TEMPLE UNIVERSITY
Department of Mathematics

Applied Mathematics and Scientific Computing Seminar

Wednesday, 19 September 2018, 4:00 p.m.
Room 617 Wachman Hall

(refreshments and social at 3:45 p.m)

Real-time imaging of invasive cancer cells in tumor microenvironment context

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Abstract. Metastasis currently causes >90% of breast cancer deaths. Tumor cell structures that have long been hypothesized as necessary for metastasis are invadopodia, invasive protrusions rich in structural proteins (Tks5, actin), adhesion proteins (eg. integrin $\beta 1$), and metalloproteases, known to degrade the extracellular matrix (ECM) proteins. Using our unique intravital imaging approaches, we previously demonstrated that invadopodia *in vivo* are necessary for intravasation and consequent lung metastasis. In primary tumors, we found that cells which assemble invadopodia migrate at Slow speeds and are seen in perivascular niches where the ECM is cross-linked. Outside of these niches, cells with Fast motility with no invadopodia were observed. The Slow phenotype can be switched to Fast by reducing the degree of ECM cross-linking at the perivascular niche, or eliminated by knocking down Tks5, without affecting the Fast phenotype. Both types of interventions reduce intravasation and metastasis. We are here presenting aspects of the Slow phenotype that allow cells to form invadopodia. By combining mathematical modeling and microscopy, we observe that the Slow phenotype consists of temporal integration of two oscillating states: i. Invadopodia state, in which a cell is relatively sessile while it assembles invadopodia and degrades ECM; ii. Locomotion state. Importantly, the Invadopodia

state only occurs in early G1, whereas the Locomotion state can be seen throughout the entire cell cycle, suggesting that the cell cycle controls invadopodia assembly (Bayarmagnai, ASCB 2018 abstract). Towards elucidating the mechanism of state oscillations, we engineered different levels of ECM cross-linking in 2D (via glutaraldehyde) or 3D environments (via transglutaminase II), discovering that state oscillation frequencies show a biphasic trend to linearly increasing levels of ECM cross-linking. We further show the oscillation dynamics between the states depend on ECM interactions with its major cellular receptor, integrin $\beta 1$. Namely, partial inhibition of the integrin $\beta 1$ activity by antibodies, or endogenous integrin $\beta 1$ inhibitor SHARPIN, not only lowers the invadopodia-mediated ECM degradation, but can also eliminate Invadopodia state. In turn, cells spend more time in Locomotion state, increasing the net distance of cell migration. Our latest data demonstrates that an ECM degradation product, 60kDa fragment of laminin which binds integrin $\beta 1$, can also act as a modulator of Locomotion-Invadopodia state balance. Overall, our data shows that invadopodia assembly is regulated by ECM components and ECM degradation products via integrin $\beta 1$ activity. This implies that breast cancer metastasis may be prevented by modulating integrin $\beta 1$ activity levels.