Modulating tissue mechanics to increase oxygen delivery to tumors

by

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Solid tumors have low oxygen tension – hypoxia – that fuels disease progression and treatment resistance. Thus, strategies for alleviating hypoxia are needed. Two factors affect tissue oxygen levels: oxygen supply via blood vessels and oxygen consumption by cells. I focused on improving supply to combat hypoxia. Two vessel abnormalities limit supply. Compression decreases the density of perfused vessels supplying tumors. Excessive leakiness slows blood flow partly by reducing the intravascular pressure drop. Strategies to repair leakiness towards decreasing hypoxia exist, so I developed approaches for overcoming compression.

In order to understand the origin of vessel compression, we developed the first ex vivo technique to estimate compressive solid stresses held in tumors. We made measurements of this residual solid stress in numerous tumor types from patients and mice to confirm that elevated stress is conserved across tumors. We then identified structural components within tumors that contribute to stress. Since cancer cells were known to compress vessels, we found that depleting them reduced stress, as did depleting fibroblasts, collagen, and hyaluronan. Depleting these components decompressed blood and lymphatic vessels.

After identifying targets to reduce stress, we sought to decrease stress therapeutically to improve treatment outcomes. First, we demonstrated that losartan, an FDA-approved therapy indicated for hypertension, decreases the activation of fibroblasts and the production and maintenance of collagen and hyaluronan. As a result, losartan decompressed vessels, restored perfusion, decreased hypoxia, and potentiated chemotherapy. These results provide a rationale for retrospective analyses demonstrating losartán’s benefit and for future clinical trials, one of which is currently underway (NCT01821729).

To understand how reversing compression modulates both individual vessels and the vascular network to improve oxygen delivery, we developed a technique using multi-photon phosphorescence quenching microscopy to map oxygenation to perfused blood vessels in live tissues. This technique allowed us to compare the effects of reversing compression to the effects of repairing leakiness on individual vessels and vascular network geometry. In comparing and contrasting these two strategies, we showed how each of these strategies could be improved to increase oxygen delivery. This work also has implications for optimally combining both treatment strategies to increase oxygen delivery to tumors.

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