A chiral attraction

The gypsy moth *Lymantria dispar* is a persistent pest in Europe, Asia and North America, causing major deforestation as a result of outbreaks approximately every ten years. Each spring the mating period is a chemical frenzy, with stationary females attracting males up to a kilometer away with released sex pheromones. Males detect these signals with sensory hairs (sensilla trichodea) on their antennae that are directly linked to olfactory neurons. It is through this sensory pathway that *L. dispar* recognizes the structure and concentration of its primary pheromone, (7*R*, 8*S*)-*cis*-2-methyl-7,8-epoxyoctadecane, (+)-disparlure. Although (+)-disparlure is the principal attractant, the antipode (−)-disparlure is also recognized by some neurons and is an antagonist of the (+)-enantiomer. The dendrites of olfactory neurons are bathed in sensillar lymph containing very high (millimolar) concentrations of pheromone-binding proteins (PBPs). *L. dispar* has two such PBPs that transport the hydrophobic pheromones through the aqueous lymph. It now appears that gypsy moth PBPs are able to distinguish between the enantiomers of disparlure.

To study the relative affinities of *L. dispar* PBP1 and PBP2 for the two enantiomers of disparlure, Plettner and co-workers first had to overcome some of the challenges inherent in working with hydrophobic molecules in aqueous solution[1]. Specifically, they needed to account for ligand adsorption on the sides of vials and separate protein-bound ligand from soluble ligand. They developed a gel-filtration method used in combination with decanol-coated vials to determine dissociation constants for recombinant PBP1 and PBP2 binding (+)- and (−)-disparlure. The results demonstrated for the first time that pheromone binding is reversible and that *L. dispar* PBPs exhibit enantiomeric specificity. PBP1 binds (−)-disparlure with an affinity more than twice that of (+)-disparlure, whereas PBP2 has a preference for (+)-disparlure. The authors propose that the difference in binding affinities might serve to fine-tune the pheromone-response threshold.

Although PBP1 and PBP2 have limited sequence homology (55%), conserved regions are expected to form pheromone-binding pockets that accommodate specific ligand features. For example, the relative orientation of binding pockets would allow recognition of the short versus long arms of disparlure. Further characterization of the structural differences responsible for the observed enantiomeric specificity should lead to identification of pheromone mimics that might irreversibly bind to a single PBP. If, indeed, the mosaic of PBP expression in sensilla determines the pheromone response threshold, such mimics could limit gypsy moth romance and reduce its devastating effects.

1 Plettner, E. *et al.* (2000) Discrimination of pheromone enantiomers by two pheromone binding proteins from the gypsy moth *Lymantria dispar*. *Biochemistry* 30, 8953–8962

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The harder the better: effects of substrate rigidity on cell motility

Cells move in response to gradients of a wide range of stimuli, the most well-known of these being soluble factors in the extracellular milieu (chemotaxis) and constituents of the extracellular matrix (hapatotaxis). Lo *et al.* now report that gradients of cell substratum rigidity can also influence the direction and speed of cell motility, an effect they term ‘durotaxis’[1]. Durotaxis could have wide-ranging implications, both on the migration of a variety of cells and on its effects on the biochemistry of cell motility.

The main result is that the NIH 3T3 cells used in this study preferentially migrate on more-rigid (‘stiff’) as opposed to less-rigid (‘soft’) substrates. The authors use a system they have developed previously to make surfaces with collagen-coated polyacrylamide substrates of varying rigidity. In this study, they make rigidity gradients and examine how cell migration changes as they encounter these changes in rigidity. Cells on a soft substrate rapidly re-orient themselves upon contact with a stiff substrate, with the cell edge that contacts the stiff substrate becoming the new leading edge. The cell then transiently accelerates and migrates onto the stiff substrate. Conversely, when cells on a stiff substrate contact a soft substrate, they change their direction to avoid the soft substrate and move parallel to it. Studies using mechanical manipulation of a homogenous substrate further support these results. The authors also provide evidence that this effect is exerted mostly through changes in the protruding leading-edge lamella of the cell.

The implications of this study on cell motility are intriguing. A long list of physiological processes rely on directional cell migration, including: migration of cells to specific locations during development; neuronal pathfinding; migration of leukocytes to sites of infection; and wound repair. It is easy to imagine that substrate rigidity might vary dramatically in these processes, and might strongly affect cell migration. In addition, the study presents questions as to the molecular mechanisms by which changes in substrate rigidity affect the intracellular machinery of cell motility. There are many possible mechanisms, including effects on the avidity or affinity of integrin receptors, or on stress-sensitive ion channels. These responses could, in turn, affect changes in actin polymerization dynamics, which is thought to provide the force for leading-edge protrusion. Alternatively, the authors propose that a member of the myosin family of actin-based motors could be affected, resulting in changes in cellular contractility. These issues are likely to keep us busy for years to come!

1 Lo, C.M. *et al.* (2000) Cell movement is guided by the rigidity of the substrate. *Biophys. J.* 79, 144–152

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HATs on tails

Despite the recent flurry of structural data that has begun to reveal details of the intricate waltz that precedes transcription of a gene, little is known about how transcription overcomes the obstacle posed by chromatin structure. Although most *in vitro* transcriptional assays are carried out on naked template DNA, in the cell it is not free but found tightly associated with the histone proteins, which are responsible for keeping the genome tidily packaged away in the nucleus. So, how does the bulky transcriptional machinery home in on its tightly guarded target and then prize it open to begin transcription? A clue to this came from the finding that histones associated with transcriptionally active genes are heavily acetylated. Given its histone acetyl transferase (HAT) activity, a component of the TFIID complex, $TAF_{II}250$, seems to be the main suspect. The $TAF_{II}250$ sequence also shows two occurrences of a small domain found in a wide variety of signalling proteins, called the bromodomain. A possible function for this domain was proposed when a structural view of a single bromodomain from another HAT protein, P/CAF, revealed a pocket where acetylated lysine residues could bind. However, the affinity of acetyllysine for this single site was found to be extremely low, leaving the mystery of the bromodomain function unresolved.

One of the leaders in the field of TAFs, Robert Tjian, and his group at UC Berkeley have now determined the structure of the double-bromodomain module from $TAF_{II}250$