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From Cell Mechanobiology to Mechanomedicine: A Research Path Inspired by Fung

—Dedicated to Prof. YC Fung on the Occasion of His Centennial Birthday

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Abstract: Decades ago YC Fung proposed that mechanical stress could have substantial impacts on remodeling and growth of living tissues. Fung also proposed the concept of residual stress in blood vessels and quantified residual stress in excised arteries [1]. However, how stress influences cell and tissue functions remains elusive. At the cellular level, we have quantified myosin II mediated pre-existing tensile stress (prestress) in living cells and demonstrated that the prestress (the endogenous cytoskeletal tension) regulates cell stiffness, gene expression, and long-distance stress propagation in the cytoplasm to activate enzymes [2]. The prestress even impacts on force-induced direct chromatin stretching and transgene transcription [3]. Mechanoresponsive genes are known to be sensitive to mechanical stimulation but it is not clear why. We show that rapid upregulation of mechanoresponsive genes by force depends on the location of the chromatin domains in the nucleus. We also reveal that low levels of 3D matrix elasticity and stress promote malignant (and stem cell like) tumor-repopulating cell growth and metastasis but 3D high matrix stiffness leads to tumor dormancy [4-7]. We then present evidence that a novel synthetic retinoid molecule inhibits tumor metastasis *in vivo* without detectable toxicity [8]. Our findings are starting to shed light on the underlying mechanisms of cell mechanobiology and mechanomedicine.

Keywords: Cellular force; mechanotransduction; cytoskeleton; gene expression

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