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DIGITAL VISION

CELL ADHESION

# Regulating RHO at adherens junctions

RHO signalling sustains the integrity of adhesion junctions, but the mechanisms that control junctional RHO activity have remained elusive. Here, Yap and colleagues identify an extramitotic role for several cytokinesis-associated components in the regulation of junctional RHO signalling, and thus in the maintenance of cell–cell contacts.

RHO proteins shuffle between their active RHO-GTP and their inactive RHO-GDP forms, and this is regulated by the local availability of activating guanine nucleotide exchange factors (GEFs) and deactivating GTPase-activating proteins (GAPs). Imaging studies with interphase epithelial cells detected RHOA-GTP at apical epithelial cadherin (E-cadherin) junctions (which form the zonula adherens), where it is known to promote the accumulation of the motor protein myosin IIA. Moreover, the localization of active RHOA at the zonula adherens required dynamic microtubules.

RHOA-GTP at the zonula adherens correlated with the presence of the GEF ECT2, which is known to activate RHOA at the contractile furrow during cytokinesis. ECT2 knockdown specifically reduced junctional RHOA-GTP, which in turn led to decreased junctional myosin IIA levels, destabilization of apical E-cadherin and the reduction of junctional tension. Thus, ECT2 maintains the integrity of adherens junctions through the local activation of RHO signalling. Notably, the junctional localization of ECT2 was also found to depend on dynamic microtubules.

So, how do microtubules recruit ECT2 to adherens junctions? Centralspindlin, a complex that consists of the kinesin MKLP1 and MGC RACGAP, recruits ECT2 to the contractile furrow during cytokinesis. Interestingly, ECT2 co-immunoprecipitated with MKLP1 in non-mitotic epithelial cells, indicating that the centralspindlin complex may be involved in junctional RHO signalling. Indeed, MKLP1 and MGC RACGAP were identified as adherens junction components, and their knockdown reduced the junctional levels of ECT2, RHO-GTP and myosin IIA. As blocking microtubule dynamics reversed its junctional localization, the authors suggest that centralspindlin provides the link between junctional RHO signalling and dynamic microtubules.

Furthermore, α-catenin was identified as a binding partner of ECT2. α-catenin knockdown experiments showed that this E-cadherin-anchored molecule is essential for the junctional localization of ECT2. Moreover, the amino-terminal domain of α-catenin interacted with centralspindlin, and this interaction was essential for the junctional localization of ECT2. Thus, the authors conclude that α-catenin supports RHO signalling at adherens junctions by localizing centralspindlin, and thereby ECT2, to apical E-cadherins.

Finally, Yap and colleagues found that dynamic microtubules and centralspindlin also act in concert to block the recruitment of the RHOGAP p190B to adherens junctions, where the latter can inhibit RHO signalling. Junctional localization of p190B depended on RAC signalling, and deletion of centralspindlin components or blocking microtubule dynamics promoted junctional p190B recruitment by allowing RAC signalling at the zonula adherens.

Thus, by identifying the molecules that regulate RHO signalling at cell–cell contacts, this study highlights the conserved role of centralspindlin and ECT2 even in an extramitotic context.

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**ORIGINAL RESEARCH PAPER** Ratheesh, A. *et al.* Centralspindlin and α-catenin regulate Rho signalling at the epithelial zonula adherens. *Nature Cell Biol.* 1 Jul 2012 (doi:10.1038/ncb2532)
**FURTHER READING** Harris, T. J. C. & Tepass, U. Adherens junctions: from molecules to morphogenesis. *Nature Rev. Mol. Cell Biol.* **11**, 502–514 (2010)