Cancer cells survive mechanical fragmentation under microcirculatory conditions
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The hemodynamic transport of circulating tumor cells (CTCs) is an essential step in cancer metastasis. It is estimated that for every gram of tumor, about a million cells are shed per day into the blood stream. Despite the hematogenous dissemination of such a large number of CTCs, less than 0.01% survive to produce metastases. In vivo imaging in mouse models show that tumor cells arrested in the microvasculature can undergo fragmentation due to fluid stresses. It has long been postulated that in addition to cytocidal factors, this mechanical trauma can contribute significantly to metastatic inefficiency. However, the flow conditions and cell properties necessary to induce cancer cell fragmentation are unknown. Importantly, from a metastasis point of view, it is unclear whether fragmented cancer cells survive or if highly metastatic cells are less prone to fragmentation.

In this study, we developed a microfluidic model of a lung capillary bed that contains an array of pillar obstacles that produce bifurcating flows (Fig. 1a). Optimal pressure drops and pillar gaps were identified to induce cancer cell fragmentation. As shown in Fig.1b, we strikingly observe that the cancer cell deforms at the bifurcation by forming fingers which elongate and eventually rupture. Additional studies reveal that the mechanism of fragmentation is consistent with the poroelastic model of cell mechanics, where the cytosol flows through the porous cytoskeletal medium and fills the membraneous vesicle prior to rupture (Fig. 1c). We characterized the fragmentation characteristics of cells of different metastatic potential and find that highly metastatic breast and prostate cancer cells take longer to rupture suggesting mechanical resistance to fragmentation. Furthermore, cell viability assays showed > 95% of fragmented cells survive (Fig. 1e) Most intriguingly, fragmented cells were found to hardly replicate even after several days of culture suggesting that they might be dormant. This finding suggests a biomechanical route to tumor cell dormancy and that fragmented cells could be a potential source of cancer relapse.

Figure 1. Fragmentation of cancer cells under microcirculatory conditions (a) Microfluidic device showing an array of pillar-based bifurcating channels to occlude and rupture cancer cells. Inset shows the pillar obstacles against which cells deform. (b) Time sequence of mechanical fragmentation of cancer cells. The nucleus is stained in blue. Scale bar is 10 um. (d) Rupture time of a library of cancer cell lines (breast: MCF-10A, MCF-7, MDA-MB-231; prostate: LNCaP, PC3; EMT: H1437 and H1299). (e) Viability of MCF-7 cells post fragmentation.