Assessment of growth-related mechanical stresses in solid tumors and their spatial correlation with extracellular matrix components

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Abstract

Mechanical stresses within solid tumors significantly influence tumor development and therapeutic outcomes, yet their comprehensive measurement remains underexplored. This study presents an integrated experimental and computational framework for quantifying growth-induced residual stresses in breast (4T1), pancreatic (PAN02), and fibrosarcoma (MCA205) murine tumor models. Orthotopic tumors grew to a size of 500-1500mm3 and shear wave elastography was employed to measure the tumor mechanical properties in vivo. After surgical excision, tumors were embedded in agarose, and two perpendicular cuts were performed to release residual stresses, captured via image processing of the resulting bulging deformations. Finite element models were constructed to quantify these stress levels and immunofluorescence staining of tumor sections was performed to quantify collagen and hyaluronan content.
Our findings reveal significant spatial variation in residual stress, driven by the tumor microenvironment's heterogeneity. The bulging displacement profiles, and average magnitudes of maximum displacement varied markedly among and within the three tumor types. The 4T1 tumors showed the lowest average displacement, while PAN02 tumors exhibited the highest. Residual stress measurements ranged from 0.22–4.18 kPa for bulk stress and 0.55–8.22 kPa for third principal stress after the first cut, with an increase to 1.73–5.61 kPa and 3.31–10.88 kPa, respectively, after the second cut. Elastic modulus measurements indicated that MCA205 tumors were the stiffest, exhibiting significant differences from PAN02 and 4T1, and that tumor volume correlated nonlinearly with elastic modulus in MCA205 and 4T1 tumors, stabilizing at an asymptotic value, likely due to extracellular matrix production dynamics.

Critically, spatial correlations were established between hyaluronan and collagen distributions and residual stress, with MCA205 and PAN02 tumors showing strong associations. For 4T1 tumors, only partial associations were noted, potentially due to localized high hyaluronan levels paired with lower cellular density and reduced stress generation. Collagen orientation did not distinctly influence residual stress, though colocalization of hyaluronan and collagen significantly correlated with stress profiles across all models, suggesting their combined role in stress generation. These findings imply that hyaluronan and collagen are pivotal factors.

This study highlights that residual stress and elastic modulus exhibit notable spatial variability, emphasizing the need for comprehensive mapping correlated to extracellular matrix

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constituents and cellular phenotypes. Insights gained might enhance estimations of mechanical stress in human tumors from biopsies and support the refinement of normalization therapies that modulate tumor mechanics for improved treatment outcomes.

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