Despite huge advances in the molecular regulators of cancer growth and metastasis, patient survival rates have largely stagnated, with over 90% of cancer deaths due to metastasis. Recent studies have demonstrated that increased understanding of the forces generated by cancer cells and their influence on tumor growth, invasion, and metastasis are essential in finding new treatments for metastatic cancer. Bone marrow derived mesenchymal stem cells (MSCs) that accumulate in the primary tumor due to their natural tropism for inflammatory tissues may also enhance the metastatic potential of cancer cells through direct interactions or paracrine signaling. Quantitative analysis of actin cytoskeletal mechanics and surface traction forces allow us to probe the biomechanical properties of cells with an extraordinary level of detail. These biophysical techniques are used to systematically investigate the parameters in the tumor microenvironment that control MSC interactions with cancer cells and to identify specific conditions that induce tumor-promoting behavior in MSCs, along with strategies for inhibiting these conditions to limit force-dependent cancer progression. By systematically investigating the conditions in the tumor microenvironment that affect MSC interactions with cancer cells, we hope to gain a fundamental understanding of the role of MSCs in cancer progression, which is essential in developing new strategies for controlling the behavior and even manipulating the fate of MSCs in the tumor. This biophysical approach has also been used to classify cancer cells by their mechanical properties and to identify therapeutic targets for metastatic cancer based on the mechanical phenotypes of different types of cancer cells.