***In vivo* extracellular pH mapping of tumors using electron paramagnetic resonance imaging**

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**Abstract:** A method of three-dimensional extracellular pH mapping using electron paramagnetic resonance (EPR) imaging is reported. EPR is a magnetic resonance based technique that detects unpaired electrons and can measure pH with an appropriate pH-sensitive spin probe. The herein proposed method of pH mapping is aimed at visualizing regional changes in the metabolism of cancer tumors non-invasively. To verify the method of pH mapping using EPR at 750 MHz, pH in solution samples was visualized. The functional resolution of pH detection was less than 0.1 pH units and the accuracy was less than 0.05 pH units. Three-dimensional extracellular pH mapping was performed on mouse tumor-bearing legs in a 7.5 min acquisition. Extracellular pH mapping showed progressive acidification in tumor tissues at 5 and 8 days after murine squamous cell carcinoma (SCC VII) cells were subcutaneously injected into the right hind leg. Moreover, EPR pH mapping in mouse tumor xenografts with human-derived pancreatic ductal adenocarcinoma cells demonstrated different acidification patterns in three types of tumor cells: MIA PaCa-2, SU.86.86, and Hs766t. Our *in vivo* results suggest that EPR-based pH mapping should be applicable to not only tumor model animals but also other disease models that show a change in metabolism and pH.

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