Thesis title: Mechanical stress-induced autophagy in cancer metastasis

Abstract

While the biochemical and molecular origins of cancer progression have been investigated extensively, the changes in metastatic cancer cells due to mechanical cues from their surroundings have barely been explored. Mechanical forces in the context of cancer may principally arise due to compression of growing solid tumors from the surrounding confined tissue environment and due to shear stress during hematogenous metastasis. Since processes like transit in circulation and extravasation at a secondary site are short-timescale processes, it is tempting to investigate adaptive responses which are elicited in cells as immediate response to mechanical stimulus. Accumulating evidences hint at autophagy as a potent mechano-adaptive response of all cell types which is responsible not only for homeostasis and survival but also for migration. Thus, it is interesting to investigate whether physiological forces relevant to the different steps of the metastatic cascade may elicit autophagic response in model cancer cells and what may be its implications in cancer progression. Towards this investigation, a solid tumor scenario has been mimicked by subjecting Sodium alginate bead encapsulated cervical cancer HeLa cells to compression on the order of a known native tumor microenvironment wherein it was observed that compressive stress induced-autophagy fosters intravasation by promoting turnover of paxillin, which is essential for focal adhesion disassembly, and enhancing production of active MMP-2, which is essential for invasion. To further replicate the metastatic dissemination of cells, a microfluidic approach has been implemented to study how cancer cells may adapt to circulatory shear stresses in narrow confinements by resorting to autophagy, which in the mooted context plays a pro-survival role thereby delaying apoptotic cell death caused due to impending circulatory shear. In the latter parts of the thesis, the role of shear-induced autophagy behind the augmented secretion of pro-invasive factors like MMP-2 and IL-6, in extravasating cancer cells has been found to be critical in cancer cell migration and invasion. Investigation of the molecular mechanism governing mechanically-induced autophagy revealed that it is a lipid raft mediated p38 MAPKinase phosphorylation-dependent process which may be regulated by depletion of cholesterol from the membranes of cancer cells. This study thus delineates the importance of a novel mechanobiological aspect of metastatic cancer progression and identifies potential anticancer drug targets.

Keywords: metastasis, compression, shear, autophagy, survival, invasion.