

### **Are biomechanical changes necessary for tumor progression?**

It has been known for a long time that malignant transformation and neoplasm are correlated with significant changes of the cellular cytoskeleton. If the cytoskeletal alterations in a tumor are necessary they have to trigger biomechanical changes that impact cellular function. In all cancers malignant neoplasm, i.e. uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and metastasis (spread in the body via lymph or blood), occurs. Recent results indicate that these three malignant processes require changes in a tumor cell's active and passive biomechanics. Thus biomechanical changes can be a general prerequisite for malignant neoplasm independent of the peculiar molecular manifestation of cancer. Undoubtedly, malignant transformation causes cell softening for small deformations. This shift can be attributed to a great part to the fact that during mitosis the actin cytoskeleton is greatly reduced. Thus cell softening is a good marker for increased cell proliferation. At first sight cell softening is contradictory to the observation that tumors are rigid masses and that palpation is used to screen for breast cancer at home. Moreover this apparent weakness of tumors would hinder their invasiveness. A cell confined by a tissue matrix can only divide if its stiffness exceeds the opposing rigidity of its direct environment. However, cytoskeletal filaments inherently strain harden, i.e. stiffen, at larger deformations and thus compensate the weak linear elastic strength of the actin cortex. Intermediate filaments such as vimentin, which expression levels increase with tumor size, are perfect candidates to support the pressure against the normal tissue matrix generated by dividing tumor cells. It is commonly thought that not all tumor cells participate in metastasis and that a process similar to the epithelial-mesenchymal transition (EMT) is required. It is the capability to move individually across a tumor's boundary that is essential for metastasis, which agrees with the differential adhesion hypothesis in developmental biology. If all cells are motile liquid-like tissue-spreading and cell segregation phenomena arise from differences in intercellular adhesiveness and stiffness that act on a boundary between different cell types similar to a surface tension. In breast tumor samples small amounts of cells can be found that actively contract when an external force tries to gently stretch them. These could play a key role in metastasis since contraction can prestrain and thus stiffen the cytoskeleton, which reduces a cells ability to form adhesive contacts with other cells. Moreover, contractile tumor cells migrate significantly better through the extracellular matrix.