Structural-Functional Imaging of Renal Tumor Xenografts in Chicken Embryo via Ultrasound Localization Microscopy

Matthew R. Lowerison[1,2,3], Chengwu Huang[3], Shigao Chen[3], Pengfei Song[1,2,3]
[1] Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL
[2] Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL
[3] Department of Radiology, Mayo Clinic College of Medicine and Science, Mayo Clinic, Rochester, MN

Background, Motivation and Objective

Contrast-enhanced ultrasound (CEUS) is a widely available and cost-effective imaging modality that offers vascular perfusion imaging with clinically relevant penetration depths. Recent imaging technologies have allowed for the localization and tracking of individual contrast microbubbles *in vivo*, ultrasound localization microscopy (ULM), permitting the reconstruction of super-resolved images that reveal tissue microvascular structure. This revolutionary technological advance can be potentially leveraged to provide noninvasive quantitative measures of tissue hemodynamics and hypoxic status. In this presentation we demonstrate a series of microbubble data processing methods that can reveal the vascular supply of *in vivo* tumor tissues to identify regions of hypoxia non-invasively, providing an imaging biomarker of tissue oxygenation status. This technique was applied to evaluate the microvascular structure, vascular perfusion, and oxygenation status of a renal cell carcinoma xenograft model grown in the chorioallantoic membrane (CAM) of chicken embryos.

Statement of Contribution/Methods

Ultrasound images were acquired from six contrast microbubble injected CAMs using 5 angle plane-wave compounding with a Vantage 256 system (L35-16vX transducer), for a total acquisition length of 3600 frames (7.2 s). Super resolution microbubble localization and velocity maps were reconstructed at a 5 µm axial/lateral resolution. Structural-functional analysis was performed on this dataset, yielding morphometric and perfusion-based quantification of tumor vascular supply. These results were validated with gold-standard fluorescent histology quantifications of microvascular density and hypoxia.

Results/Discussion

We observed intratumoral structural-functional heterogeneity within this tumor cohort. Histological microvascular density was significantly correlated ($p < 0.05$) to ULM measures of vascular density ($R = 0.9$) and intervessel distance ($R = -0.92$). We produced 'oxygen delivery' maps that were moderately, but significantly, correlated to hypoxyprobe signal ($R = -0.56$, $p < 0.01$). ULM, by providing non-invasive *in vivo* microvascular structural and functional information, has the potential to be a crucial clinical imaging modality for the diagnosis and therapy monitoring of solid tumors.

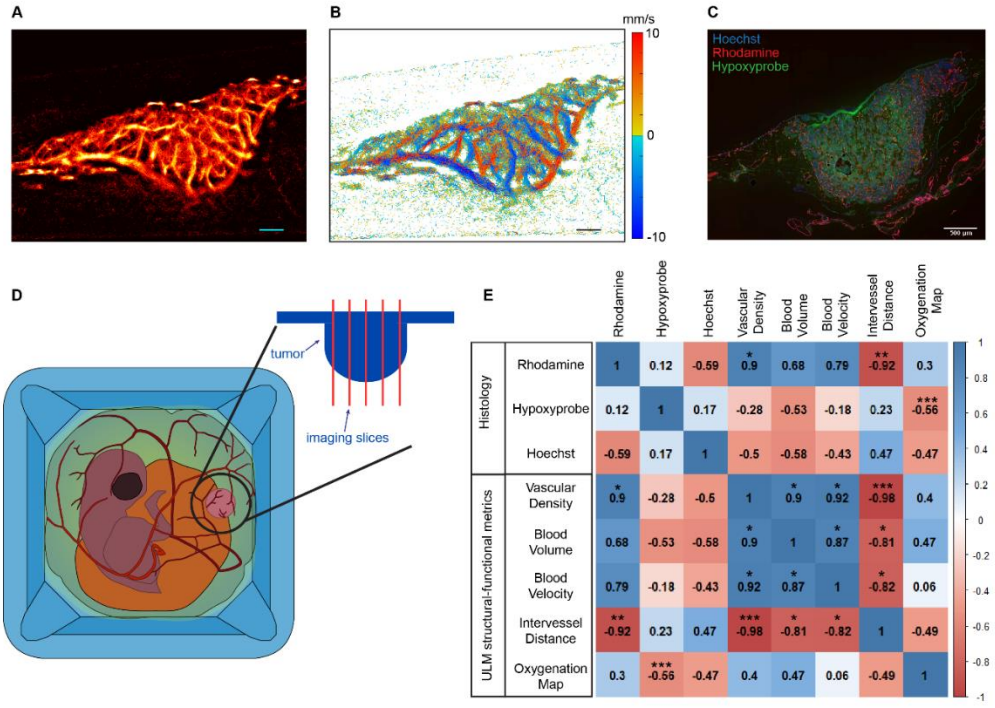

Fig 1. A) Representative ULM microbubble localization image acquired from CAM tumor xenograft model. B) Blood flow velocity map reveals fast blood flow in periphery, with low velocity microvascular flow in tumor center. C) Histology confirmed high degree of intratumoral vascularization and regions of hypoxia. D) Diagrammatic example of volumetric tumor imaging protocol. E) Correlogram of ULM and histological measurements Scalebars are 500 µm in length.
(* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).