In vivo imaging of tumor physiological, metabolic and redox changes in response to the anti-angiogenic agent sunitinib: Longitudinal assessment to indentify the transient vascular re-normalization.

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Target audience:

Clinicians and researchers of oncology

Purpose:

Tumor micro-environment is characterized by a redox status which is highly reducing, low in pH, and hypoxia. Anti-angiogenic therapies of solid tumors frequently proceed in two steps: transient normalization of structurally and functionally aberrant tumor blood vessels with increased blood perfusion, followed by pruning the tumor blood vessels and resultant cessation of nutrients and oxygen delivery required for tumor growth. Conventional anatomic or vascular imaging is impractical or insufficient to distinguish the two steps of tumor response to anti-angiogenic therapies. Herein, we investigated if non-invasive imaging of tumor redox state and energy metabolism can serve as early surrogate markers for the anti-angiogenic drug induced transient vascular normalization process.

Methods:

C3H mice subcutaneously bearing squamous cell carcinoma (SCCVII) were daily treated with multi-tyrosine kinase inhibitor sunitinib (50 mg/kg) when tumor size becomes 1 cm. Redox images were obtained pre- and post treatment by FLASH sequence using 7T MRI and carbamoyl-PROXYL as a redox sensitive contrast agent. Metabolic images were obtained by chemical shift imaging using 4.7T MRI and hyperpolarized [1-^{13}C] pyruvate.

Results:

Daily treatment of SCCVII tumor bearing mouse with sunitinib resulted in rapid decrease in tumor microvessel density and suppression of tumor growth. Tumor pO_2 imaging by electron paramagnetic resonance imaging (EPRI) showed transient increase in tumor oxygenation 2-4 days following sunitinib treatment, implying improved tumor perfusion (1), which is further supported by increased Gd-DTPA uptake in dynamic contrast enhanced (DCE) MRI study. During this time window of vascular normalization, magnetic resonance imaging (MRI) of the redox status using an exogenously administrated nitroxide probe and hyperpolarized ^{13}C MRI of energy metabolic flux of pyruvate/lactate couple revealed oxidative shift in tumor redox status.

Conclusion:

Imaging of redox status governed by redox sensitive metabolic couples in tumors can serve as non-invasive surrogate makers for the vascular normalization window. Multimodal imaging approach of tumor physiological, metabolic and redox changes is useful to distinguish different stages in the course of anti-angiogenic treatment.

Reference:

Matsumoto S. et al. Antiangiogenic agent sunitinib transiently increases tumor oxygenation and suppresses cycling hypoxia. Cancer Res. 2011;71:6350-9.

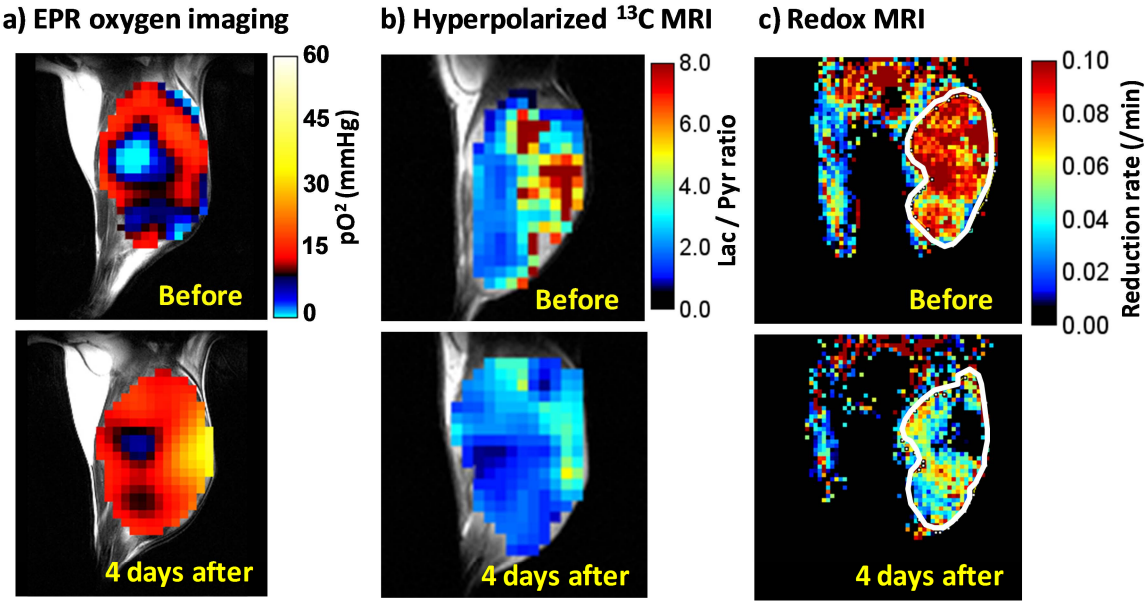

Fig.1 Anti-angiogenic treatment with sunitinib induced transient shift in tumor oxygenation by EPR imaging, energy metabolism by hyperpolarized ^{13}C MRI of pyruvate metabolism, and redox state by MRI with nitroxide probe in SCCVII tumor.