In This Issue

PINCHing together integrins and signaling

Integrin-mediated adhesion and intracellular signaling by JNK are both required for proper cell migration, but it isn’t clear what factors integrate the two information systems. Kadrmas et al. show on page 1019 that the integrin effector protein PINCH provides such a link during Drosophila dorsal closure, which involves coordinated migration and adhesion of epithelial sheets.

PINCH interacts with integrin-linked kinase and with Nck2, which is involved in regulation of JNK pathway through MAP4 kinase, making it a likely candidate for bridging the two information sources. Using a series of maternal and zygotic mutants, the team found that PINCH was required for proper dorsal closure and that it acted as a negative regulator of the JNK cascade. Moreover, Kadrmas et al. affinity purified a novel PINCH partner RSU-1, a previously identified suppressor of ras-mediated transformation in mammalian cells. PINCH and RSU-1 stabilized one another and were required for proper JNK activity.

Exactly where in the process of dorsal closure PINCH and RSU-1 are required is the subject of the group’s future work. But the current study does imply that integrin-associated junctional complexes may act as signal coordination points, and that JNK signaling must be finely tuned for proper zipping of the epithelial sheet. JCB

Clustering in integrin binding

The adhesiveness of integrin binding is determined by both the affinity of individual heterodimers for their ligand and the clustering of multiple heterodimers. Kim et al. show, on page 1241, that clustering does not precede binding but rather functions in adhesion strengthening following binding to multivalent ligands.

To probe the question of whether clustering or affinity are primary factors in leukocyte integrin binding, Kim et al. devised a FRET system in which either the α or β subunits of the integrin LFA-1 (αβ) were labeled with nonmerizing forms of YFP and CFP. Under basal conditions, no micro-clustering was evident, as cells expressing αmCFP, αmYFP, and wild-type β2 showed little FRET. Nor did the researchers observe FRET when cells were stimulated to activate LFA-1 adhesiveness. Furthermore, activation of LFA-1 with cytoskeletal-disrupting agents did not induce microclusters or macroclusters, visible by confocal microscopy, in the absence of multivalent ligands.

However, addition of multivalent (but not monovalent) ICAM-1 ligand to stimulated cells induced FRET. Macro- and microclusters did form when cells expressing both the ligand and the integrin heterodimer were cultured together in a manner that stimulated aggregation.

Kim et al. conclude that clustering is involved in strengthening the adhesion force, after initial binding of a multivalent ligand. They hypothesize that conformational changes within the integrin heterodimer—which they were able to confirm with intramolecular FRET—is the key factor in activating integrin adhesiveness. JCB