

Exercise inhibits cancer: the mechanosensitive state of tumor cells

Surprisingly, researchers find that tumor cells are sensitive to mechanical stresses. This may provide new ways to treat cancers without the severe side-effects of many therapies. Because mechanosensitivity of cancer cells is found quite generally, it appears to be a property of the state of most cancer cells. For example, there is evidence that mechanical exercise inhibits cancer growth. If you Google “exercise and cancer”, there are many links to studies reporting benefits of exercise for cancer patients. A National Cancer Institute site reports that exercise has proven beneficial for seven different cancers and is suspected to benefit another eight. This raises the question does mechanical distortion of tumor cells inhibit their growth or is this simply a secondary benefit of exercise? One possibility is that tumor cells are in an altered mechanical state. Some of the earliest studies of tumor cells showed that they grew on soft surfaces, whereas normal cells from the same tissue required rigid surfaces. This implies a general state difference between tumor cells and normal cells that could also involve a change in tumor cell mechanosensitivity.

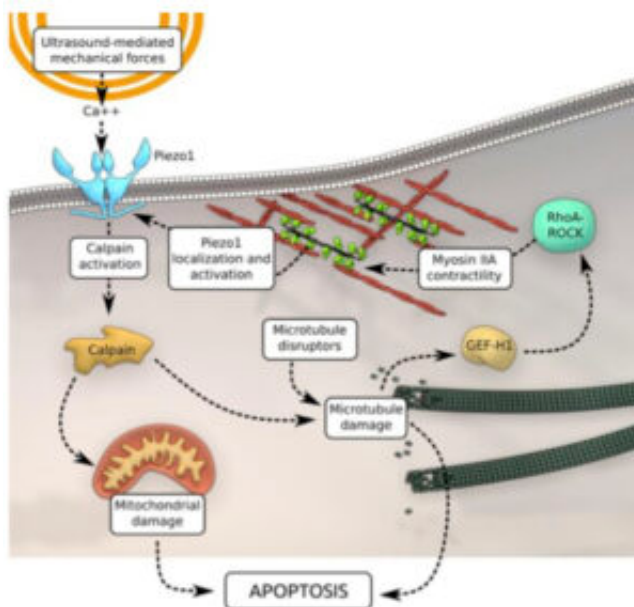


Fig. 1. Mechanical killing of tumor cells requires a mechanosensitive ion channel, Piezo1, that transduces force into calcium ion uptake. Calcium entry activates a protease, calpain, that both damages mitochondria to stimulate cell killing and depolymerizes microtubules that then stimulates myosin to increase Piezo1 sensitivity in a positive feedback cycle.

Our results explain this difference as a change in cell state caused by the depletion of a type of

rigidity sensor in tumor cells. Normal cells assemble contractile units (similar to the units that make up muscles) that are connected through the cell membrane to surrounding fibers. The units contract to a fixed distance that creates a tension proportional to the rigidity of the surroundings (we pinch materials to a defined distance and the force is a measure of rigidity). The loss of the rigidity sensor causes tumor cells to be in a different cell state that enables growth on soft surfaces and is mechanosensitive. Rigidity sensing provides a block to normal cell growth in improper environments. Our results show that normal cells will grow on soft surfaces if they lose rigidity sensing and cancer cells will stop growing to form tumors if rigidity sensing is restored. In the tumor state, cells without rigidity sensors are mechanosensitive and die upon stretch. This is true for tumor cells from many different tissues and normal cells depleted of rigidity sensors irrespective of tissue of origin. Thus, it seems that the presence or absence of rigidity sensing puts cells in different states that have different growth and mechanical properties. When we measure the changes in cell proteins with or without rigidity sensing, we find that the levels of over 700 proteins change upon the loss of rigidity sensing. Thus, we suggest that tumor cells without the sensor are in a different state than normal cells.

Why might it be useful for cells to be able to switch from a normal to a growth state (an answer lies in wound repair)? Since the 18th century, it was evident that repeated wound healing and inflammation in a tissue increased the risk of tumor growth (e.g. chimney sweeps and squamous cell carcinoma). This can be explained because blocks to adult cell growth need to be removed for growth in wound healing or inflammation; and if the normal blocks are not restored, there is a finite probability that the cell growth state persists aberrantly and results in tumor growth. Although most of such tumors are unlikely to cause a serious cancer, the ability to continue to grow and adapt opens the possibility that enabling adaptations will occur and the benign tumor cells will become metastatic and life-threatening. For different tissues, the enabling adaptations will likely be different but most tumor cells share the common feature of growth because of a stable change in the cell state. They also share the feature of mechanosensitivity and there are potentially ways to mechanically damage tumor cells in situ. For example, some types of ultrasound can damage tumor cells as illustrated in Figure 1 and that may be adapted to augment current therapies. Thus, state differences of tumor and normal cells may enable more general cancer therapies.

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Publication

[A Tale of Two States: Normal and Transformed, With and Without Rigidity Sensing](#)

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