):1029-33.



MRI of Tumor Microenvironment

- Obtaining tumor microenvironment information can improve our knowledge about cancer and potentially provide a better treatment.
- MRI provides a non-invasive way to probe tumor microenvironment.

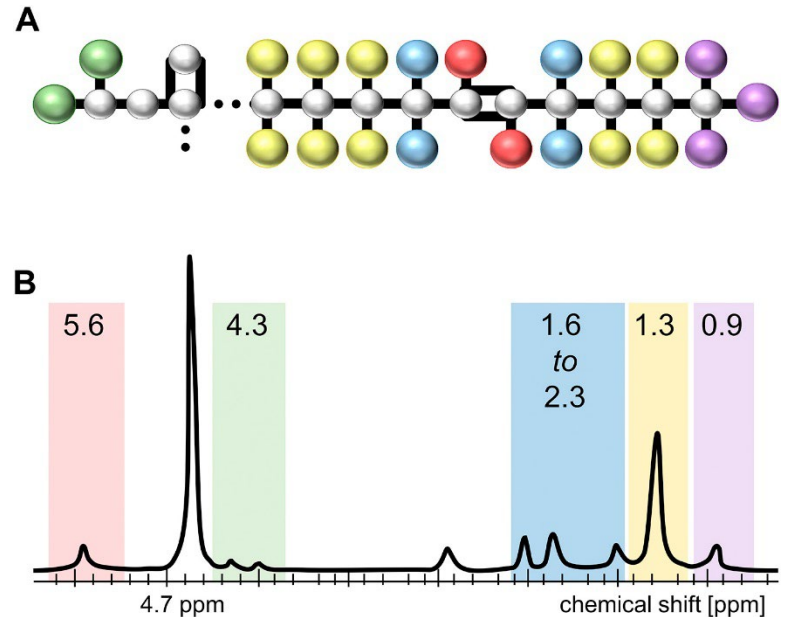


MRI of Tumor Microenvironment

- Tumor hypoxia can be evaluated using blood oxygen level dependent (BOLD) MRI, tissue oxygen level dependent (TOLD) MRI, oxygen-enhanced (OE) MRI, and dynamic contrast enhanced (DCE) MRI.
- Changes in metabolites such as **N-Acetyl aspartate (NAA), Choline (Cho) and lactate** can be tracked using MR spectroscopy (MRS)
- Tumor acidosis can be evaluated using chemical exchange saturation transfer (CEST) MRI.
- CEST MRI is also able to provide information regarding glutamate, creatine and lactate.

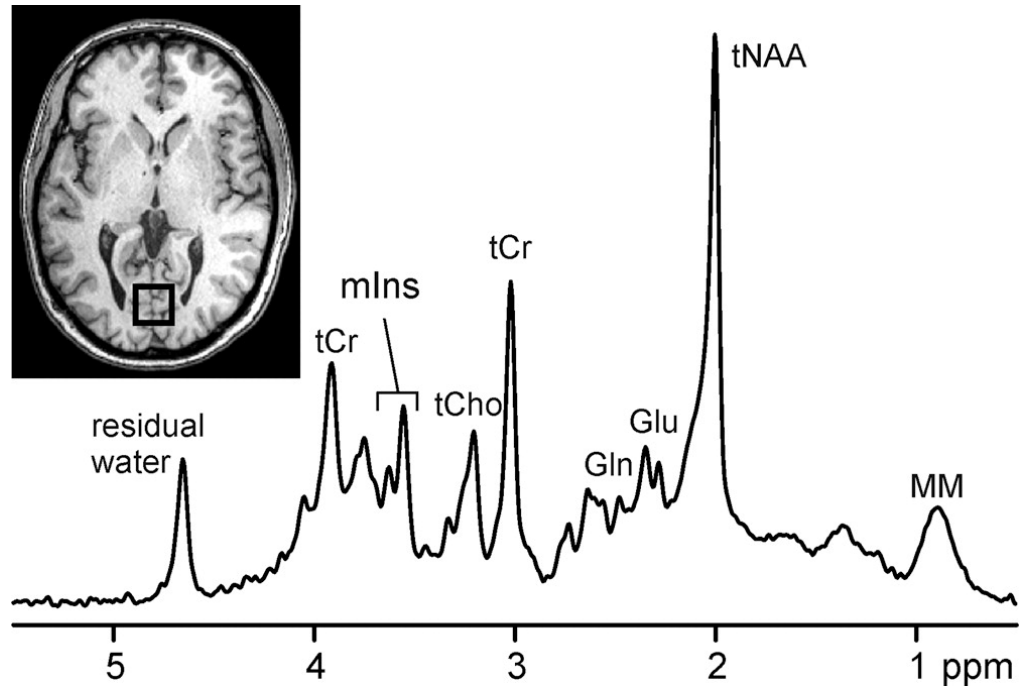
MR Spectroscopy

- MR spectroscopy is based on the chemical shift effect.
- It utilizes the fact that nuclei in different molecules experience a slightly different magnetic field, causing them to resonate at slightly different frequencies.



Munz E, Jakob PM, Borisjuk L. *Biochimie*. 2016 Nov;130:97-108.

MR Spectroscopy



¹H MR spectrum acquired at 3.0 T from a volume of interest in occipital lobe.

tNAA = total *N*-acetylaspartate (NAA),
tCr = total creatine (Cr), *t*
Cho = total choline,
Glu = glutamate,
Gln = glutamine,
mIns = *myo*-inositol,
MM = macromolecules.

Radiology

Öz G. Published Online: March 01, 2014
<https://doi.org/10.1148/radiol.13130531>

MR Spectroscopy

- Metabolites of interest:

- ❖ N-Acetyl Aspartate (NAA)

- NAA is widely interpreted as the loss, dysfunction, or displacement of normal neuronal tissue.

- ❖ Choline

- Choline comes from several Choline containing compounds which are involved in membrane synthesis and degradation.**

- ❖ Lactate

- Increase in lactate is likely the result of aerobic glycolysis.

MR Spectroscopy and CEST MRI

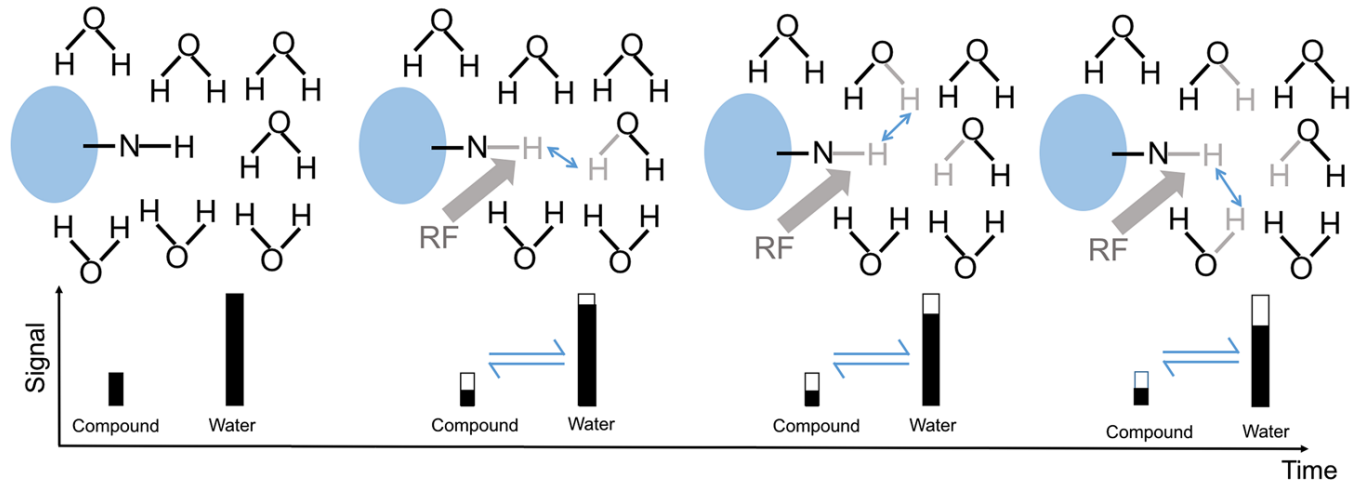
- MR spectroscopy has a few limitations
 - MRS has low sensitivity due to low concentration of metabolites.
 - MRS uses long acquisition time to achieve sufficient SNR
 - MRS has limited spatial coverage and resolution.
- CEST MRI was developed to overcome the low concentration limitation of MRS.
- CEST stands for chemical exchange saturation transfer. It utilizes the chemical property that protons in certain metabolites can exchange with those in water.

Chemical Exchange Saturation Transfer (CEST)

- In MR, saturation is a temporary state in which tissue shows no net magnetization.
- CEST MRI saturates signal from metabolites under investigation, instead of that from water.
- The saturated protons in metabolites then exchange with those fresh proton in water.
- MR signal from water decreases due to this exchange of protons, creating a contrast depending on the proton exchange rate.

Chemical Exchange Saturation Transfer (CEST)

- Illustration of CEST MRI



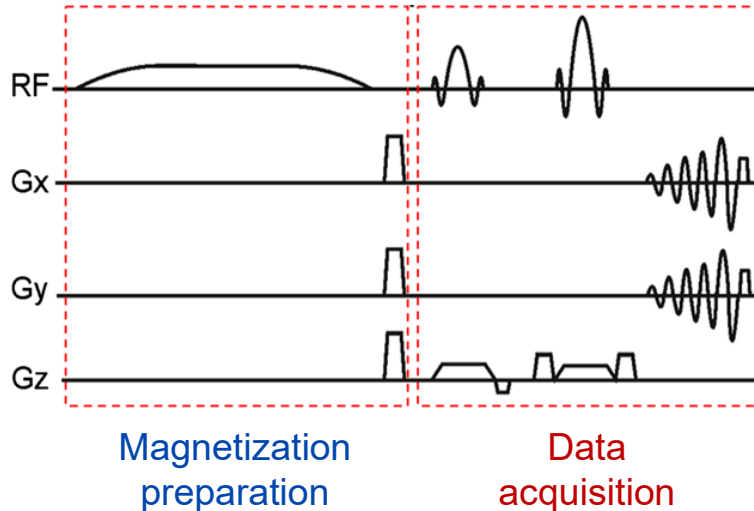
Wu B, Warnock G, Zaiss M, et al. *EJNMMI Phys.* 2016;3(1):19.

Chemical Exchange Saturation Transfer (CEST)

- CEST MRI can significantly increase the metabolite detection sensitivity through the continuous transfer of saturated protons.
- Continuous transfer is achieved using repeated saturation of protons in metabolites, resulting in a buildup of saturation in water.
- Increase in sensitivity can be one to three orders of magnitude.
- CEST MRI data acquisition is the same as other imaging techniques which makes it possible to use MRI sequences with high SNR and short scan time.

Chemical Exchange Saturation Transfer (CEST)

- CEST MRI implementation includes two components: magnetization preparation (MP) and data acquisition (DA).



Magnetization preparation:

- Can be achieved through RF saturation
- Determine image contrast

Data acquisition:

- Determine image quality
- Affect scan time

Wu B, Warnock G, Zaiss M, et al. *EJNMMI Phys.* 2016;3(1):19.

Chemical Exchange Saturation Transfer (CEST)

- CEST allows indirect detection of metabolites via the reduction of the water signal. The simplest form of CEST MRI only provides qualitative evaluation.
- Quantification requires additional effort as it is complicated by a few competing effects, e.g., magnetization transfer contrast (MTC) and direct water saturation (DS).
 - MTC and CEST share some similarities but are not exactly the same. MTC is based on exchange of energy through cross-relaxation, whereas CEST is based on exchange of protons.
 - DS is due to imperfect saturation RF, which inevitably saturate water magnetization to a certain degree.

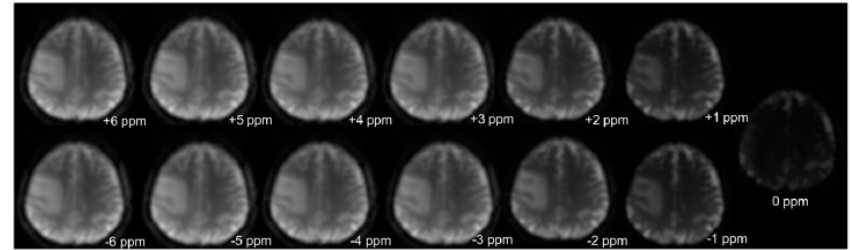
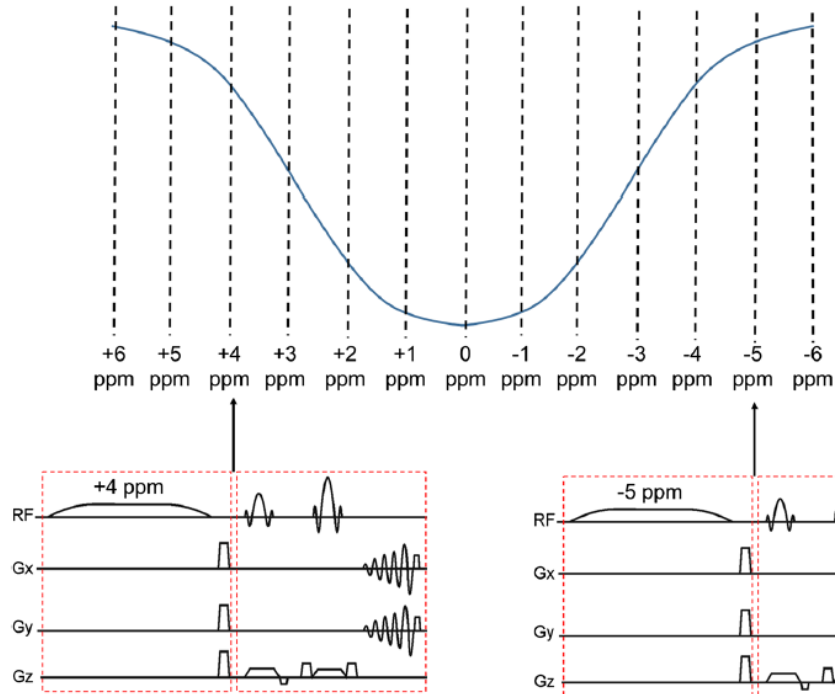
Chemical Exchange Saturation Transfer (CEST)

- To eliminate MTC and DS effects, CEST MRI acquires two sets of images with the saturation pulse placed at the target spectral location as well as the opposite spectral location with regarding to water, assuming MTC and DS are symmetric about the water frequency.

$$MTR_{asym}(+\tau) = \frac{S_{-\tau} - S_{+\tau}}{S_0}$$

- In reality, the practice is to sample the spectral region and obtain a curve of MTR_{asym} , instead of just a single point at the target spectral location.

Chemical Exchange Saturation Transfer (CEST)

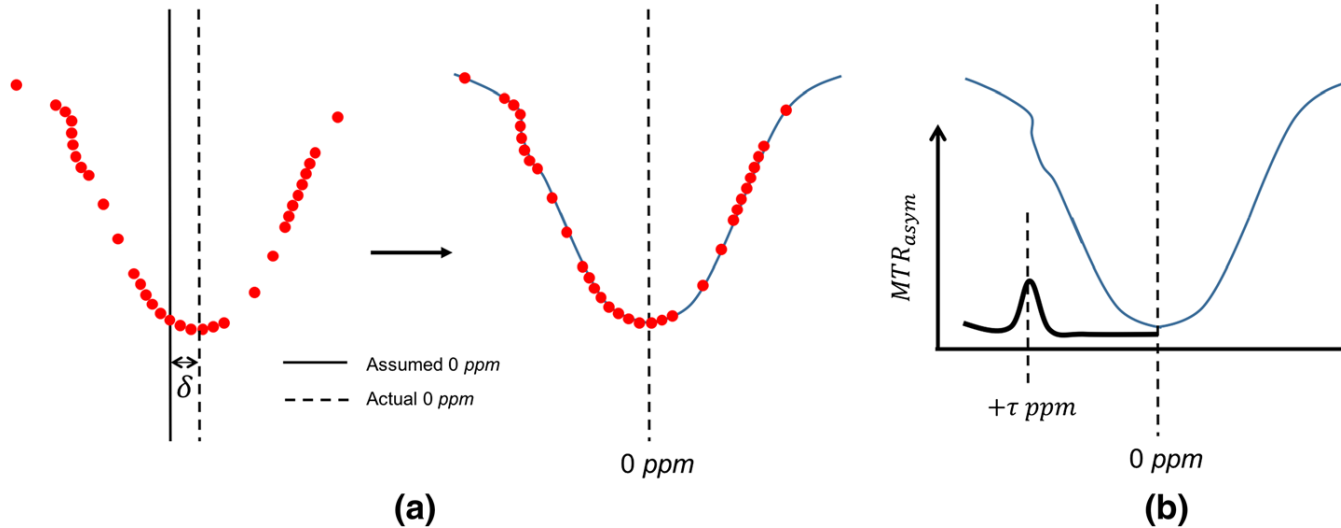


Wu B, Warnock G, Zaiss M, et al. *EJNMMI Phys.* 2016;3(1):19.

Chemical Exchange Saturation Transfer (CEST)

- Previously, we assume MTC and DS are symmetric about the water frequency.
- This assumption no longer holds due to magnetic field inhomogeneity.
- To overcome this challenge, it often densely samples the spectral regions around the water and $\pm\tau$.

Chemical Exchange Saturation Transfer (CEST) MRI



a). Illustration of spectral sampling for CEST MRI.

b). The derived MTR_{asym} curve.

Wu B, Warnock G, Zaiss M, et al. *EJNMMI Phys.* 2016;3(1):19.

Chemical Exchange Saturation Transfer (CEST)

- CEST allows us to obtain information regarding a metabolite if it has exchangeable protons and its MR frequency is not overlapping with other metabolites.
- CEST MRI typically involves exchangeable groups of $-NH$, $-NH_2$, and $-OH$, corresponding to chemical shifts of $\sim 3.5\text{ppm}$, $\sim 1.8\text{-}3.0\text{ppm}$, and $\sim 0.5\text{-}1.5\text{ppm}$, respectively.
 - CEST of amide protons ($-NH$)
 - CEST of amine protons ($-NH_2$)
 - CEST of hydroxyl protons ($-OH$)

Imaging tumor acidosis using CEST

- CEST MRI can be used to evaluate acidosis.
- Using CEST MRI to measure pH is based on the property that proton exchange rate depends on many factors including pH.
- Lower pH \longrightarrow Lower proton exchange rate
- Amide protons contained in endogenous proteins and peptides have shown dependence of CEST contrast on pH.
- Amide CEST, **also known as amide proton transfer (APT) imaging**, has demonstrated its ability to measure pH change during ischemia.

Imaging tumor acidosis using CEST

- Amide CEST was also applied to image tumor acidosis. But there are a few limitations that need to be addressed.
 - ❖ APT weight MRI can't distinguish between the intra- and extra-cellular contribution of amide protons.
 - ❖ The concentration of amide protons may vary in tumors, making it challenging to obtain accurate pH values.

Imaging tumor acidosis using CEST

- To eliminate the concentration term, Bartha's group proposed an amine/amide concentration-independent detection method (AACID) based on the ratio of CEST effect originating at 2.75 ppm for amine groups and at 3.5 ppm for amide groups.
- Even though AACID CEST is predominantly weighted to the intracellular space, it does have contributions from both intra- and extra-cellular compartments.

Imaging tumor acidosis using CEST

- To provide a net quantification of extracellular pH, exogenous DIACEST agents containing exchanging protons in diamagnetic molecules are often used.
- These agents remains in the extracellular space and do not enter the intracellular compartment following the extravasation from the leaky tumor vasculature.
- Iodinated or X-ray contrast agents gained attention due to their safety profile, enough chemical shift separation from the water to be selectively saturated, and concentration-independent pH measurement through a ratiometric approach.

Imaging tumor acidosis using CEST

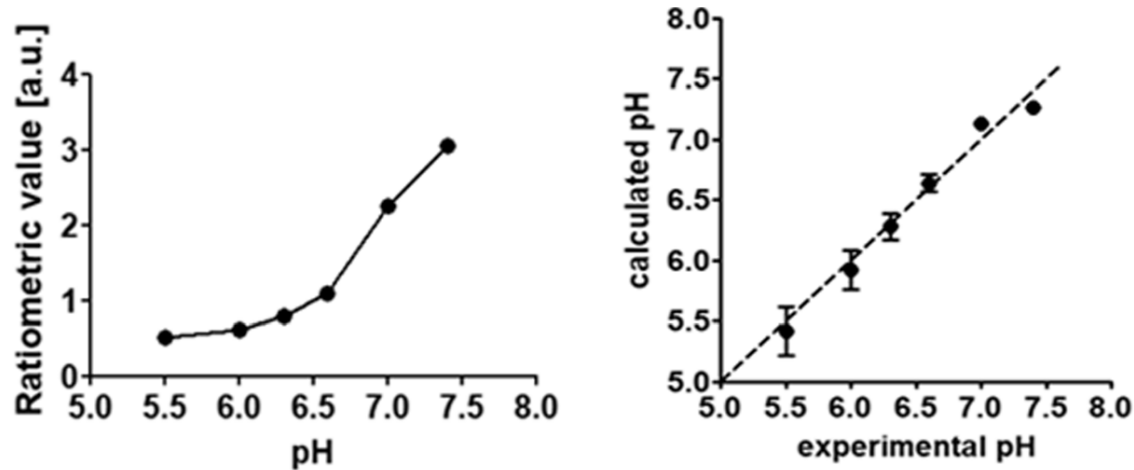
- Iopamidol was the first CT agent investigated as a CEST contrast agent, which has two amide groups resonating at 4.2 and 5.5 ppm.



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Imaging tumor acidosis using CEST

- With the proper ratiometric approach, it is possible to establish a calibration curve and achieve a good pH measurement accuracy in the range of 5.5–7.9.



Anemone A, et al. *Cancer and Metastasis Reviews* (2019) 38:25–49

Imaging tumor acidosis using CEST

- CEST MRI provides a valuable tool for monitoring therapeutic effect of anticancer therapies.
- In an animal study, breast tumors treated with Dichloroacetate (DCA) showed a marked increase in pH 3 days after DCA administration. But after 15 days, the extracellular pH returned to more acidic values, indicating onset of resistance.

Imaging tumor acidosis using CEST

- Besides tumor acidosis imaging, CEST MRI can provide information about other tumor metabolites.
- Three commonly detected tumor metabolites by CEST MRI are glutamate, creatine and lactate.
- The specificity of detecting individual metabolites with CEST MRI, however, is compromised by the fact that most metabolites have overlapping MR frequencies.

Conclusion

- In summary, MR spectroscopy and CEST MRI provide powerful tools to investigate tumor microenvironment.
- Although these tools demonstrate great potential, they are not mature and still require significant developmental efforts.
- Being familiar with these tools allows medical physicists to understand the capabilities we have at this moment in studying tumor micro-environment, to engaging interests in advancing these technologies, and to assist clinical implementation to improve cancer treatment.

Thank you