Emerging Tumor Resistance and Sodium-Diffusion MRI

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Introduction

MRI is an important tool in cancer detection and treatment. The high magnetic field of 21.1 T dramatically improves our capability to perform *in vivo* MRI. It is known that tumor progression, especially after therapeutic intervention, may dramatically change tumor resistance to therapies. Consequently, a much higher concentration of a chemotherapeutic drug is required to achieve the same response; otherwise, the chemotherapy is unlikely to be successful. Sodium concentration and diffusion are usually higher in brain tumors than in a normal brain and our studies reveal an attractive correlation between sodium/diffusion concentrations and glioma drug resistance (1, 2). The hypothesis in this study is that the increased tumor resistance is determined by a more efficient energy metabolism in such cells which can be detected by the corresponding decrease of glioma sodium concentration and diffusion.

Experimental

Sodium MRI in this study was performed using advanced *in vivo* sodium MRI capability at 21.1T. Complete sodium signal from rat head was detected by back-projection MRI with a short readout time of 2.2 ms. Diffusion MRI pulse sequence had a special shape of the diffusion gradients and the back projection acquisition. Both measures were selected to allow for motion compensations. 9L rat glioma model, was used in this study, sodium MRI was done by 3D pulse sequence with repetition time of 100 ms to avoid saturation of the MR signal which required a total scan time of 27 min. Resolution of sodium images was 0.5 mm. Diffusion MRI was performed by 2D pulse sequence with a slice thickness of 0.7 mm, the rest of parameters are often used by others.

Results and Discussion

Sodium concentration in glioma at ~ 11 days after tumor implantation is given at **Figure 1**. The difference is very noticeable without processing. The naïve 9L cells generated tumor with a high tumor sodium concentration relative to the normal brain, while the resistant glioma line showed a much lower sodium contrast pattern.

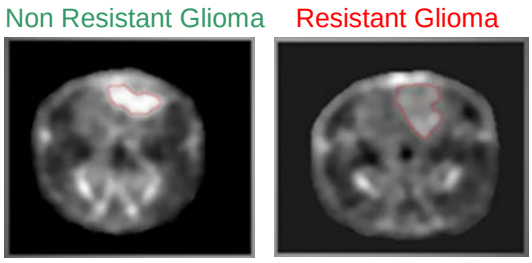

Figure 1. Sodium MRI of non-treated rat glioma originated from 9L cells having different chemotherapeutic resistances to carmustine. Sodium MRI with resolution 0.5x0.5x0.5 mm demonstrate energy deficit in non-resistant glioma (left) and superior prognosis for chemotherapy.

The most resistant glioma has the lowest tumor sodium concentration and the lowest diffusion values. The question arises whether sodium in tumors can be related to energy metabolism in cancer cells. The Na/K pump is the major extrusion mechanism of sodium out of the intracellular space, and it may consume up to ~ 60% of total ATP to perform this task. It is also known that increased intracellular Na content leads to an additional activation of the Na/K pump and to a higher consumption rate of ATP. Thus, increased sodium can be an indicator of energy deficit in cancer cells and it can be detectable by MRI. Naïve cells (less resistant) have the largest deficit of energy and such cells are the most vulnerable to therapeutic interventions. The absence of an energy deficit in resistant tumor cells is an advantage to such cells in their fight against drug interventions.

Conclusions

The results of this study demonstrate that emerging tumor resistance can be detected by sodium and diffusion MRI. The evaluation can be done noninvasively and prior to therapy. It is important to note here that we are speaking not only about resistance to carmustine. It is expected that an energy-based MRI indicator of tumor resistance can be predictive for a range of different therapeutic interventions. The prompt evaluation of tumor resistance may help to formulate individual treatment and avoid unsuccessful therapies.

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References

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