Title: Growth Control in Cancer: An Computational Model of YAP/TAZ Integrating cell-ECM Mechanosensing and Hippo pathway

Meng Sun, Muhammad Zaman

With enormous progress recently in uncovering roles of YAP/TAZ in cell proliferation, differentiation, tissue organization and tumorgenesis, the crosstalk mechanism of YAP/TAZ upstream mechanical regulators and the cell-cell adhesion related Hippo pathway regulators remains largely elusive. To bridge current gap in our understanding, we present a computational model predicting YAP/TAZ activity depending on ECM mechanical properties (Sun et al, Biophysical Journal, 2016), cell-cell adhesions, and more importantly, the crosstalk between the two. We propose a mechanism of the interaction between LIMK and LATS to explain the unresolved synergistic effect of YAP/TAZ activity between the mechano-sensing and the Hippo pathways (Aragona et al, Cell, 2013). Using this computational model, we are able to analyze the synergistic effects of YAP/TAZ driven by the LIMK-Lats mechanism under different cell densities. To test the efficacy of our strategy, we apply the model to both the normal and tumor cell lines. The breast cancer cell line MDA-MB-231 cells lack E-cadherin and hence able to overcome the LATS-dependent YAP/TAZ contact inhibition regulation. Thus the mechanical sensing of YAP/TAZ serves as an important checkpoint for regulating tumor progression. We predict the YAP/TAZ activity as a function of mechanical ECM properties (stiffness response function) and cell density in both normal breast epithelial cells MCF10A and MDA-MBA-231. Our model aims to bridge the gap by including mechano-to-biochemical signal conversion by adhesion molecules, intracellular signal transmission, cytoskeleton dynamics, and regulation of effectors relevant to directing transcriptional programs, such as YAP/TAZ activity using the ordinary differentiation equations. Such an integrated molecular model predicts effects of molecular inhibitors or changes in mechanical properties *in silico*. For example, adhesion molecules such as FAK can shift the stiffness response function horizontally, such that FAK overexpression rescues YAP/TAZ activity in soft environments, which has been tested later (Elosegui-Artola et al, Nature cell biology, 2016). Overall, our model provides a novel platform of studying YAP/TAZ activity in the context of integrating different signaling pathways. This platform can be used to gain new fundamental insights into the role of key molecular and mechanical regulators on development, tissue engineering or tumor progression.

CA177799