Bristle Patterning in *Drosophila*

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Summary

The 5000 bristles that protrude from the cuticle of a *Drosophila* adult function as either mechanosensors or chemosensors, and they are arranged in surprisingly intricate patterns. Development of the patterns appears to involve five stages: (1) establishment of a coordinate system of 'positional information'; (2) partitioning of the epidermis into areas where bristles either can or cannot originate; (3) selection of one or more bristle mother cells within each permissible area; (4) suppression of bristle development in the neighborhood of each mother cell; and (5) differentiation of the mother cell to produce four or more descendant cells, each of which forms part of the bristle apparatus. Some of the genes that control these events participate in more than one stage, and others play key roles in seemingly unrelated developmental pathways, including embryonic neurogenesis, body segmentation, and sex determination.

Adaptations or Accidents?

Like a turtle's shell, the cuticle of arthropods shields the body but prevents sensations from reaching the skin. Insects have evolutionarily solved this problem by studding their cuticle with miniature sense organs[1]. In flies, the most common such organ is the bristle, and most bristles function as mechanosensory devices. Deflection of a bristle triggers an underlying neuron to fire a signal to the brain. Other bristles function as chemoreceptors, and their neurons extend up the shaft to a pore at the tip where they can smell or taste the environment directly.

A priori, it would be reasonable to imagine that sensory bristles might be arranged with no more precision than the hairs on your arm. In many insects, however, they form intricate patterns. In the fruitfly *Drosophila melanogaster* there are about 5000 bristles. The 'macrochaetes' (large bristles) have peculiar configurations that have been evolutionarily conserved for 50 million years[2]. The 'microchaetes' (small bristles) are typically arranged in rows and can manifest strikingly regular spacing (Fig. 1). Why such patterns? Some undoubtedly are adaptive. For example, the rows of adjacent bristles on the forelegs are used as brushes to wipe dust from the eyes. Many of the patterns, however, may have no function. Most rows are aligned parallel to the long axis of the body or the limbs, and

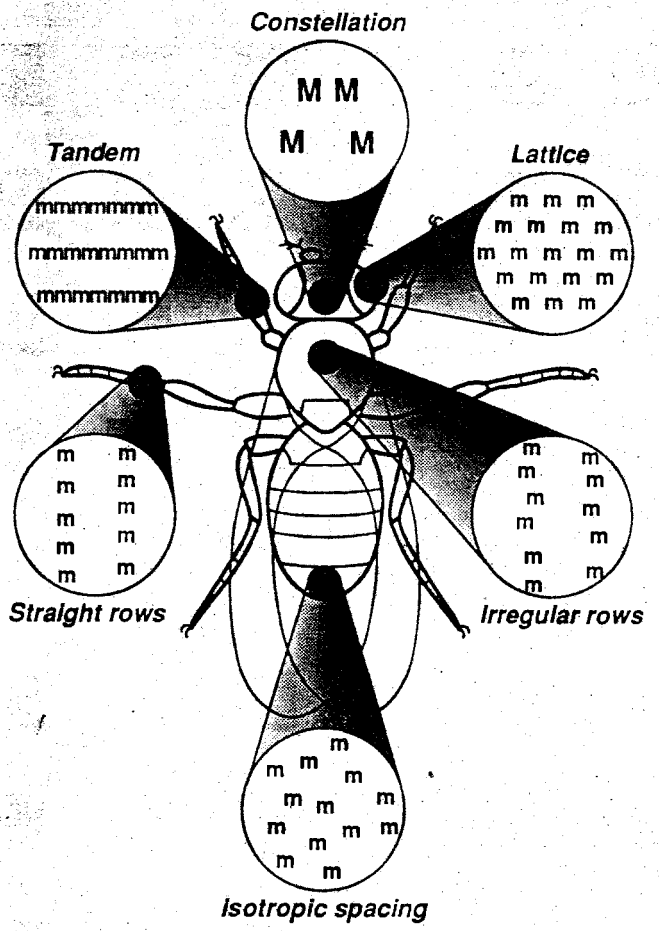

Fig. 1. Diversity of bristle arrangements in *Drosophila*. Large bristles ('M'=macrochaetes) are arranged in invariant patterns ('constellations') which typically lack rows. Smaller bristles ('m'=microchaetes) are commonly organized in rows that are aligned parallel to the axes of the body or limbs. The bristles on the back of the abdomen are spaced uniformly but arranged randomly ('isotropic spacing'), except along the posterior edge of each segment (not shown) where they form rows. Rows of abutting bristles are found on certain segments of the forelegs and hindlegs but not the middle legs. On the middle legs the most prevalent motif is a straight row of evenly spaced bristles.

they may arise along contour lines in the coordinate systems that direct development (see below). Moreover, there is mounting evidence that a single basic mechanism dictates the positions of bristles in the adult and neuroblasts in the embryo (Table 1). The mechanism may have originally evolved to generate regular matrices of neuroblasts, which are needed for circuitry in the central nervous system. If it subsequently acquired the task of directing the development of adult bristle patterns, part of the peripheral nervous system, then the orderliness of those patterns could be an automatic but incidental consequence of the mechanism's mode of operation.

The Problem

Why do certain skin cells develop as bristles, while

Table 1. *Development of adult bristle patterns vs. embryonic neuroblast patterns*[a]

Feature	Bristle patterns	Neuroblast patterns
Nervous system	Adult peripheral N.S.	Embryonic central N.S.
Pattern element	Bristle mother cell	Neuroblast
Arrangement	Rows, etc.	Rows
Equivalence groups	Proneural clusters, etc.	Neurogenic region
Lateral inhibition	Yes	Yes[b]
Spatiotemporal birth sequence	Nonlinear, except eye	Nonlinear
Morphogenesis	Delamination of neuron, thecogen, and trichogen	Delamination of neuroblast
Differentiation	Stereotyped cell lineage	Stereotyped cell lineage
EG genes	AS-C, *da*, *h*, *emc*, (*sgg*?)	AS-C, *da*, *sgg*, *elav*, *vnd*
IF genes	*N*, *shi*, *Dl*, *pyd*, *sca*, (*sgg*?, *top*?)	*N*, *shi*, *Dl*, *bib*, *mam*, *neu*, *E(spl)*, *amx*

[a] References for aspects of bristle patterning not discussed in the text are 41 and 53. References for neurogenesis include 38, 44 and 45. The term 'nonlinear' indicates that pattern elements do not originate in a linear sequence across the array in any direction, and 'delamination' means a movement of the cell body to a layer beneath the epithelium. Abbreviations: *amx* (*almondex*), AS-C (*achaete-scute* complex), *bib* (*big brain*), *da* (*daughterless*), *Dl* (*Delta*), *elav* (*embryonic lethal, abnormal visual system*), *emc* (*extramacrochaetae*), *E(spl)* (*Enhancer of split*), *h* (*hairy*), *mam* (*master mind*), *N* (*Notch*), *neu* (*neuralized*), *pyd* (*polychaetoid*), *sca* (*scabrous*), *sgg* (*shaggy*), *shi* (*shibire*), *top* (*torpedo*), and *vnd* (*ventral nervous system condensation defective*).

[b] Inferred from ablation experiments with grasshopper embryos.

others do not? This question of how cells become different from one another is a fundamental one in developmental biology, and most researchers deal with embryos or organs that are 3-dimensional and contain many types of cells. Because bristles develop within an epidermal monolayer[3], the question of differentiation is reduced to a simple Hamletian choice (to be or not to be a bristle) within a Euclidean plane. The problem is made even simpler by the fact that all bristles, regardless of their size, develop from single cells[4]. These bristle mother cells (BMCs) divide several times to produce the four or more cells that comprise the bristle organ.

Bristle patterns do not develop in a single step. The strategy seems to involve successively refined approximations of the final patterns. The phases of the process are described below (Fig. 2).

The Coordinate System

The skin of an adult fruitfly is a quilt of pieces that develop separately. The structures of the thorax and head come from 'imaginal discs'[5], which grow as pockets inside the larva. The ability of discs to regenerate missing pieces when fragments are removed led to a model of regeneration which also explains their normal development. The 'Polar Coordinate Model'[6] is based on the notion that cells have information about their locations within a disc ('positional information'[7]), which they use to make choices during development or regeneration. How they acquire that information is not known. There are hints that the 'segment polarity' genes, which control the patterning

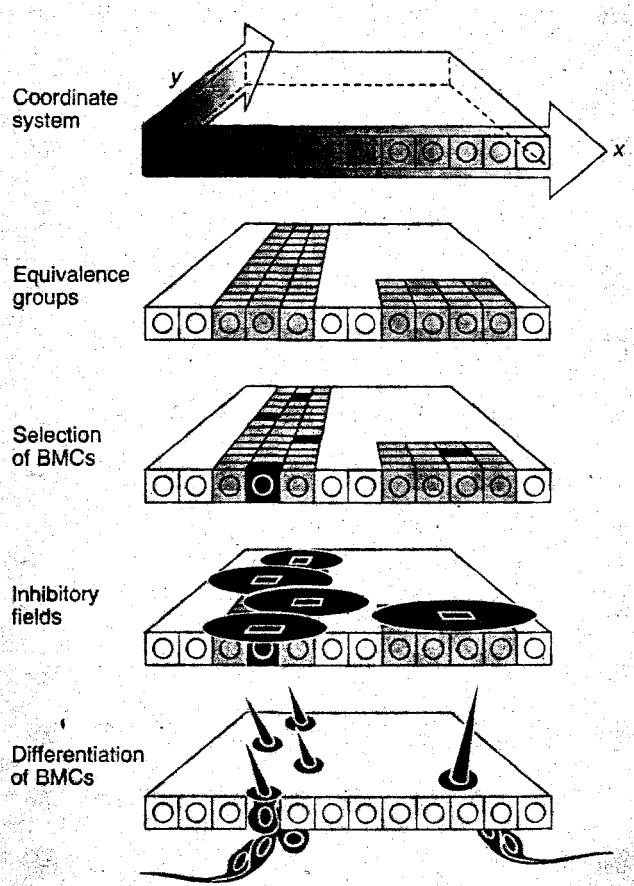

Fig. 2. Stages in bristle pattern development. (1) A coordinate system informs each cell of its position. The system (Cartesian in this illustration though imaginal discs probably use polar coordinates) is established at early stage, with an intervening period of growth leading to this final size. Shading denotes a gradient in the intensity of the positional signal along each axis. (2) Certain coordinates endow cells with the competence to become bristle mother cells. In this illustration, there are two 'equivalence groups' of such 'proneural' cells (shaded areas) – a stripe at $3 \leq x \leq 5$ and a spot at $8 \leq x \leq 11$ and $1 \leq y \leq 4$. (3) Bristle mother cells (BMCs, black cells) are selected within each equivalence group. (4) Each BMC uses an inhibitory field (black circle) to inhibit surrounding cells from becoming BMCs. (5) Each BMC undergoes differentiative mitoses to produce the four (or more) cells of the bristle organ. The tormogen resides in the plane of the epidermis, whereas the remaining cells sink beneath it.

of embryonic body segments, may also be responsible for encoding positional information around the circumference of each disc, while the radial coordinate may be encoded by genes whose mutant alleles cause distal deficiencies in the appendages[8].

In theory, coordinate systems of positional information should be able to specify any bristle pattern, just as algebraic equations of Cartesian coodinates can encode different curves in a plane. However, mature discs contain as many as 50,000 cells[9], and the selection of individual cells as BMCs would require extreme precision in cellular communication, regardless of the physical nature of the signaling mode (*e.g.*, diffusible molecules or cell-surface interactions). Furthermore, cells would have to compute decisions based upon enormous numbers of possible coordinates, requiring extremely complex genetic circuitry. The actual role of the coordinate system appears to be more limited: it demarcates areas, while other mechanisms designate points within those areas.

Equivalence Groups

The first evidence for 'fine-tuning' mechanisms in bristle patterning came from an analysis of flies that were genetically prevented from making a macrochaete at a certain site. In such flies, a new macrochaete can develop nearby, evidently substituting for the suppressed one[10]. This finding led to the hypothesis that each BMC develops within a group of cells, any one of which is 'competent' to become a BMC. Only one cell usually does so, but other cells within the group can apparently substitute if it cannot. Similar 'equivalence groups' (EGs) of redundantly equipotent cells are found in diverse organisms. Because the epidermal cells in the EG at each macrochaete site are potential precursors for a neural fate, they have been termed 'proneural clusters'[11–13]. Microchaetes may likewise develop from such clusters[14].

What phenotypes are expected for genes controlling the development of EGs? Loss-of-function mutations should eliminate EGs, and gain-of-function mutations should enlarge existing EGs or create new ones. Thus, the predicted phenotypes would be nude or hirsute flies respectively. Genes that satisfy these criteria are nested in the *achaete-scute* complex near the tip of the X chromosome[11,15]. Deletions of the complex suppress nearly all bristles, and gain-of-function '*Hairy wing*' mutations[16] cause extra bristles in various parts of the body, including regions that normally have none. Partial-loss-of-function *scute* and *achaete* mutations tend to remove either macrochaetes or microchaetes respectively, and individual *scute* alleles remove characteristic subsets of macrochaetes. The subsets are enigmatic and have baffled investigators for decades (but see refs 15 and 17).

The molecular machinery of the EG gene network has proven even more fascinating than the puzzling phenotypes. The *achaete-scute* complex contains four genes, all of whose DNA sequences share homology with the mammalian *myc* oncogene[18]. The homologous region includes a 'helix-loop-helix' (HLH) motif that enables proteins to form dimers, plus a basic domain that allows them to bind specific DNA sequences. Searches for trans-acting regulators of the *achaete-scute* locus have identified three additional genes outside the complex – *hairy* (*h*), *extramacrochaetae* (*emc*), and *daughterless* (*da*) – and all of them contain the *myc* HLH motif[19–24]. Strangely, *h* is a 'pair-rule' gene involved in the patterning of embryonic body segments, and *da* is part of the genetic hierarchy that controls sex determination. What could segmentation, bristles, and gender possibly have in common? All of them involve binary cellular decisions (segment/intersegment, bristle/epidermis, male/female) that affect the fly's anatomy. Decisions are digital 'on-or-off' events, whereas the factors that influence decisions may be analog summations of various inputs (from gap genes, positional-information genes, and X/A-ratio genes respectively). Thus, the ability of HLH proteins to form heterodimers (*e.g.*, a *h* monomer binding to a *da* monomer) permits the combining of positive and negative inputs, and the ability of these dimers to bind to DNA allows the sum of the inputs to regulate the transcription of 'switch' genes that determine cell identities. As odd as it may seem for a single analog-to-digital transducing device to be used for such diverse developmental processes, some bizarre facts support this conclusion: (1) the transcript of one of the *achaete-scute* genes is used as a numerator element in the X/A ratio (number of X chromosomes relative to number of sets of autosomes) that determines gender[25], and (2) misexpression of the *h* gene (driven by a gap-gene promoter) can cause 100% lethality of female embryos without affecting the viability of male embryos[26]. In mammals, expression of the HLH-containing gene MyoD can convert fibroblasts into myoblasts, implying an ancient origin for this sort of determinative mechanism[27].

The models that have been proposed to explain HLH protein interactions in *Drosophila* assume that positive regulators form functional heterodimers with key proteins from the *achaete-scute* complex, and negative regulators form nonfunctional heterodimers that are unable to bind DNA[23,24,26]. Among the trans-regulators of the *achaete-scute* locus, *da* acts in a cooperative manner[21] whereas *h* and *emc* act as titratable competitive inhibitors[28]. Loss-of-function mutations in *h* and *emc* cause extra bristles: microchaetes in the case of *h*, macrochaetes in the case of *emc*. At the tissue level, the implication is that *da* and one or more *achaete-scute* proteins form functional heterodimers that define EGs, whereas cells outside of EGs might be prevented from entering a proneural pathway because they contain *h* or *emc* proteins. In fact, *achaete-scute* proteins are expressed only in clusters of cells at macrochaete sites (microchaete sites, which develop later, have not been analyzed)[29,30], and

da is expressed ubiquitously, so their combined domains are indeed coextensive with the supposed areas of EGs. However, *emc* is transcribed ubiquitously[24], and *h* protein is present both inside and outside macrochaete EGs, though it is excluded from bristle neurons[31]. In the legs, *h* protein is expressed in four stripes that run parallel to the bristle rows, but the relation of the stripes to the rows is uncertain. How the intracellular models of HLH-protein interaction might be reconciled with these findings is not clear. Another unexplained result is that when the *achaete-scute* or *h* genes are artificially expressed ubiquitously (*via* heat-shock promoters), the resulting flies are virtually normal in bristle pattern[22,32]. One might have expected a ubiquitous presence or absence of bristles respectively.

Selection of BMCs

In the original experiment that revealed the existence of EGs, the absence of a macrochaete at its normal location permitted the development of a 'replacement' macrochaete either anterior or posterior to this position[10]. The normal site, in this case, must reside at roughly the center of the EG. How is the cell in the center chosen? One idea is that all cells within an EG secrete a 'chaetogen' molecule that diffuses in all directions and thus reaches its greatest concentration in the center of the group[33]. If bristle initiation were triggered by concentrations above a certain threshold, then the cell at the center would usually form the bristle. The chaetogen may be regulated by the *achaete-scute* locus, since expression of *achaete-scute* proteins is highest in the center of most proneural clusters[29,30]. Additional evidence comes from studies of mosaic flies which begin development as heterozygotes carrying both *Hairy wing* (*Hw*) and its wild-type allele[34]. Somatic recombination in such flies leads to clones of homozygous *Hw/Hw* and +/+ cells. The bristle density in the *Hw/Hw* clones is lower than in purely *Hw/Hw* flies, and the density in the +/+ clones is higher than in purely +/+ flies – results that are consistent with local diffusion of a chaetogen. A similar local 'nonautonomy' characterizes *achaete* clones[10].

Inhibitory Fields

Diffusible signals are subject to 'noise' from statistical fluctuations in concentration. Errors in the hypothetical chaetogen mechanism should lead to two or more bristles at a site where only one is supposed to develop. In fact, such errors are rare. Mistakes might be prevented if the first cell to commence bristle development inhibits its neighbors from doing so. The notion of inhibitory 'fields' (IFs) is an old one in developmental biology, and the mechanism that is usually envisioned involves the production of an inhibitory molecule which diffuses in all directions.

If all cells within an EG would eventually initiate bristle development in the absence of inhibition, then loss-of-function mutations in IF genes should yield tufts of bristles wherever a single bristle would normally form. Unlike EG mutants, the extra bristles of IF mutants should be confined to existing EGs. Mutations that cause this sort of phenotype are found in *Notch*, *shibire*, *Delta*, *polychaetoid*, and *scabrous*[35] (see refs 36 and 37 for reviews). Mutations in a sixth gene – *shaggy* – cause a similar phenotype but also induce bristles on the wing surface, which is normally bare[38].

Temperature-sensitive mutations in *Notch* and *shibire* cause extra bristles when mutant individuals are exposed to pulses of high temperature during discrete sensitive periods. Although tufts of bristles are found at macrochaete sites as expected, clumps of microchaetes are not common[39–41]. Instead, there is a general increase in microchaete density within certain areas or stripes. On the thorax the stripes develop where individual rows of microchaetes would normally be found[42]. Are the EGs of microchaete rows shaped like stripes, rather than as a series of spots? It would appear so, and this conclusion forces a re-examination of the role of IFs.

According to the notion of 'proneural clusters' each bristle site has its own IF, and the area of the IF is nearly congruent with the EG so that all other cells are inhibited. To accommodate more than one BMC per EG, the IFs would have to be smaller than the EG (Fig. 2). This poses no special theoretical problem. However, if the positions of individual sites are no longer specified by the coordinate system, then how are they selected? Perhaps the selection is somewhat random, and the IF mechanism ensures a certain minimum distance between the sites. In such a scenario, the IF is playing a new role: it controls bristle spacing. The idea that fields of influence around bristle sites might determine bristle spacing was proposed long ago for isotropically spaced bristles on the abdomen of a hemipteran insect[43]. For such patterns, the EG would be a broad area, much larger than IF diameters. Much the same situation prevails in the neurogenic region of the *Drosophila* embryo. Within that region, one fourth of the cells normally develop as neuroblasts, whereas in embryos that are mutant for 'neurogenic' genes (including *Notch* and *shibire*; Table 1) nearly all of the cells develop as neuroblasts[44,45]. Presumably, the same IF mechanism is operating there[38,44]. Random initiation of sites cannot lead to the kind of uniform spacing that characterizes many bristle patterns (unless cells rearrange after initiation). However, if the sites were to develop sequentially from one end of the future pattern to the other, then new BMCs would arise precisely one IF radius from previous sites. This sort of mechanism may operate in the eye, where ommatidia develop in a wave from posterior to anterior, but no comparable waves have been found for other patterns[41]. In those cases, additional fine-tuning mechanisms may be involved.

Notice that IFs are supposed to be properties of

single BMCs, whereas EGs are assumed to be controlled by the coordinate system. It should therefore be possible to test the logic of the preceding argument by changing the sizes of cells (and their IFs) relative to the body (and its EGs). If cells were made smaller in an otherwise normal body, then IFs should shrink relative to EGs and extra bristles should arise. The phenotype should be similar to that of *Notch* and *shibire*: extra macrochaetes should be clustered around the normal sites, and extra microchaetes should be evenly distributed throughout their normal areas (EGs). A suitable test situation is provided by diploid flies that contain patches of haploid tissue, since cell size is proportional to ploidy but body size is unaffected. As expected, the diploid regions in such flies are normal, and the haploid territories have extra macrochaetes (though they tend to be aligned rather than clumped) and a denser spacing of microchaetes[46].

For the IF interaction to function properly, the BMC must emit the signal, and the surrounding EG cells must receive it. Thus, two classes of IF genes should exist: those that control signaling and those that control reception. From the phenotype alone, it would be impossible to distinguish between mutants whose BMCs are 'mute' and those whose EG cells are 'deaf'. Based upon an analysis of mosaic flies containing both mutant and wild-type cells, it has been argued that *Delta* provides the signal and *Notch* the receptor[37,47]. Both of these genes contain a repeated motif related to vertebrate epidermal growth factor, and similar domains have been found in *lin-12*, a nematode gene that also appears to mediate lateral inhibition. Thus, the IF mechanism may have as old an evolutionary ancestry as the EG mechanism. *In vitro* cell-mixing experiments demonstrate cell-surface binding of the *Notch* and *Delta* proteins, implying that they could mediate intercellular communication *in vivo* through physical contact instead of diffusion[48]. Direct contact in a close-packed epidermis would mean that only five or six cells immediately adjacent to the BMC could be inhibited, but the average number of cells in each macrochaete EG cluster is more than 20 (as assessed by expression of *achaete-scute* proteins)[29,30]. Conceivably, the BMC could touch this many cells if it had filopodial extensions spanning several cell diameters[36].

Given the relatedness of *Notch* and *Delta* to vertebrate epidermal growth factor, one might ask whether there is a *Drosophila* homolog of the vertebrate receptor for this factor and, if so, whether mutations in the gene affect bristle patterning. The answer to both questions is yes. The homolog is the gene *torpedo* (a.k.a. *faint little ball* and *Ellipse*) and its mutant alleles can cause extra or missing bristles, depending upon the allele and the epidermal location[49,50]. Shouldn't mutations in an IF receptor lead only to 'deafness' and hence only extra (not missing) bristles? Not necessarily, as revealed by *Abruptex* mutations, which affect the extracellular domain of the *Notch* protein and cause an autonomous loss of bristles – as if the epidermal cells are deliriously 'hearing' an inhibitory signal even when it is absent[47]. The *shibire* gene encodes a protein which is 69% identical to rat dynamin, a molecule that drives microtubule movements *in vitro* and may motorize vesicles during endocytosis[51]. Whether endocytosis is involved in BMC communication is unknown. Another possible signal transducer is *shaggy*, which encodes a serine-threonine protein kinase, though its effects in genetic mosaics suggest a role in signaling as well as reception[37]. Finally, *scabrous* encodes a protein related to human fibrinogen, and the likelihood that this protein is secreted makes it a good candidate for the IF signal[35].

If the IF signal were a diffusible protein, then it should be highest in BMCs and detectable throughout EGs, but absent elsewhere. *In situ* localizations have been reported for *Notch* protein, which is found throughout the epidermis[52], and *scabrous* protein, which is confined to the same EG clusters as *achaete-scute* proteins and has an elevated level of expression for one cell therein (presumably the BMC)[35]. Although the spatial expression of *scabrous* agrees with the predicted distribution, the absence-of-function phenotype has far lower bristle densities than are obtainable with alleles of either *Notch* or *Delta*. Hence, the issue of which gene encodes the inhibitor remains unresolved.

BMC Differentiation

The final stage of bristle pattern development is differentiation of the BMCs. Each BMC divides several times to produce one cell that makes the bristle shaft (the 'trichogen'), another that makes a socket ('tormogen'), one or more neurons (mechanosensory bristles have one, chemosensory bristles five), and an accessory cell ('thecogen') that surrounds the dendrite of the neuron[1]. In the mechanosensory lineage, the two pairs of sisters are trichogen-tormogen and neuron-thecogen[53].

Surprisingly, some of the same genes that control IFs also seem to be involved in establishing the identity of the BMC descendants. For *Notch*, the temperature-sensitive period when extra microchaetes can be induced is followed by a period when most microchaetes are superficially missing. Beneath each site there are typically four neurons, suggesting that all four descendant cells have acquired a neural fate[42]. Conceivably, the four cells may constitute a miniature EG wherein the neuron inhibits the other three cells from becoming neurons[42]. However, during the sensitive period for missing bristles in *shibire*, the bristles often have two trichogens and no tormogens, implying that the tormogen has become a trichogen[39,41]. Likewise, a double-trichogen phenotype has been described for *Notch*[41,47] (especially its allele *split*) and other odd mixtures of bristle-cell types have

been found in *Delta* mutants (M. Muskavitch, pers. comm.). Thus, an alternative explanation would be that IF genes are used in a combinatorial manner to specify all of the cell identities within the bristle organ, not merely to distinguish neuronal from nonneuronal cells. The difference between these hypotheses is important, because the stereotyped lineage of the BMC is theoretically sufficient for allocating cell fates based upon pedigrees, with no need for communication among the descendant cells. Additional genes may be involved in establishing cell identities, including *Hairless* whose mutant alleles cause a transformation of trichogens into tormogens[54]. The identity of the sensory organ as a whole may be controlled by still other genes, such as *cut*, whose mutant phenotype shows a 'homeotic' transformation of mechanosensory bristles into chordotonal organs[55].

The Eye: A Special Case

Eye bristles occupy alternating vertices around each hexagon-shaped ommatidium, and there are about 800 ommatidia per eye. The ommatidia and bristles are arranged in a nearly perfect hexagonal lattice, which is constructed by a morphogenetic wave that sweeps across the eye disc during the larval period. Two plausible theories of eye development have been disproven: (1) that each ommatidium is a clone of cells descended from a single mother cell; and (2) that the lattice grows like a crystal – recruiting naive cells and assigning them fates based upon their positions on the template surface[56]. Instead, many lines of evidence have converged upon a model that was originally proposed to explain hexagonal patterns of feathers in birds[57]. The lattice is apparently built by means of inhibitory fields. Cells are competent to emit IFs if (1) the morphogenetic wavefront has reached them and (2) they are not within the IF of another cell. These rules generate a hexagonal lattice of points because each successive row arises in the interstices of the IFs of the previous row, which are one-half IF-radius out of phase (Fig. 3). In the case of the eye, the R8 photoreceptor cell presumably emits the IF signal, and all of the other cells of the ommatidium accrete in a shell around it *via* a cascade of inductive interactions between adjacent cells[56].

Some of the same mutations that affect bristle IFs have comparable effects on the patterning of R8 cells (and hence ommatidia). Mutations in *scabrous* cause irregularities in IF radii (leading to fusions of ommatidia), the temperature-sensitive *Notch* mutation reduces the IF radius extremely (causing densely packed R8 cells and eye scarring), and dominant mutations in *torpedo* cause many R8 cells (and hence whole regions of ommatidia) to be missing[58–60]. Perhaps the same IF signal is being used for two different purposes in the eye: (1) by R8 cells to create a lattice and (2) by bristle cells to ensure one bristle per EG (where the EG spans two vertices). Chaotic 'cross-talk' between R8 cells and bristle cells is evidently avoided because the ommatidia develop before the bristles, and the two arrays are constructed in different directions: the extra-R8 phenotype of the temperature-sensitive *Notch* mutation develops from posterior to anterior (following the morphogenetic wavefront), whereas the extra-bristle phenotype develops later from the center of the eye to the periphery (tracing the same path as BMC mitoses)[59,60].

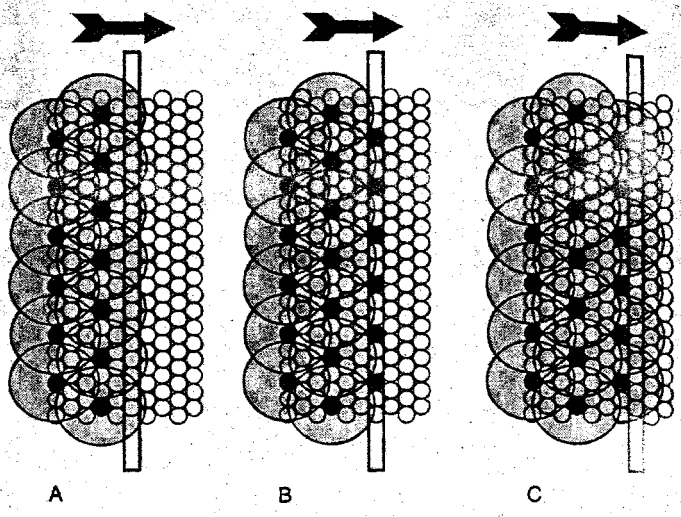

Fig. 3. Hypothetical model for the patterning of R8 photoreceptor cells in the eye. A morphogenetic wavefront (rectangle) progresses across the eye in the direction of the arrow. The only uncommitted cells (unfilled circles) that can become R8 cells (filled circles) are those which (1) are within the wavefront and (2) are not inhibited by other R8 cells. Each R8 cell inhibits its neighbors *via* an inhibitory field (grey circle). A–C: successive stages of development. New R8 cells arise within the crevices between previous inhibitory fields thereby generating a hexagonal lattice. After Ede[57].

Other Fine-Tuning Steps?

Another odd feature of the eye involves misplaced bristles. Normally, bristles are found on the anterior corner of each horizontal edge between ommatidia, but whenever a bristle is present at the posterior corner, the one at the anterior corner is missing[61] – as if the BMC had moved from one vertex to another. When marked clones of hairs and bristles are induced in other regions of the body (*e.g.*, see ref. 37), marked bristles are often found outside the marked-hair territories – again suggesting that they have moved.

Corrective movements of bristle cells could fine-tune the spacing of an initially irregular array. Just such a process has been observed for scale cells on the wings of moths[62], and scale cells may be homologous to bristle cells[4,63]. Evidence from cell-lineage studies, heat-induced disruptions, and mutant phenotypes suggests that both the alignment and spacing of the bristle cells on the legs may be adjusted by short-range cell movements[41], which would help explain why they are among the most orderly patterns on the fly surface.

Conclusions

Drosophila has about as many genes as it does bristles: roughly 5000. Studies of the mechanisms of bristle patterning have revealed how a dozen-or-so genes can be used to construct a variety of anatomies. Subsets of the same genes, rewired into different circuits, also build the ommatidial scaffolding of the eye and the generative matrix of the embryonic nervous system. Even smaller subsets are shared with the mechanisms that govern gender and segmentation. This efficient usage of a limited number of genes is not an invention of the Drosophilids or even the arthropods. The evolutionary relatedness of many of the genes to vertebrate and nematode counterparts indicates that the core networks were probably invented and 'debugged' in unicellular ancestors more than 600 million years ago.

As elegant as bristle patterning may seem from an engineering standpoint, the elements of its strategy are more akin to the style of an artist than an engineer. First the canvas is stretched and a broadbrush rendition of the design is painted. Then the details are added, and the final image is retouched until it is perfect or nearly so. For developmental biologists working in this field, dissecting the machinery behind the patterns has only served to deepen our appreciation for the patterns themselves.

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