Assessing and removing biophysical barriers to treatment

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Pancreatic ductal adenocarcinoma (PDA) is a confounding cancer with a penchant for metastasis and resistance to therapy. Cell autonomous events, such as mutations in the *Kras* proto-oncogene, are essential for the initiation and maintenance of PDA; however non-malignant cells as well as non-cellular components have been shown to contribute to tumor growth, immunosuppression, and chemotherapeutic resistance. The stromal compartment can comprise more than 80% of tumor content and is characterized by a dynamic and deregulated extracellular matrix (ECM). In addition to a role in tissue structure, the ECM provides biophysical and biochemical cues that determine cell responses. PDA presents its own characteristic ECM signature including large deposits of the negatively charged glycosaminoglycan (GAG) hyaluronan (HA), as well as fibrillary collagens which increases matrix stiffness. We have previously demonstrated that high levels of HA in PDA contribute to extraordinary interstitial fluid pressures (IFP) and vascular collapse. We show here that IFP is comprised of both freely mobile and immobile fluid phases. Due to its highly charged nature, HA binds large amounts of water to create an immobile-fluid phase with a significant swelling pressure. This pressure is not detected by conventional methods that can measure only free fluid pressure. The swelling pressure stresses abundant collagen fibrils which contract through cellular efforts to maintain homeostasis, further contributing to IFP. Targeting HA through systemic administration of pegylated hyaluronidase (PEGPH20) liberates the immobile fluid phase and dramatically reduces IFP, increasing vessel patency and bioavailability of systemically delivered agents. We present results on the effects of targeting additional ECM components and signaling pathways to help remove biophysical barriers to chemotherapeutic access. We also compare the abilities of different methodologies to measure interstitial pressures associated with the distinct fluid phases in a variety of experimental contexts.