CELL ADHESION

Myosin anchors junctional signalling

> NMII acts as an anchor to generate a stable zone of RhoA activity

The presence of an actomyosin belt at the adherens junctions (also known as zonula adherens (ZA)) in epithelia is crucial for apical contractility, and this in turn sustains epithelial homeostasis. Formation of the contractile ZA depends on RhoA signalling, but exactly how a stable ZA is maintained has been elusive. Now, Priya *et al.* identify a molecular feedback mechanism that acts through non-muscle myosin II (NMII) to stabilize active RhoA at the ZA. This mechanism has bistable properties, which can confer robustness on the system.

The authors first dissected the molecular pathway involved in the maintenance of apical contractility at the epithelial ZA. This contractility is known to be regulated by RhoA, which acts via Rho-associated protein kinase I (ROCKI) to drive NMII phosphorylation and its junctional localization. The authors found that active RhoA is stably localized at the ZA and that such stable localization depends on NMII, which acts as a scaffold to recruit ROCKI. ROCKI was shown to phosphorylate the Rnd3 protein, and this phosphorylation restricted Rnd3 and, consequently, the Rnd3-interacting protein p190B, from localizing to the ZA. As p190B is a Rho GTPase activation protein that inhibits RhoA, its exclusion from the ZA prevented RhoA inactivation in this zone. Thus, active RhoA maintains actomyosin contractility at the ZA via ROCKI-mediated phosphorylation of NMII and, at the same time, NMII feeds back to maintain RhoA activity at the ZA, also via ROCKI (which excludes RhoA inhibiting factor from the ZA). Collectively, these results show that two intricate feedback loops, intersecting at ROCKI, operate at the epithelial ZA and maintain apical epithelial contractility.

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To gain further insights into how this pathway operates, the authors developed a numerical model. When applying this model to a system in which all components were assumed to be present at the ZA at equal levels, the feedback between NMII and ROCKI was shown to actively drive local enrichment of RhoA. However, a system devoid of this feedback could not achieve accumulation of RhoA, thus confirming the importance of NMII–ROCKI interaction in the functionality of this network. Moreover, this modelling approach revealed that when the affinity between NMII and ROCKI was set to intermediate values, the system could achieve two different states: one with high and one with low RhoA concentrations. This suggests that the NMII–ROCKI feedback loop can generate bistability within the system. When analysed in cell culture, such bistability could indeed be detected and manifested itself by the presence of cells with either high or low RhoA at the ZA within a cell population.

Altogether, Priya *et al.* uncover a feedback network that operates at the epithelial ZA to maintain a stable apical actomyosin belt, which is necessary for apical contractility and proper epithelial functioning. In this system, NMII acts as an anchor to generate a stable zone of RhoA activity that in turn sustains the stability of the actomyosin belt. Notably, the bistability of this network could provide a robust mechanism, buffering against biological noise. It will be important to understand how the robustness of this network is set up in the complex cellular environment and how it is affected in different pathological conditions that compromise cell–cell interactions.

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ORIGINAL RESEARCH PAPER Priya, R. *et al.* Feedback regulation through myosin II confers robustness on RhoA signalling at E-cadherin junctions. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3239 (2015)

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