Self-organized coordination between morphological dynamics and cell movement in single *Dictyostelium discoideum* cells

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Cell migration is one of the ways that cells respond signals from the fluctuating extracellular environment. It supports various cellular processes, ranging from chemotaxis of microorganisms to immune responses and wound healing in higher organisms. Cell migration involves morphological dynamics of cell shape and cell movement. However, how both processes are orderly orchestrated remains unclear. To address this issue, we performed systems-biological approach and here show that morphological dynamics together with its coordination with cell movement is conserved regardless of the state of Dictyostelium discoideum cells and is regulated by PTEN and PI3K without the need for external stimuli.

We observed spontaneous cell migration of individual *Dictyostelium discoideum* cells in a homogeneous environment in the absence of external stimuli. Kymograph was constructed around centroid of individual cell images and then calculated both long axis of cell shape and the angle of moving velocity by image processing.

We found that morphological dynamics of single *Dictyostelium discoideum* cells are not random but organized into orderly patterns into stretching, rotating and oscillating. A representative orderly pattern in the starving stage is shown in Figure 1. Interestingly, these orderly patterns are conserved at both the vegetative stage where morphological dynamics and cell movement seem random and the starved stage where both processes seem orchestrated. In both of the cells, inhibition of PI3K suppressed membrane deformation and resulted in disorganization of orderly patterns. In addition, loss of PTEN causes the irregular pseudopodia. Both of two molecules are required for self-organization of morphological dynamics into orderly patterns.

Next, we examined whether cell shape determines moving direction by comparing the direction of long axis of cell shape θ_{Mem} with the direction of moving velocity θ_V. Remarkably, we found that probability distribution function (PDF) of $\theta_{Mem}(t)-\theta_V(t)$ had the peak at $\theta_{Mem}(t)=\theta_V(t)$ (Figure 2), suggesting morphological orientation determines moving direction. This bias was also observed in the PTEN disrupted mutant (*pten*$^-$). PTEN is pivotal to cell polarity, however, it is not necessary for coordinating morphological orientation and moving direction. In contrast, PI3K inhibition or disruption abolished the observed peak on PDF. This result indicates that PI3K inhibited cells (*pi3k*$^-$) cannot coordinate the extension and retraction of new pseudopodia with cell movement. Thus our findings provide that PTEN and PI3K constitute a novel functional module for self-organizing morphological dynamics and coordinating morphological dynamics with cell movement.

Figure 1

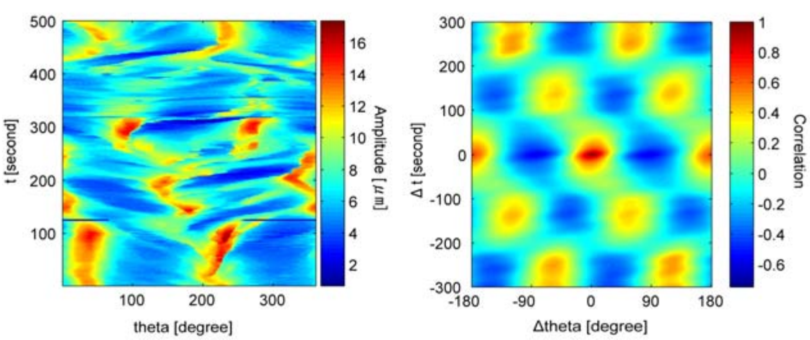

Figure 2

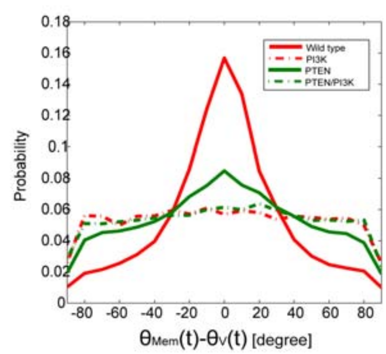

Figure 1: Morphological dynamics of *Dictyostelium discoideum.* Left: kymograph of morphological dynamics, right: auto-correlation function. Morphological dynamics are noisy, however, we can find an orderly pattern in auto-correlation function.

Figure 2: Coordination of long axis of cell morphology and moving velocity. Red: WT (solid), *pten*$^-$ (dashed), Green: *pi3k*$^-$(solid), *pi3k*$^-$/*pten*$^-$ (dashed).