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Force-induced regulation of epigenetic state in cancer cells

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Stem-cell-like cancer cells are thought to play a key role in the initiation, growth, and relapse of malignant tumors. Recently, our group has shown that culturing melanoma cells in soft 3D Fibrin matrices can promote selection and growth of such tumorigenic cells. We defined these cells as tumor repopulating cells (TRCs). When injected in the tail vein, as few as 10 TRCs can generate metastatic tumors in the lungs of wild-type non-syngeneic mice. These cells express higher levels of Sox2, a self-renewal gene, whose down-regulation leads to differentiation of TRCs on 2D soft matrices. This paper studies the force-induced epigenetic modification as a possible mechanism that links matrix-induced mechanical cues to Sox2 down regulation and differentiation of TRCs. Particularly, we focus on methylation of histone 3 lysine 9 (H3K9) and lysine 27 (H3K27). Using a H3K9 biosensor based on Forster Resonance Energy Transfer (FRET), we show that H3K9 methylation is lower in melanoma cells cultured in soft fibrin gels compared to control cells cultured on rigid plastic dish. Application of local forces via with an RGD-coated magnetic bead increase H3K9 methylation in control melanoma cells, but not in TRCs. Disruption of cytoskeletal filaments and inhibition of acto-myosin contractility blocks force induced H3K9 methylation. In contrast, H3K27 methylation does not depend on forces and remains unchanged both in control melanoma cells and TRCs. Silencing G9a or SUV39h1, a methyltransferase for H3K9, abolishes force-induced H3K9 methylation and elevates Sox2 expression in control melanoma cells.

Biography

Arash Tajik is a PhD candidate in Mechanical Engineering at the University of Illinois at Urbana-Champaign. His research mainly focuses on the biophysical regulation of epigenetic state in cancer and chromatin organization in single living cells. He has developed novel tools and biosensors to quantify gene expression regulation in live cells. He has received his Master's degree from the University of Waterloo, Canada and Bachelor's degree from Iran University of Science and Technology, in 2008 and 2005, respectively. He has won multiple national and institutional awards during his undergraduate and graduate studies.

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