Perturbed microenvironmental conditions play important roles in tumor initiation, progression, and therapy response; however, the underlying molecular, cellular, and tissue-level mechanisms remain relatively poorly understood. By integrating biomaterials, tissue engineering, and microfabrication strategies our lab has developed a variety of in vitro and in vivo models to study tumorigenesis under pathologically relevant conditions. In particular, we are applying these model systems to evaluate the regulatory roles of extracellular matrix (ECM) physicochemical properties on tumor-stroma interactions with a focus on tumor angiogenesis and metastasis. This talk will summarize some of our efforts in this area and discuss tumor-mediated differences in mesenchymal stem cell fate, the effect of these changes on ECM physicochemical properties, and the resulting functional consequences on endothelial and tumor cell behavior.