Mechano-mediated metastatic switching state of circulating tumour cells

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During metastasis, cancer cells travel through the vascular circulatory system as circulating tumour cells (CTCs) and encounter capillary beds, where they initiate extravasation. Biomechanical forces exerted by the microcirculation pose challenges to the survival of tumour cells within capillaries, yet a fraction of CTCs successfully extravasate and establish distant metastases. Despite the critical role of this process in metastatic progression, factors governing the behaviour of these resilient cells remain poorly understood. Emerging evidence suggests that mechanical forces encountered in capillaries may trigger adaptive responses in CTCs, enhancing their survival and metastatic potential. Microfluidic platforms, which can replicate capillary constriction geometries and physiological fluid flows, offer a promising avenue to investigate the complex interplay between CTCs and capillaries.

Using a microfluidic device mimicking gradual capillary narrowing, our study reveals a mechano-mediated adaptive mechanism employed by CTCs to withstand microvascular constraints, which induces survival strategies and phenotype switching towards a more invasive state. We demonstrate that the mechanotransduction of restrictive deformation is regulated by ion channels on the cellular membrane and that the mechanosensitive PIEZO molecule plays a central role in downstream signalling pathways which modulates CTC adaptation. Additionally, our vascularized tumour *in vitro* model suggests that compressed tumour cells are more likely to interact with the endothelial monolayer, extravasate and colonize surrounding microenvironments, a process hindered by deletion of the PIEZO molecule. These findings highlight a molecular basis for the survival of metastatic cells under microvasculature-induced biomechanical stress. Understanding how CTCs respond to capillary migration and the impact of constriction forces on their behaviour can provide insights into the role of the microcirculation in the metastatic cascade. This knowledge may inform the development of targeted therapeutics aimed at inhibiting adaptive mechanisms adopted by CTCs within the capillary bed, thereby improving strategies for metastasis management.