



Hokkaido University
Leading Graduate School
Veterinary Science for One Health

The 14th Leading Special Lecture

Janus-Faced Tumor Microenvironment: from multifunctional EPR tumor tissue profiling towards diagnostics and therapy

Dr. Valery V. Khrantsov

Associate Professor

**The Department of Internal Medicine,
The Ohio State University**

Date: July 28, 2014, 16 : 00~17 : 00

**Venue: Lecture Room 3, Graduate School of Veterinary
Medicine, Hokkaido University**

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Tumor microenvironment (TME) is now widely recognized as a major contributor to cancer aggression and treatment resistance and as a potential target for therapeutic intervention. Among the TME parameters playing important roles in tumor pathophysiology, hypoxia is considered to be a consequence of imbalanced angiogenesis and is associated with changes in metabolism including higher dependence on glycolysis resulting in extracellular tissue acidosis and elevated levels of inorganic phosphate (Pi). Both hypoxia and acidosis affect tissue redox status and its key intracellular component, glutathione (GSH). Numerous publications support that these local TME conditions select for outgrowth of cells with appropriate phenotypes, which can reflect underlying genetics. We hypothesized Janus-faced properties of TME¹, proposing that specific patterns of tissue oxygenation, extracellular pH (pH_e), Pi, redox and GSH homeostasis act to utilize an orchestrated mechanism to promote cancer cell survival while at the same time being highly toxic and mutagenic for normal cells. Therefore, noninvasive *in vivo* assessment of these parameters provides important knowledge for advanced TME-targeted anticancer therapies. To this aim we developed a set of unique paramagnetic probes for multifunctional TME profiling using electron paramagnetic resonance (EPR)- and nuclear magnetic resonance (NMR)-based techniques. Specifically we utilize trityl probes for concurrent *in vivo* monitoring of pO_2 , pH_e and $Pi^{2,3}$, and nitroxide probes^{4,5} for pH, GSH and reducing capacity measurements, using *in vivo* L-band EPR spectroscopy and MRI-based functional proton-electron double-resonance imaging (PEDRI)⁵. The *in vivo* studies performed in breast tumor-bearing mice show that all the measured parameters, pO_2 , pH, Pi, redox and GSH, tend to deviate from the pattern characteristic of normal tissue upon progression to malignancy. Normalizing the TME parameters may decrease the selection pressure for malignant phenotypes, therefore providing a tool for TME-targeted anticancer therapy. A capacity of specific TME pattern to be used as a prognostic factor in tumorigenesis and the approaches for normalizing chemical tumor microenvironment for anticancer TME-targeted therapeutic interventions will be discussed.