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CELL MIGRATION

# Group voyage

Collective cell movements — the movement of cells in clusters, strands, sheets and tubes — are a driving force in development, tissue repair and tumour metastasis. Despite the importance of these movements in both normal and pathological conditions, the molecular mechanisms that control them remain unknown. Two studies now show that an evolutionarily conserved cascade that involves the Jun N-terminal kinase (JNK) signalling pathway regulates collective cell migration.

Migrations that occur during *Drosophila melanogaster* oogenesis provide a genetically tractable model to study collective cell movements. The egg chambers contain 15 nurse cells and a single oocyte surrounded by somatic follicle cells. At their anterior end, polar cells recruit several neighbouring follicle cells to form the border-cell cluster. Initially, all of the follicle cells are cuboidal in shape and adhere through adherens junctions. These cell–cell contacts are remodelled as egg-chamber development progresses. By stage 9, border cells migrate as a cohort between nurse cells towards the oocyte. So, how are border cells held together while they migrate?


A dissociating border-cell cluster after overexpression of Puckered-Myc (JNK phosphatase) and RNAi-mediated inhibition of myospheroid (β-integrin) expression in border cells. GFP marks border cells (green) and anti-Myc antibody shows Puckered expression (red). Image courtesy of E. Martin-Blanco, Instituto de Biologia Molecular de Barcelona (CSIC), Barcelona, Spain.

The group of Denise Montell found that *hindsight (hnt)*-deficient anterior follicle cells accumulated excess cell-adhesion molecules and failed to undergo normal collective movements. Overexpression of HNT — a zinc-finger-containing transcription factor — in border-cell clusters resulted in dramatic changes in motility, morphology and cluster cohesion: the border cells were elongated and splayed apart and the disassembled clusters failed to complete migration. Simultaneous overexpression of E-cadherin or β-catenin rescued the cluster-disassembly phenotype but not the migration phenotype, which indicates that cohesion and motility are separable features of this type of collective cell migration. How does HNT affect cluster cohesion and motility? Analysis of known signalling pathways revealed that HNT regulates cell adhesion and morphology through the JNK cascade, whereas its tissue-specific role in motility is mediated through the signal transducers and activators of transcription (STAT) pathway.

In a related paper, Flora Llense and Enrique Martin-Blanco report that the loss of JNK function causes a phenotype that resembles the cluster dissociation phenotype caused by HNT overexpression, and they identify a negative-feedback loop that controls JNK activity and regulates the integrity of the border-cell cluster. Analysis of the polarity of border cells and signalling pathways that are involved in adhesion and migration, such as integrins and actin scaffolding proteins, showed that JNK signalling modulates contacts between border cells, and between border cells and the substratum, to sustain collective migration by regulating several effectors, including the polarity factor Bazooka and the cytoskeletal adaptor D-paxillin.

Small interfering RNA-mediated knockdown of the mammalian homologue of HNT inhibited collective cell migration in a scratch-wound healing assay of mammary epithelial cells and led to the formation of immobile, tightly adherent cell colonies. So, HNT and JNK control border-cell cluster integrity and collective cell migration during *D. melanogaster* oogenesis; these mechanisms are likely to be conserved in other morphogenetic models as well as in cancer metastasis and invasiveness.

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**ORIGINAL RESEARCH PAPERS** Melani, M. *et al.* Regulation of cell adhesion and collective cell migration by Hindsight and its human homolog RREB1. *Curr. Biol.* 3 April 2008 (doi: 10.1016/j.cub.2008.03.024) | Llense, F. & Martín-Blanco, E. JNK signaling controls border cell cluster integrity and collective cell migration. *Curr. Biol.* 3 April 2008 (doi:10.1016/j.cub.2008.03.029)