Author's response to reviews

Title: Collagen reorganization at the tumor-stromal interface facilitates local invasion

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Author's response to reviews:

Dear Editor,

We are submitting our manuscript entitled "Collagen reorganization at the tumor-stromal interface facilitates local invasion" by Paolo P. Provenzano, Kevin W. Eliceiri, Jay M. Campbell, David R. Inman, John G. White Patricia J. Keely for possible publication as an article in BMC Cancer. We have made the necessary changes to meet the formatting requirements of BMC Cancer.

Our work provides unique insight into epithelial/tumor-stromal interactions using novel nonlinear optical imaging techniques. Most importantly we identify specific tumor associated collagen structures and demonstrate the first in vivo examination of local invasion in breast carcinoma. By utilizing both laser-scanning multiphoton and second harmonic microscopy, we were able to obtain three-dimensional information from normal glands as well as characterize a mouse model for increased breast tissue density. Breast tissue density is a major risk factor for developing breast carcinoma (as highlighted recently in Science: Couzin J, Breast Cancer: Dissecting a Hidden Breast Cancer Risk, Science 9 September 2005: 1664-1666) and one primary reason it is poorly understood has been the lack of an adequate animal model systems for studying the effects of increased collagen density in vivo.

In this work we defined three "Tumor-Associated Collagen Signatures" (TACS) that provide novel hallmarks to locate and characterize tumors. Of particular significance is the fact that we were able to image local invasion that was facilitated by radially aligned collagen fibers perpendicular to the tumor boundary; demonstrating the first in vivo examination of local invasion of endogenous tumor cells. This represents a significant step forward from in vitro studies that show matrix alignment during invasion within three-dimensional matrices. Hence, our work should serve to elucidate mechanisms of tumor formation and progression in vivo, as well as characterize human tumor biopsies. For instance, the identification of these signatures has important diagnostic implications for the future identification and classification of tumors in human pathology.

Overall, we believe that this manuscript, which contains novel biological information and utilizes innovative nonlinear imaging modalities, will be of great interest to researchers and clinicians in fields ranging from oncology and pathology to developmental and cancer cell biology to biophysics and engineering. Therefore, this manuscript is of broad interest to cancer researchers and as such will be valuable to the diverse readership of BMC Cancer.

I thank you for your time and look forward to hearing from you regarding our manuscript.

Best regards,

Paolo Provenzano and Patricia Keely