ABSTRACT

Despite rapid advancements in the miniaturization of flow devices for biological applications, the possibility of confinement induced alternation in intracellular signal transduction dynamics remains largely elusive. While such possibilities provoke changes in the generic designing strategies for futuristic lab-on-a-chip devices, these should additionally illuminate on the intrinsic nature of stress-responsive cellular adaptations within physiologically relevant confinements of the vasculature and tissue-matrices. As degree of adaptation to coupled chemo-mechanical stresses becomes a pivotal survival-factor for metastasizing cancer cells, the prospect of confinement induced alterations in the stress adaptive behavior of cancer cells vis-à-vis normal ones is investigated.

Towards this, firstly, a novel microfabrication compatible traction force microscopy technique is introduced to delineate the changes in cell-substrate adhesion in the purview of cell culture in microchannels under quiescent and flow conditions. Subsequently, the aforementioned system has been utilized to quantify the stress adaptive abilities of five different mammalian cell types within microconfinement. Within the parametric variations of the channel height (H) and the flow shear stress (τ), a sigmoid shaped diminutive transition in the characteristic time scale of cellular response to the perturbation signals is delineated when H is decreased below a threshold value and concurrently, τ is elevated beyond a critical limit. Origin of this transition, exclusively observable for cancer cells, is probed to be connected to a cooperative interaction between an augmentation of ligand concentration due to confinement-induced restrictive diffusion effects and amplification of effective shear stress due to dimensional compatibility between the cellular length-scale and the channel height, leading to an elevated level of activation of Epidermal Growth Factor Receptors (EGFRs) that are inherently over-expressed in cancer cells.

Next, the stress induced activation of EGFR has been revealed to occur through the disruption of membrane lipid-raft microdomains. The activated receptors have been, then, illustrated to stimulate two intracellular signaling molecules which confer counteracting influences on intracellular viscosity, exhibiting cytosol hardening and softening respectively at low and high stress regimes. The findings, thus, reveal a hitherto unknown cancer cell-microconfinement adaptive interaction and several new insights to cancer biophysics, which may be exploited in microfluidics based anti-cancer drug screening platforms.

Keywords: Microchannel, Microfluidics, Microconfinement, Lab-on-a-Chip, Cell Culture, Cancer, Traction Force Microscopy, Advection-Diffusion, Mechanotransduction, Flow Shear Stress, Focal Adhesion, Plasma Membrane, Lipid Raft, Intracellular Viscosity, Metastasis.