CDB SEMINAR

Speaker: Valerie M. Weaver

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Title: "Spatial-mechanical regulation of morphogenesis and malignancy"

Date:	**Tuesday, June 7**
Time:	**10:30 -12:00**
Place:	**1F Auditorium of Building C,CDB**

Summary:

Stromal-epithelial interactions drive development and maintain homeostasis through a network of soluble and insoluble factors that operate within the three dimensional (3D) tissue. Mechanical force can regulate tissue behavior by modifying how a cell will respond to these exogenous cues. Using animal models, 3D mammary epithelial cultures (MECs) and mechanically-defined extracellular matrices (ECMs) we have been studying how physical force could modulate the normal and malignant tissue phenotype. We found that malignant transformation of the breast is associated with a sustained and progressive increase in ECM stiffness. Evoking a similar incremental increase in ECM stiffness ex vivo progressively perturbs MEC morphogenesis by enhancing growth factor-dependent ERK and PI3 kinase stimulation to destabilize cell-cell adherens junctions, compromise basal polarity, modify cytoskeletal organization, increase growth and survival and alter gene expression. ECM stiffness elicits these cellular effects by driving integrin aggregation to facilitate focal adhesion maturation through induction of Rho-dependent intracellular tension. A growth factor transformed mammary epithelium that exerts abnormally high integrin-generated tension could be phenotypically-reverted if rho-dependent force was normalized. This implies that tissue homeostasis is functionally linked to tensional-homeostasis through integrin-growth factor receptor-gtpase crosstalk. The relevance of this paradigm to tissue morphogenesis and malignancy will be discussed.

Host: **Yoshiko Takahashi** **<Body Patterning,CDB>**
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