

out blow. They found that inhibitors of the earliest stages of autophagosome formation had no effect, but the anti-malaria drug chloroquine, which inhibits the degradative function of autolysosomes, dramatically increased cell death. Affected cells accumulated grossly distorted autophagic vacuoles, lost their mitochondrial membrane potential almost completely, and suffered a large increase in reactive oxygen species within the cell, both a consequence of incomplete organelle destruction.

The authors suggest that preventing digestion of autophagosome contents might help kill the cancer cells because the accumulating toxic debris could leak out. Whatever the reason, when tumors received this one-two punch of Akt suppression and chloroquine-induced autophagy disruption, tumor remission was substantially increased.

Degtyarev, M., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200801099.

Tre1 says when, and where, to go

For migrants heading out on a journey, it's not enough to just pull up their stakes—they need to know where they're going. According to [Kunwar et al.](#), migrating germ cells take their cues from the G protein-coupled receptor Tre1, which not only loosens the cells' ties to home, but also points them in the right direction.

Drosophila germ cells arise next to the endoderm, but must migrate through the developing midgut to reach their final destination in the gonads. The researchers had previously shown that Tre1 ("trapped in endoderm") was essential for this transepithelial migration, but not for general cell motility, suggesting it might play a specific role at the start of migration.

Here, using live cell imaging, the team showed that when Tre1 function was lost, the cells remained in a disorganized clump at the endoderm and failed to assume the polarized shape characteristic of normal migrating cells. This mutant phenotype could be recapitulated by mutating G proteins, confirming that Tre1's role in migration was through its known function as a canonical G protein-coupled receptor.

So, was Tre1's role to start migration or to set up polarization? In fact, it was both. Tre1 signaling led to concentration of certain proteins towards the tail end of the cell, including Rho1, whose relocation had been implicated in germ cell migration, and E-cadherin. In Tre1 mutant cells E-cadherin remained at the cell periphery and kept germ cells attached to their neighbors. The authors wondered if this failure to separate from neighboring cells might account by itself for the loss of migratory ability. But by disabling cadherin in the mutant cells to loosen cell-cell adhesion, the team observed that germ cells dispersed randomly, but did not to move in an orderly way through the epithelium. "There is more to migration than the down-regulation of cadherin," concludes Ruth Lehmann, who led the study. "It requires polarization, and Tre1 appears to organize it."

Kunwar, P.S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200807049.

Random, fast, and out of control

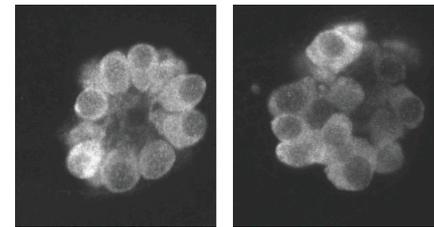
[Caswell et al.](#) report how the altered behavior of integrins can prompt metastatic movement in tumor cells.

On 2D surfaces, cells may migrate randomly, or be strongly unidirectional. Integrins, which link the cell to the extracellular matrix, are known to influence the mode of migration, but exactly how has been unclear. Recent work has suggested that an integrin called $\alpha5\beta1$ drives random movement, while an integrin called $\alpha v\beta3$ has been associated with unidirectional migration—the balance of activity between the two determining the type of movement. To further explore the contribution of $\alpha5\beta1$ to random migration, the authors thus blocked $\alpha v\beta3$.

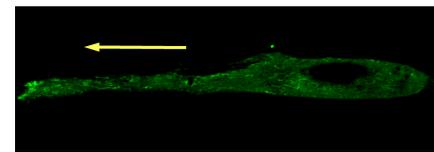
The treated cells changed their mode of migration from unidirectional to random, and their ability to invade 3D gels increased. The changed behavior correlated with an increase in trafficking of $\alpha5\beta1$ from intracellular compartments to anterior membrane protrusions. But this increase in trafficking did not significantly alter $\alpha5\beta1$'s contribution to cell adhesion—the ease with which cells were dislodged from a spinning disk increased as the amount of $\alpha v\beta3$ was reduced, but was not correlated with any change in $\alpha5\beta1$. This suggested that the cells' increased invasive ability was due to alteration in some other property. That property turned out to be activation of a proinvasive pathway headed by a kinase called Akt.

In $\alpha v\beta3$ -blocked cells, $\alpha5\beta1$ became associated with epidermal growth factor receptor 1 (EGFR1), which increased EGFR1's abundance at the membrane protrusions, as well as its autophosphorylation. Because EGFR1 is an activator of the Akt pathway, hey presto, the cells took on some new moves.

Caswell, P.T., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200804140.



The radial organization of germ cells is lost in the Tre1 mutant (right).



An increase in $\alpha5\beta1$ recycling promotes extension of long pseudopods at the cell front (arrow shows direction) in a 3D matrix.