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Planar cell polarity

Fashioning solutions

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Scientists like to consider themselves as especially objective, but however hard we try we cannot be very different from everyone else. Like them we helplessly absorb our knowledge, our perspectives, our valuation of whether something is exciting or boring from those around us. In this "extra view" I reflect on fashion, illustrating by a small discovery of ours,[1] and discussing why it was not made before.

Beauty is bought by judgement of the eye,
Not utter'd by base sale of chapmen's tongues
Love's Labour's Lost 2(i)
(William Shakespeare)

Our finding is in the field called "planar cell polarity" (PCP). PCP refers not the apico-basal polarity of an epithelial cell, but to its orientation within the plane of the cell sheet. The PCP field is tiny and well defined, with a long history of little progress towards a mechanistic understanding. What is most interesting about PCP is the central problem: how do cells orient themselves within the context of an embryo, how do they "know" which is the head end, so they can beat cilia in the right direction, point extending axons, grow a limb and align it correctly? This is a deep problem, intrinsic to the process of animal design yet, strangely, few have acknowledged this in well over a century of embryology. One exception is Sydney Brenner who realized in the 1960s how important planar polarity is; he argued that genetics can give us a point of entry into this and other intractable problems.[2]

The use of genetics for investigating PCP began with David Gubb and Antonio Garcia-Bellido who studied mutations that disturbed bristle orientation in Drosophila.[3] They found that a small clone of cells that lacked the *frizzled* gene (*fz*) changed the polarity of a few rows of wild-type cells around. Paul Adler, who built up the genetics of PCP from the beginning, called this phenomenon "domineering nonautonomy". The term is not perfect as it gives the impression that the clone imposes something on the surround, when a more apposite term might have indicated that it is the interaction between the cells of the clone and its neighbors that produces the repolarization. Indeed usually there are changes of polarity both inside and outside the clone. Never mind, Adler's group undertook systematic screens to identify other genes that are needed for normal polarity; he identified several including the important genes *starry night* (*stan,* also called *flamingo*) and *Van Gogh* (*Vang* also called *strabismus*).[4] Earlier it had been argued that cell polarity in the insect epidermis is fixed by the vectors of a gradient field[5] and Adler proposed that a pertinent factor in Drosophila is a gradient of Fz activity that polarizes epithelial cells to point their hairs down the local slope. This idea has considerable explanatory force, and he and colleagues provided evidence: they engineered a reversed gradient of Fz in the wing that, in effect, turned around the little hairs on the wing blade.[6] Frizzled is a very marketable gene; it is a trendy looking receptor that responds to the morphogen Wingless. So it was not so surprising that the vast majority of experiments and papers on PCP—right up to now—have concentrated on Fz itself and the other genes,

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such as *Vang* and *stan*, that work with Fz to effect PCP. Adler named these genes the "core PCP genes" in order to enshrine their central importance and to place *fz* at the centre of mechanistic models of PCP.

Long ago, in the first half of the 20th century, four genes *dachs*, *dachsous(ds)*, *fat(ft)* and *four-jointed* (*fj*) were discovered in Drosophila; *ds* and *ft* were found to encode cadherin proteins that are dauntingly large. Mutations in these three genes affect organ shape and growth but also disturb polarity of the tarsal segments. Much later it was found that *ds*, *ft* and *fj* also caused domineering nonautonomy when tested in mosaics and it therefore became necessary to fit these genes somewhere into models of PCP. Although there were no obvious mechanistic connections, there was the attractive possibility that they might provide an upstream cue that orients the slope of the Fz gradient (if there were one) or in some other way help steer the core genes. Then it was found that, in the absence of *fz*, ft^- clones in eyes did not show the same behavior as ft^- clones do in the wild-type.[7] The data supporting this finding were poor: it was certainly not clear that removing *fz* cancelled the ability of cells to respond to Ft (which it should have done if Ft works on cell allocation in the eye via Fz). Nevertheless the authors concluded that "Ft, Ds and Fj collaborate to regulate Fz signaling", to provide a global cue that directs the core proteins. The paper was published in *Cell* and this improved the impact of the conclusion without having the slightest effect on the quality of the evidence. Nevertheless, this precarious conclusion had been launched and it rapidly gained verisimilitude and respectability. For example in an influential paper[8] it was stated that "Ft signaling requires Fz activity, as loss of *ft* function in large or small clones does not alter the characteristic polarity pattern of *fz* mutant wings (not shown)". More tangential observations were marshaled in an illogical attempt to justify the general statement that "in the wing, as in the eye, Fj, Ds and Ft orient the direction of the Fz-mediated intercellular feedback loop". This was then reified in a diagram. Unfortunately this conclusion was given the imprimatur of Nature and that helped the single pathway model into everyone's embrace. The model had appeal as it brought all the genes together; it also sidelined Ft and Ds so that people could stop worrying about them—and they could go on working on the core genes, which were seen as nearer the kitchens of both fashion and function. By the turn of the century most workers on PCP were researching vertebrate systems and, perhaps because methods are nowhere near as good as they are in Drosophila, these workers, naturally, followed the paths beaten out in the fly papers. Nearly all those interested in PCP continued to concentrate on the core proteins and left *ds* and *ft* largely alone. A quick search of Pubmed tells me that 129 papers about PCP in 2000–2010 mentioned Fz in the abstract while only 28 mentioned Dachsous.

In 2006, we published a number of tests of the single pathway model (that *ds* and *ft* lie upstream of *fz* and its helpers) and all these tests denied it. We concluded that PCP has at least two *independent* inputs, one from what we call the Stan system (the core proteins) and one we call the Ds/Ft system.[9] It would follow that the Ds/Ft system has its own independent inputs into the orientation of the hairs. Some say the jury is out on this one, we say just weigh the evidence. If we are right the finding raises two big unanswered questions; first, what is the mechanism that the Ds/Ft system uses to orient hairs and second, how do the two systems liaise in the cell to produce the structural outputs of PCP?

We are closing in on our current little paper, which is concerned to answer a simple question: what orients the denticles of the Drosophila larva? These denticles are in six rows, seven in older larvae; they point forwards in rows 1 and 2 and backwards in rows 3–6 (apart from row 4 which seems to be oriented by a separate mechanism[10]). Up to our work it had, inevitably, been assumed that the core proteins were responsible for polarity of the larval denticles. However there was a serious problem with this hypothesis—remove Fz and the polarity of the denticles look very normal.[11,12] Instead of moving on and asking, if not Fz, what else might be orienting the denticles, the several scientists continued to describe a more or less non-effect. However, a few years ago, while investigating *ds* mutants, we found that the larvae have seriously disoriented denticles.[9] We had earlier found evidence for a gradient of Ds, that declined one way in the A compartment of adults and the other way in the P compartments.[13] Since the denticles in the larva point forwards in the P compartment and backwards in the A, perhaps the denticles just pointed down the Ds gradients in both compartments? We test this simple hypothesis in the current paper and the answer seems to be yes. We could not find evidence for significant input from the Stan system. I am not going to summarize the paper further here as you can read it if you like.

However I hope you find this story instructive. PCP, like many other research subjects, has suffered considerably because scientists have fixed their eyes on a small and fashionable area that has been well sold. They have made many illuminating findings, but they have tended to bypass a group of genes that has been known for the larger part of 100 years. Why? Mostly because they are not in the limelight, and also because Ds and Ft are large proteins and therefore more difficult to work with. We agree with earlier workers on these genes[14] that the Ds/Ft system is involved in more than only PCP, and we think they may be more fundamental and informative than the Stan system. I hope that workers with vertebrate PCP will turn their attention increasingly towards the Ds/Ft system, as up to now very few have done so. The message is a general one: even if many scientists work on one approach it doesn't mean it is the right approach or that a scientist casting around for a fresh project should go and join them. I think it will almost always be more creative and more useful to go to unfrequented places to look for new approaches to old problems.

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Note

*Referencing this piece properly would take about 100 references so apologies to all as there is no space to do so. For detailed profiles of genes, please use Flybase. For a primer on PCP review, see references 15 and 16.

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