Relationship between tumor microenvironment and oxidative stress: in vivo EPR studies

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Study Goal: Specific patterns of chemical tumor microenvironment (cTME) parameters associated with cancer metabolism, namely high reducing capacity, hypoxia (pO2) and extracellular acidosis (pHe), expose both cancer and non-transformed cells to elevated levels of reactive oxygen species (ROS). The goal of this work was an in vivo profiling of cTME using in vivo electron paramagnetic resonance (EPR) that provides insight into the mechanisms of tumorigenesis and specific roles of ROS.

Abstract: EPR-based spectroscopy and imaging were used for cTME profiling in mouse models of various cancers, including in vivo assessment of tissue redox, GSH, pO2, pHe, and concentration of interstitial phosphate (Pi) using functional paramagnetic probes. cTME profiling were performed as tumors progressed to malignancy and during application of metabolically-active drugs. A deviation of the cTME parameters in tumors from those in normal mammary tissue during malignant progression, initially characterized by an increase in Pi level followed by a decrease in pHe and then pO2, was observed. Interstitial Pi has been identified as a potential prognostic factor in tumorigenesis. EPR profiling cTME in human tumor xenografts showed discriminative difference between metastatic and non-metastatic tumors in interstitial Pi and pHe. Strong negative correlation in normal mammary glands vs. no correlation in breast tumors were found between interstitial pO2 and Pi measured in PyMT mice in vivo, therefore supporting tumor reliance on glycolysis independent of oxygen availability. The opposite effects of glucose oxidase/glucose (pO2 decrease and [Pi] increase) and 2,4-dinitrophenol (pO2 increase and [Pi] decrease) measured in vivo indicate a relationship between these cTME parameters and metabolic alterations. Normalizing cTME parameters (e.g., increase of pHe upon phosphate buffer treatment; increase of pHe, decrease reducing capacity and GSH content upon GM-CSF treatment, etc.) correlated with partial inhibition of tumor growth.

Conclusion: In vivo EPR profiling of cTME provides a tool for assessment of cancer progression, aggressiveness, metastatic potential and efficacy of the anticancer therapy.

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