Mapping tumor microenvironment using photoacoustic imaging powered by functional nanoparticles

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Background, Motivation and Objective

The tumor microenvironment (TME) is characterized by a variety of aberrant physiological properties including increased acidity (acidosis), depleted oxygen levels (hypoxia), and increased potassium ion (K^+) concentrations. Acidosis and hypoxia are consequences of increased fermentative metabolism and poor perfusion in a tumor, while increased K^+ is due to the development of a necrotic core from the rapid expansion of the tumor. It is evident that successful measurements of the TME can contribute to clinical management of cancer and basic science research. We herein report on the development of multi-wavelength photoacoustic imaging (PAI) powered by a multi-functional nanoprobe for mapping the levels of pH, oxygen, and K^+ and their changes in the TME.

Statement of Contribution/Methods

Three separate optical nanoprobes for sensing pH, oxygen, and K^+ were synthesized, all developed upon hydrogel based nanoparticles. The pH and oxygen indicators were encapsulated using a similar polyacrylamide matrix to form nanoparticles with surface modification for tumor targeting. The K^+ nanoprobe is similarly protected by use of a Pluronic-based micelle that encapsulates the sensing components of the nanoparticle. Facilitated by the multi-wavelength PAI plus spectral unmixing technique, these three chemical properties in the entire tumor can be quantitatively evaluated with high sensitivity and spatial resolution, also in a non-invasive manner.

Results/Discussion

The phantom and *in vitro* experiments validated the accuracy and robustness of the pH, oxygen, and K^+ imaging technology; while the later experiments on a mouse cancer model demonstrated its good performance *in vivo*. The statistical analysis shows that the average pH and oxygen levels quantified in tumors were lower than those in normal tissue, which was verified by relevant control measurements. Using the K^+ nanoprobe, the K^+ concentration in a solid tumor can also be quantitatively mapped, which will also be presented in this paper. The imaging technology reported here holds potential to be developed into a new and powerful tool for real-time evaluation and repeated monitoring of the TME.

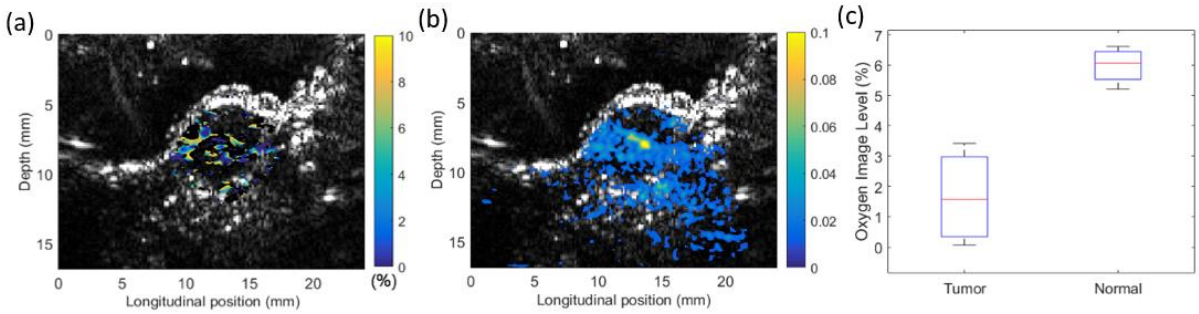

Figure 1. Photoacoustic lifetime (PALT) based oxygen images of *in vivo* tumor and the statistical results. (a) Mouse tumor PALT oxygen image. (b) PA images showing the distribution of the oxygen nanoprobe in the tumor region. (c) The boxplot showing the oxygen levels in *in vivo* tumors (n = 4) vs the oxygen levels in normal tissues (n=4).