Traction peak oscillation optimizes focal adhesion mechanosensing

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***Short Abstract* — Focal adhesion (FA) is a dynamically formed organelle, serving as cells' "foot". Combining theory and experiment, we established the first coherent model of FA formation that integrates the coordinated action from branched actin network and stress fiber. We showed that FA interaction with retrograde actin flux and stress fiber results in the distal and proximal traction peaks, respectively. Stress fiber elongation negatively feedback with the actomyosin contractility, conferring the proximal traction peak oscillation. Such traction oscillation optimizes the range over which FA traction can sensitively size up the substrate stiffness, shedding light on the mechanism of FA mechanosensing.**

***Keywords* — Cell migration, Mechanosensing, Theory and experiment.**

I. Background

Cells prefer to migrate toward stiffer substrate, so called "durotaxis" [1]. Such mechanosensation underlies many physiological functions, such as cancer metastasis [2] and tissue formation [3]. To move around, cells dynamically form a complex organelle called focal adhesion (FA), which connects the cell with the external substrate. Focal adhesions are the "feet" of the cell that sense and response to mechanical cues [4]. It forms near the leading edge of the cell, mediating cell front protrusion, and generating traction force that pulls the cell body forward. In the cell retracting rear, FAs dissolve in time to facilitate cell migration. Therefore, the life cycles of the FA ensemble are spatially and temporally regulated inside migrating cells. Actin cytoskeleton is the major determinant that dictates such spatial-temporal regulation of FA dynamics. Two types of actin network structures are involved [5]. Branching actin network polymerization against the cell membrane gives rise to a combination of forward protrusion and retrograde flow of the F-actin network relative to the substrate, called "retrograde actin flux". The retrograde actin flux promotes the growth of FA from its infancy stage. Further back in the cell, stress fiber – bundled actin filaments, engages with FA. It mediates actomyosin contraction that drives the FA maturation both in terms of size and composition. It remains unclear how the dynamics of branched and bundled actin networks are integrated in FA formation, and how they contribute to FA mechanosensing on substrate stiffness. A coherent model that can account for the entire life cycle of FA has yet to emerge.

II. Results

Here, we combined theoretical modeling and experiment approaches, and established an integrated model, focusing on how the branched and bundled actin networks coherently govern the FA growth from its nascent stage to maturation. Our work revealed that the two distinct actin networks each contribute a traction force peak within the single FA, respectively. The resulting total traction force profile within the FA reflects a combination of such two distinct origins. While the engagement with retrograde actin flux results in the distal traction peak, stress fiber contractions lead to the center traction peak. Moreover, a negative feedback emerges from the load-dependence of both myosin II contractility and bundled actin polymerization, resulting in the oscillation of the central traction peak. Thereby, it is the competition between the two traction peaks that gives rise to the observed traction peak oscillation. Finally, we showed that the condition conferring the central traction peak oscillation optimize the range of FA mechanosensation of substrate stiffness, which points to the functional significance.

III. Conclusion

We therefore provided a general framework of FA dynamics, in which FA formation integrates the dynamics of the two distinct actin networks to confer mechanosensing on substrate stiffness.

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