Cell migration in the embryo and adult organism

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Introduction

At numerous times during embryonic development, and in the adult organism, cells are motile and actively move from one position to another (Trinkaus, *Cells Into Organs* 2nd edn. Prentis-Hall, 1984). During development, morphogenetic movements are critical in shaping the embryo. In the normal adult, white blood cells circulate through the capillaries and into the tissues, and keratinocytes as well as blood cells migrate into wounds to produce healing. Finally, in a pathological condition, tumor invasion and metastasis are the result of cell migration.

The means by which cells migrate have been studied extensively in tissue culture where the cells can be subjected to high resolution optical techniques and experimental perturbation. The peculiar crawling movement of cells and its underlying biochemical mechanisms are just beginning to be worked out and are the subject of other reviews in this issue. Less well analyzed is how cells move within a tissue or organism and what controls the pathways the cells take to their final destination. The control of these migratory movements within the organism is the subject of this review.

Observation of cell movement in the organism

Because most embryonic and adult tissues are opaque precluding direct observation of individual cells, most of what we know about cell movement in the organism is based on indirect observations, generally of fixed tissue. Recently, several techniques have been devised to label individual or groups of cells with vital dyes (Honig and Hume, *Trends Neurosci* 1989, 12:333–341) and to observe their subsequent migration using sophisticated imaging systems (Harris *et al., Development* 1987, 101:123–133; O'Rourke and Fraser, *Dev Biol* 1986, 114:265–276).

In a recent series of papers [1,2] the movements of mesoderm cells within the developing notochord and somites of the *Xenopus* gastrula were observed by explanting intact portions of the gastrula into organ culture, where their morphogenetic behavior is normal, and by labelling individual cells with the fluorescent vital dye DiI (Fig. 1). Time-lapse images of living cells were compared with traditionally fixed tissue that was observed by scanning electron microscopy. The movements that control the shaping of these two tissues, and their separation from each other, have now been carefully mapped. With such detailed knowledge of interactions at the cellular level, we are now in a position to examine the molecular interactions that drive these movements. Such techniques are certain to be useful in studying morphogenetic movements in other, similarly complicated and visually obscure, systems.

Cell adhesion

In order to move, cells must adhere to a substratum or surface against which they generate a tractional force. At least two classes of adhesion molecules have been identified: (1) those that mediate cell attachment to the extracellular matrix (cell–matrix adhesion molecules), and (2) those that mediate cell attachment to other cells (cell–cell adhesion molecules).

The group of cell-surface receptors that mediate adhesion to the extracellular matrix and have been studied most is the family of receptors known as the integrins (for review see Hynes, *Cell* 1987, 48:549–554; Ruoslahti and Pierschbacher, *Science* 1987, 238:491–497). They consist of two polypeptides, the α and β chains, and include receptors that mediate adhesion to most of the known matrix molecules including fibronectin, laminin, collagens, vitronectin and tenascin. Many of the receptors recognize the sequence Arg-Asp-Gly (RGD) on the matrix molecule, which in some way mediates binding specificity.

Cells migrating in the embryo or adult use integrin receptors to mediate their attachment to the extracellular matrix and this then facilitates migration. Integrins are found on many cells in the embryo (Duband *et al., J Cell Biol* 1986, 102:160–178; Krotoski *et al., J Cell Biol*

Abbreviations

bFGF—basic fibroblast growth factor; **EGF**—epidermal growth factor; **O/2A**—oligodendrocyte/type-2 astrocyte; **PA**—plasminogen activator; **PDGF**—platelet-derived growth factor; **PI-G**—phosphatidylinositol-glycan; **TGF**—transforming growth factor.

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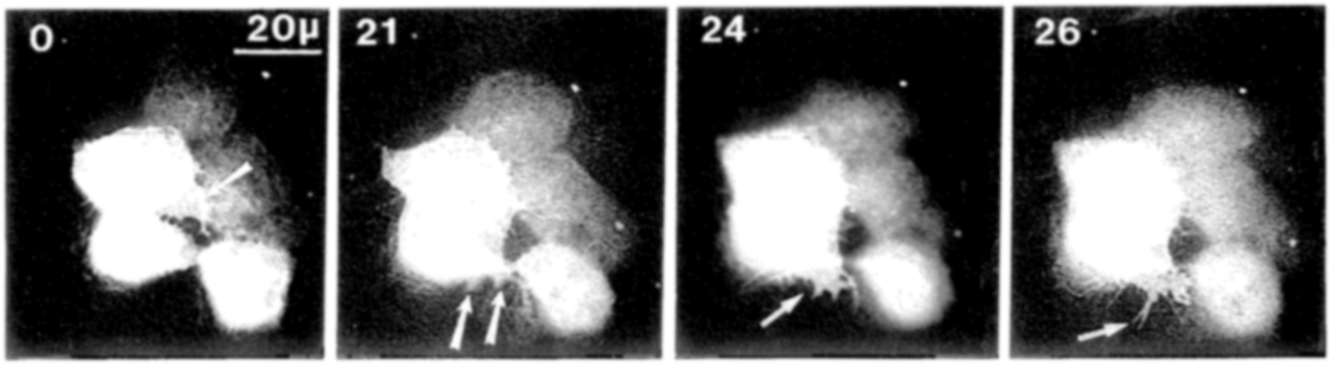

Fig. 1. Photographs taken from a time-lapse optical disc record of a DiI-labeled notochord cell, detailing its protrusive activity. Time elapsed in minutes is indicated in the upper left corner. Such innovative labeling techniques now allow us to observe cell movement in opaque embryos. Published with permission [1], © Alan R. Liss Inc., 1989.

1986, 103:1061–1071) and injection into the embryo of antibodies that perturb integrin function will also inhibit movement of neural crest cells (antibody JG22, Bronner-Fraser, *J Cell biol* 1985, 101:610–617; antibody CSAT, Bronner-Fraser, *Dev Biol* 1986, 117:528–536). Recently, the injection of the antibody CSAT into the chicken embryo was shown to inhibit the migration of myotome cells and the migration of muscle cell precursors to the body wall and gut [3].

Other molecules also mediate adhesion between cells and their extracellular matrix. For example, galactosyltransferase mediates adhesion to laminin [4] and heparan sulfate proteoglycan covalently-linked to phosphatidylinositol (Carey and Evans, *J Cell Biol* 1989, 108: 1891–1897) has been shown to mediate cell–matrix adhesion. In fact, a cell probably has several means of adhering to an individual matrix molecule.

Evidence is now accumulating that cell–matrix adhesion receptors are developmentally regulated. For example, premigratory mesodermal cells from the urodele gastrula have few if any fibronectin receptors, but as gastrulation proceeds they acquire more and maximum adherence to fibronectin occurs near the end of gastrulation [5].

Cell–cell adhesion molecules have been implicated in the control of many developmental processes (Edelman, *Annu Rev Cell Biol* 1986, 2:81–116; Takeichi, *Development* 1988, 102:639–655), and are known to control cell locomotion in a few instances. For example, it has recently been shown that the loss of liver-cell adhesion molecule in MDCK epithelial cells results in invasive behavior (Behrens *et al., J Cell Biol* 1989, 108:2435–2477).

The best known interactions in which cell motility is generated through cell–cell adhesion molecules are between several neurons or between neurons and glial cells. Neugebauer *et al.* [6], by using antibodies that block cell receptor function, discovered that the migration of retinal ganglion axons on astroglial cells in the optic pathway is mediated by the cell–cell adhesion molecules neural-cell adhesion molecule and N-cadherin, as well as an integrin that binds to laminin. Furthermore, these molecules are developmentally regulated so that neural-cell adhesion molecule functions only during the later stages of this migration. Because a combination of antibodies against all three of these adhesion regulating molecules does not completely block axon migration, additional adhesive interactions must be involved in this migration. Many more instances of cell–cell adhesions having a role in motility are certain to be discovered as more examples of cells migrating over other cells (such as the movement of notochord cells over each other as described above) are examined in detail.

Guidance of cell motility

Given that cells must adhere to a substratum to translocate, what mechanisms do they use to guide them to their destinations? Recently, the various mechanisms have been reviewed from the perspective of neuron migration [7] and neural crest cell migration [8]. I will list briefly these possibilities and then review the literature from the last year that supports some of these mechanisms.

Cues that could determine pathways include: (1) spaces that would provide pathways of least resistance, (2) adhesive pathways on which cells would preferentially attach because they are bordered by areas that are relatively non-adhesive, and (3) substrata that contain discontinuities on which cells would align (contact guidance). Although each of these cues could orient a cell, none determines the direction of migration. Thus, they could be likened to a street that orients the traveller but does not indicate whether to go north or south.

Other mechanisms may provide directional information, however. These include: (1) adhesive gradients (haptotaxis), (2) chemotactic gradients (chemotaxis), (3) electric fields (galvanotaxis), and (4) contact-induced directional migration (contact inhibition). Recently, convincing evidence for the role of some of these mechanisms in guiding fibroblast motility has been published. Guidance of growth cones and axons will be considered in a separate review in this issue (Lankford *et al.*, this issue, pp 80–85).

Adhesive tracks

Given that cells will often choose to move onto more adhesive substrata when presented with a choice in tissue culture (e.g. Rovasio *et al., J Cell Biol* 1983, 96:462–473), it is probable that cells might use an adhesive track for guidance in the organism. However, there is only limited evidence for such a mechanism at work on the organism. Recently, striking localization of the molecule tenascin has been shown in the pathways followed by neural crest cells in birds and rodents (Mackie *et al., Development* 1988, 102:237–250). Its distribution has now been determined in amphibians [9] where it appears in the neural crest pathways just prior to the initiation of migration, suggesting that this molecule may act as a substratum that directs the migration of neural crest cells. Furthermore, when antibodies against tenascin are injected into a chick embryo, they interfere with neural crest migration, at least in the head (Bronner-Fraser, *J Neurol Res* 1988, 21:135–147).

However, when neural crest cells are grown on tenascin in culture, they move fairly rapidly along it but are less adhesive than they are to fibronectin [10]. Thus, it seems unlikely that tenascin facilitates migration or determines pathways by being more adhesive than surrounding matrix molecules. Since tenascin and fibronectin compete for binding to integrin receptors [11], tenascin may modulate cell migration on fibronectin in an as yet unknown fashion.

Adhesive tracks play a role in directing premelanocyte (neural crest) migration under the ectoderm. Löfberg *et al.* [12] used Nucleopore filters to collect extracellular matrix deposited by the ectoderm of normal (dark) axolotl embryos and mutant whites, in which pigment cell migration does not occur initially. The normal matrix supports the migration of both dark and white neural crest cells, but the white matrix does not stimulate migration of either. The components of the extracellular matrix that support neural crest-derived pigment cell migration have not yet been identified.

Haptotaxis (adhesive gradients)

Early evidence from tissue culture studies suggested that cells will migrate up an adhesive gradient (Carter, *Nature* 1967, 213:256–260). Evidence for such a mechanism in the embryo had, until recently, been slim. Now there is good evidence from several systems that haptotaxis can direct embryonic cell migration.

The precursor cells of the heart in the chick embryo are derived from the lateral plate mesoderm, from which they migrate anteriorly as single cells on the endoderm to form paired endocardial tubes. Fibronectin is associated with the endoderm in a gradient which increases in the anterior direction, and which correlates with the direction of heart cell migration (Linask and Lash, *Dev Biol* 1986, 114:87–101). Linask and Lash [13] show that antibodies to fibronectin and the RGD peptides that interfere with cell adhesion to fibronectin stop presumptive heart cell migration. Thus, these cells are likely to use at least fibronectin to mediate their attachment and migration. Furthermore, if the endoderm on which the heart cells migrate is removed and rotated through 180° so that the fibronectin gradient is reversed, heart cell migration halts prematurely when the cells arrive at the boundary that represents the high end of the gradient [14]. Migration is normal when this area is removed surgically and reinserted in its original orientation. These experiments strongly suggest that the gradient of fibronectin not only sustains, but also directs, heart mesenchyme migration.

Evidence from grafting experiments by Poole and Steinberg (*Dev Biol* 1982, 92:144–158) was consistent with the notion that the pronephric duct in the axolotl embryo follows an adhesive gradient along the flank to the cloaca. Zackson and Steinberg [15] have now discovered that there is a gradient of cell surface alkaline phosphatase along the axolotl flank in a pattern predicted for an adhesive gradient from previous studies. Furthermore, if alkaline phosphatase is cleaved from the surface using phospholipase C, pronephric duct migration ceases [16]. Other adhesive molecules may also be removed using phospholipase C, and this possibility (which these workers readily acknowledge) must be examined.

In the urodele embryo, gastrulation proceeds by involuting mesoderm cells moving individually along the roof of the blastocoel cavity. These cells are aligned on, and migrate on, fibrils composed of fibronectin and laminin. Shi *et al.* [17] explanted blastocoel roofs from *Pleurodeles waltl* gastrulae into culture where they deposited an extracellular matrix on the plastic dish. When placed on these matrices, mesoderm explants spread in a directed fashion on the gastrula-derived matrix from what would have been the blastopore end to the anterior end of the embryo. These studies suggest that the extracellular matrix produced by the blastocoel roof is responsible for the directed migration of mesoderm from the point of involution at the blastopore to the future anterior end of the embryo.

Galvanotaxis

It has been proposed that electrical fields direct cell movement *in vivo* because many embryonic and adult cells are galvanotactic in culture (*Ionic Currents in Development.* Alan R. Liss Inc., 1986). Electrical currents are especially strong when epithelia are wounded and a case of directed migration after wounding has recently been observed. Fink and Trinkaus [18] wounded the enveloping layer of a *Fundulus* embryo and the underlying deep cells migrated directly to the area of the wound where they accumulated until the wound was closed, whereupon they resumed their random movement on the yolk sac. Because an electric field emanates from the wound, galvanotaxis may be responsible for directing this migration. Another possibility is that growth factors that have chemotactic qualities (see below) are released from the

wounded epithelium and attract the deep cells. The advantages of using this system for study are that the directed cell movements can be readily observed in the nearly transparent *Fundulus* embryo and that migration is perturbed easily by applying agents to the bath in which the embryos lie.

Chemotaxis

Only two developmental events have been shown to be controlled by chemotaxis, namely primordial germ cell migration (Dubois, *J Embryol Exp Morphol* 1968, 20:189–213) and axon outgrowth to specific targets (Lumsden and Davies, *Nature* 1986, 323:538–539). In neither of these instances has the responsible chemotactic molecule been isolated.

Another developmental event that may be regulated by chemotaxis is the migration of the oligodendrocyte/type-2 astrocyte (O/2A) precursors along the optic nerve. Type-1 astrocytes, also present in the optic nerve, are known to stimulate mitosis, migration and chemotaxis of the O/2A precursor. Noble *et al.* [19] have now shown that platelet-derived growth factor (PDGF) can mimic all the effects of the type-1 astrocyte and thus may be the mediator of all these events.

Growth factors also have a chemotactic role in pathological and wound-healing events. PDGF, and to a lesser extent transforming growth factor (TGF)β, initiates a substantial influx of macrophages and fibroblasts when injected into a wound (Pierce *et al., J Cell Biol* 1989, 109:429–440). It has recently been demonstrated that insulin-like growth factors stimulate chemotaxis in human melanoma cells [20] and colony-stimulating factor is chemotactic for human granulocytes [21].

Freely diffusible extracellular matrix molecules may also be chemotactic. For example, human monocytes are chemotactic to the 120 kD RGD-containing fragment of fibronectin [22]. This seems to be consistent with their normal behavior since monocytes accumulate as the second stage of infiltration into the wound, following neutrophils, which probably produce the fibronectin fragments.

Initiation and stimulation of migration

Having discussed what may control the directed migration of cells, we now turn to the factors that allow many embryonic and adult cells to be motile, while many others are stationary in the organism. Most of the factors that initiate migration of such cells as those of the neural crest, *Fundulus* deep cells or involuting mesoderm cells at the start of gastrulation are unknown. It is not clear either why some embryonic or adult cells are so motile whereas other cells are stationary. During the last year, several interesting studies have concluded that growth factors and proteases are involved in the initiation of migration and the stimulation of motility.

Progenitor cells of the heart valves and septae, the endocardial cushion cells, are derived from the cardiac endothelium via an epithelial–mesenchymal transition. Previous studies have suggested that the matrix into which they migrate, the cardiac jelly, and the mesocardium, are stimuli for the epithelial–mesenchymal transition of the endocardial cushion cells (Runyan and Markwald, *Dev Biol* 1983, 95:108–114; Krug *et al., Dev Biol* 1987, 112:414–426). Potts and Runyan [23] now show that this transition is controlled, in part, by TGFβ since purified TGFβ stimulates this mesenchymal transformation, and antibodies that block TGFβ function inhibit it. Another growth factor, Müllerian inhibiting substance, which is part of the TGFβ family, controls a similar epithelial–mesenchymal transition of the Müllerian duct (Donahoe *et al., Rec Prog Horm Res* 1987, 43:431–467). It seems likely that growth factors control epithelial–mesenchymal transition during other developmental events.

In addition to initiating migration, growth factors also appear to enhance motility itself. Nickoloff *et al.* [24] showed that keratinocyte motility is stimulated by TGFβ and epidermal growth factor (EGF). Furthermore, this stimulation is probably mediated by the production of fibronectin by the keratinocytes, since antibodies to fibronectin inhibit migration and substances that interfere with motility, such as interferon-γ, also suppress fibronectin production.

In other instances, growth factors induce motility by controlling the production of proteases. Sato and Rifkin [25] showed that when bovine endothelial cell monolayers are wounded they release basic fibroblast growth factor (bFGF). Movement of cells into the wound is prevented by antibodies that block bFGF function. Furthermore, bFGF stimulates the production of the serine protease plasminogen activator (PA), which the authors show is critical in cell motility, since inhibition of PA function stops cell movement.

There are other instances where proteases stimulate cell movement in an organism, perhaps without involving growth factors, and these are generating increasing interest. Proteases may cause the detachment of adhesions so that a cell is not tethered to its substratum, but instead can pick up its feet to take another step. Therefore, the localization of proteases such as PA in focal contacts (Hébert and Baker, *J Cell Biol* 1988, 106:1241–1247), and the apparent degradation of extracellular matrix molecules under these contacts (Chen *et al., J Cell Biol* 1984, 98:1546–1555), has engendered much interest. Chen [26] has now shown that novel cell contacts are formed in transformed cells, which he terms 'invadopodia', from which proteases are released and under which the fibronectin substratum is degraded (Fig. 2). He suggests that protease release allows transformed cells to be more migratory and invasive *in vivo*.

The production of proteases may well account for the exceptional motility of embryonic migratory cells. Neural crest cells produce proteases, in particular PA (Valinsky and Le Douarin, *EMBO J* 1985, 4:1403–1406) [27,28] and

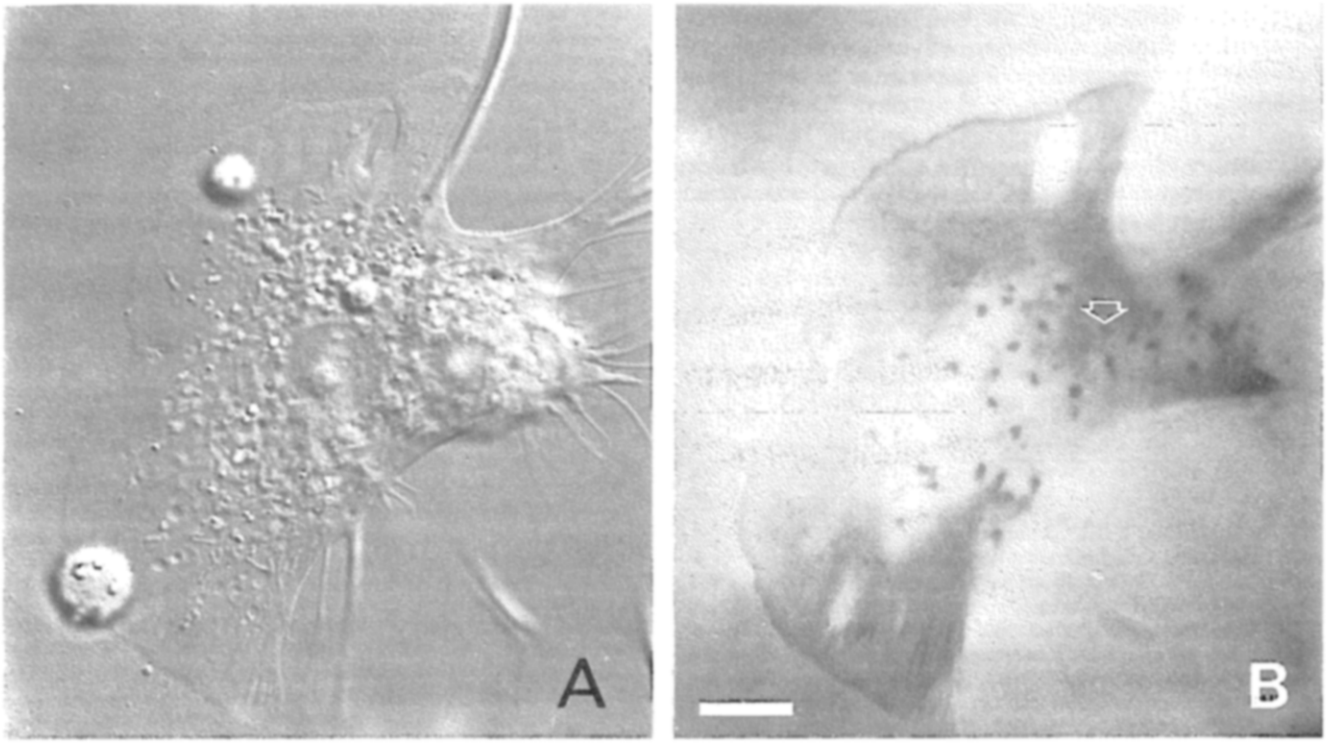

Fig. 2. A chick embryo fibroblast infected with Rous sarcoma virus and observed with differential interference contrast optics (A) and interference reflection optics (B). The dark spots in B represent the invadopodia, under which fibronectin degradation takes place. Published with permission [26], © Alan R. Liss Inc., 1989.

these appear to be necessary for migration, at least in tissue culture [28]. Further experiments will be necessary to show whether proteases are critical in the migration of these cells in their natural environment.

Proteases also appear to have a role in cell invasion through other tissues. Fisher *et al.* [29] have recently developed an *in vitro* assay to look at the ability of cytotrophoblast cells that are normally invasive for a short period of time during the establishment of the placenta to invade. They found that the trophoblast cells are maximally invasive *in vivo* concomitantly with the highest production of proteases, specifically metalloproteases. Mignatti *et al.* [30] similarly demonstrated that the invasion of angiogenic cords into the placental amnion depends on a protease cascade, including PA/plasmin and metalloproteases.

Another group of molecules that undoubtedly has a role in regulating motility are the so-called 'motility-stimulating factors'. These are distinguished from growth factors, which also have motility-stimulating functions, because they have no effect on mitosis. These can either be produced by the motile cells themselves and are therefore autocrine in function (migration stimulating factor, Schor *et al., J Cell Sci* 1988, 90:391–399; autocrine motility factor, Liotta *et al., Proc Natl Acad Sci USA* 1986, 83:3302–3306), or are produced by fibroblasts that induce epithelial sheets to break up into single cells and begin migrating and are, therefore, paracrine in function (scatter factor, Stoker *et al., Nature* 1987, 327:239–242). The role of these factors in development and tumorigenesis has not yet been established but the recent purification of scatter factor [31] and motility-stimulating factor [32] will surely now allow investigation of their possible roles in morphogenetic movements.

The future

Imaging and visualization techniques have become so sophisticated that they are now being applied to living organisms. The ability to observe cells migrating in the organism should revolutionize our understanding of the processes initiating and directing migration.

The recent illumination of factors that stimulate motility in culture, specifically growth factors, motility factors and proteases, open up novel avenues for the biologist to explore. We are likely to discover that these factors play important roles in the control of cell movement *in vivo*.

The role of cell adhesions in the control of cell motility will continue to be explored. More emphasis on the regulation of integrins will undoubtedly show how changes in cell–matrix adhesions control changes in morphogenetic behavior. In addition as we learn more about the pathways along which cells move in the embryo and what they use as substrata for that movement (e.g. [1,2]), it seems likely that cell–cell adhesions will also be shown to be important in directing morphogenetic movements.

Finally, the ability to manipulate cells genetically and perturb their cytoskeleton or adhesive contacts has allowed us to ask directly what the roles of these specific elements are in cell movement (Knecht and Loomis, *Science* 1987, 236:1081–1086; DeLozanne and Spudich, *Science* 1987, 236:1086–1091). These techniques can now be used to alter embryonic cells in specific ways. Such genetically designed cells could be grafted into their normal embryonic environment, to see how these perturbations of the cytoskeleton or adhesions alter their migratory capabilities and behavior.

Annotated references and recommended reading

- • Of interest
- •• Of outstanding interest

1. •• KELLER R, COOPER MS, DANILCHIK M, TIBBETTS P, WILSON PA: **Cell intercalation during notochord development in *Xenopus laevis*.** *J Exp Zool* 1989, 251:134–154.

The cellular interactions underlying notochord morphogenesis were analysed using scanning electron microscopy, time-lapse studies of notochord explanted from early gastrulae and high resolution filming of individual DiI-labeled notochord cells. Protrusive activity and directional cell movement control the convergent cell movements responsible for notochord morphogenesis.

2. • WILSON PA, OSTER G, KELLER R: **Cell rearrangement and segmentation in *Xenopus*: direct observation of cultured explants.** *Development* 1989, 105:155–166.

Using the same techniques as in [1], the morphogenesis of the somites was followed. Interesting from both the technical and a mechanistic viewpoint.

3. • JAFFREDO T, HORWITZ AF, BUCK CA, RONG PM, DIETERLEN-LIEVRE F: **Myoblast migration specifically inhibited in the chick embryo by grafted CSAT hybridoma cells secreting an anti-integrin antibody.** *Development* 1988, 103:431–446.

The CSAT hybridoma, which secretes an antibody against the avian integrin complex, inhibited the migration of the myotome when injected into the somites or produced total agenesis of the abdominal muscles when grafted into the coelom.

4. • ECKSTEIN DJ, SHUR BD: **Laminin induces the stable expression of surface galactosyltransferase on lamellipodia of migrating cells.** *J Cell Biol* 1989, 108:2507–2517.

Cell surface galactosyltransferase mediates cell spreading on laminin and antibodies against galactosyltransferase inhibit spreading on laminin but not on fibronectin. There is a laminin-dependent increase in the amount of galactosyltransferase on the cell surface that is concentrated in the lamellipodia, where it presumably mediates migration.

5. • JOHNSON KE, SILVER MH: **Cells from *Rana pipiens* gastrulae and arrested hybrid gastrulae show differences in adhesion to fibronectin-sepharose beads.** *J Exp Zool* 1989, 251:155–166.

Gastrula cells from different developmental stages have varying ability to adhere to fibronectin-Sepharose beads. These differences correlate in time with the gradual deposition of a fibronectin substratum and the onset of gastrulation movements. Cells from hybrid gastrulae arrested at various stages in gastrulation have different abilities to bind to the beads. One of the first demonstrations that regulation of fibronectin receptors may control morphogenetic events.

6. •• NEUGEBAUER KM, TOMASELLI KJ, LILIEN J, REICHARDT LF: **N-cadherin, NCAM, and integrins promote retinal neurite outgrowth on astrocytes *in vitro*.** *J Cell Biol* 1988, 107:1177–1187.

Several factors mediate the migration of retinal ganglion neurons on astroglial cells in the developing optic pathway. Only by perturbing several factors at once is there substantial inhibition of migration.

7. • DODD J, JESSELL TM: **Axons guidance and the patterning of neuronal projections in vertebrates.** *Science* 1988, 242:692–699.

A succint review of the various mechanisms by which axons select pathways of migration. Emphasizes that several mechanisms may operate together to guide specific neurons.

8. • ERICKSON CA: **Control of pathfinding by the avian trunk neural crest.** *Development* 1988, 103 (suppl):63–80.

Factors controlling the directional movement of embryonic cells are reviewed, paying special attention to the neural crest cells.

9. • EPPERLEIN H-H, HALFTER W, TUCKER RP: **The distribution of fibronectin and tenascin along migratory pathways of the neural crest in the trunk of amphibian embryos.** *Development* 1988, 103:743–756.

The pathways of neural crest cell migration were traced in *Xenopus* using the *X. laevis-borealis* nuclear marker. Both fibronectin and tenascin are present in the pathways of *Xenopus* and the axolotl although tenascin appears at the beginning of migration. Crest cells adhere *in vitro* and spread well on fibronectin, but adhere poorly to tenascin.

10. • HALFTER W, CHIQUET-EHRISMANN R, TUCKER RP: **The effect of tenascin and embryonic basal lamina on the behavior and morphology of neural crest cells *in vitro*.** *Dev Biol* 1989, 132:14–25.

Quail neural crest cells adhere weakly to substratum-bound tenascin but move rapidly on it, possibly because they detach readily. Tenascin in the medium severely reduces the speed of movement on fibronectin or basal lamina. These studies suggest that tenascin and fibronectin can interact with each other to regulate movement.

11. • BOURDON MA, RUOSLAHTI E: **Tenascin mediates cell attachment through an RGD-dependent receptor.** *J Cell Biol* 1989, 108:1149–1155.

Affinity chromatography was used to isolate a putative tenascin receptor from a human glioma cell line. Attachment of tenascin to the receptor was inhibited by the RGD peptide. The β subunit migrated with the fibronectin β subunit, suggesting that the tenascin receptor is a member of the fibronectin receptor family.

12. •• LÖFBERG J, PERRIS R, EPPERLEIN HH: **Timing in the regulation of neural crest cell migration: retarded 'maturation' of regional extracellular matrix inhibits pigment cell migration in embryos of the white axolotl mutant.** *Dev Biol* 1989, 131:168–181.

Microcarriers were used to collect extracellular matrix from beneath the epidermis of normal dark axolotls and from the mutant white axolotl in which pigment cell migration is inhibited. The matrix from the white embryos inhibits migration, whereas the matrix from the dark embryos supports migration of both white and dark neural crest cells. Matrix from white embryos at later stages of development will support crest cell migration.

13. • LINASK KK, LASH JW: **A role for fibronectin in the migration of avian precardiac cells. I. Dose-dependent effects of fibronectin antibody.** *Dev Biol* 1988, 129:315–323.

Precardiac mesoderm cells migrate from posterior to anterior along a gradient of fibronectin. Antibodies against fibronectin inhibit this migration, suggesting that fibronectin is used as a migratory substratum.

14. •• LINASK KK, LASH JW: **A role for fibronectin in the migration of avian precardiac cells. II. Rotation of the heart-forming region during different stages and its effects.** *Dev Biol* 1988, 129:324–329.

The previous paper suggested that precardiac cells followed a haptotactic gradient of fibronectin. In this study, the migratory substratum was removed and rotated so that the cardiac cells confronted the high end of the gradient first. They were unable to move to the anterior, suggesting that directional migration is controlled by a gradient of adhesiveness.

15. • ZACKSON SL, STEINBERG MS: **A molecular marker for cell guidance information in the axolotl embryo.** *Dev Biol* 1988, 127:435–442.

Previous studies suggested that the migration of the axolotl pronephric duct is directed along an adhesive gradient. The cell-surface enzyme alkaline phosphatase is found in a gradient extending from the pronephric duct to the cloaca in a pattern predicted for an adhesive gradient from previous experimental work.

16. • ZACKSON SL, STEINBERG MS: **Axolotl pronephric duct cell migration is sensitive to phosphatidylinositol-specific phospholipase C.** *Development* 1989, 105:1–7.

Alkaline phosphatase, which is thought to guide the migration of the pronephric duct, is covalently linked to the cell surface by a phosphatidylinositol-glycan (PI-G). A phospholipase C will release all molecules anchored to the cell surface at a PI-G. Phospholipase C when implanted into an axolotl embryo inhibits pronephric duct migration, suggesting that alkaline phosphatase (or another PI-G-linked molecule) is important in pronephric duct migration.

17. • SHI D-L, DARRIBÉRE T, JOHNSON KE, BOUCAUT J-C: **Initiation of mesodermal cell migration and spreading relative to gastrulation in the urodele amphibian *Pleurodeles waltl*.** *Development* 1989, 105:351–363.

Dorsal marginal zone mesoderm cells migrate from the blastopore to the future anterior end of the urodele gastrula on the underside of the roof of the gastrula. When explanted into culture, these cells begin to migrate when gastrulation begins in control embryos, showing that timing of onset is autonomous. When the gastrula roof is explanted into culture it will condition the substratum with extracellular matrix. Mesoderm cells migrate directionally on this matrix toward what would have been the animal pole.

18. • FINK RD, TRINKAUS JP: ***Fundulus* deep cells: directional migration in response to epithelial wounding.** *Dev Biol* 1988, 129:179–190.

Deep cells migrate randomly in the subepithelial space of the yolk sac of the *Fundulus* embryo. If the yolk sac epithelium is wounded, deep cells migrate towards the wound, where they aggregate. These clear embryos provide an opportunity to observe directly a directional movement and analyse its control. Possible cues include galvanotaxis or release of a chemotactic agent from the wounded cells.

19. • NOBLE M, MURRAY K, STROOBANT P, WATERFIELD MD, RIDDLE P: **Platelet-derived growth factor promotes division and motility and inhibits premature differentiation of the oligodendrocyte/type-2 astrocyte progenitor cell.** *Nature* 1988, 333:560–562.

Type-1 astrocytes are known to promote division and motility and chemotaxis and to inhibit premature differentiation of the O/2A progenitor cells derived from the optic nerve. PDGF can mimic all the effects of type-1 astrocytes in culture and may therefore be the factor that mediates their effects *in vivo*.

20. • STRACKE ML, KOHN EC, AZNAVOORIAN SA, WILSON LL, SALOMON D, KRUTZSCH HC, LIOTTA LA, SCHIFFMANN E: **Insulin-like growth factors stimulate chemotaxis in human melanoma cells.** *Biochem Biophys Res Commun* 1988, 153:1076–1083.

Using a Boyden chamber assay, insulin-like growth factor is shown to be chemotactic for the melanoma cell line A2058 but not chemokinetic, using a checkerboard assay.

21. • WANG JM, CHEN ZG, COLELLA S, BONILLA MA, WELTE K, MANTOVANI A, BORDIGNON C: **Chemotactic activity of recombinant human granulocyte colony-stimulating factor.** *Blood* 1988, 72:1456–1460.

Recombinant colony-stimulating factor is chemotactic for human polys (7–70 ng/ml) in a Boyden chamber assay, but inactive for lymphocytes or endothelial cells.

22. • CLARK RAF, WIKNER NE, DOHERTY DE, NORRIS DA: **Cryptic chemotactic activity of fibronectin for human monocytes resides in the 120-kD a fibroblastic cell-binding fragment.** *J Biol Chem* 1988, 163:12115–12123.

Human monocytes (but not lymphocytes) are chemotactic to the 120 kD RGD-containing fragment of fibronectin, but not to the intact molecule. Monocytes accumulate at the second stage of infiltration after the neutrophils, which produce the fibronectin fragments.

23. •• POTTS JD, RUNYAN RB: **Epithelial-mesenchymal cell transformation in the embryonic heart can be mediated, in part, by transforming growth factor β.** *Dev Biol* 1989, 134:392–401.

Progenitor cells of the heart valves are derived from an epithelial–mesenchymal transformation of the cardiac endothelial cells. In culture, TGFβ in conjunction with the myocardium will produce this transformation and it is blocked by the addition of antibodies to TGFβ. TGFβ can be demonstrated immunologically in the heart at the time of valve formation.

24. • NICKOLOFF BJ, MITRA RS, RISER BL, DIXIT VM, VARANI J: **Modulation of keratinocyte motility: correlation with production of extracellular matrix in response to growth promoting and antiproliferative factors.** *Am J Pathol* 1988, 132:543–551.

TGFβ and EGF stimulate keratinocyte motility. This effect is probably mediated by extracellular matrix production since these factors stimulate fibronectin production by the keratinocytes and antibodies to fibronectin inhibit the stimulation of migration. Substances such as interferon-γ, which decrease motility, also suppress fibronectin production.

25. • SATO Y, RIFKIN DB: **Autocrine activities of basic fibroblast growth factor: Regulation of endothelial cell movement, plasminogen activator synthesis, and DNA synthesis.** *J Cell Biol* 1988, 107:1199–1205.

When monolayers of bovine endothelial cells are wounded the cells release bFGF. Cell movement into the wound area is prevented by antibodies against bFGF. bFGF added to wounded cultures accelerates movement into the denuded area. TGFβ antagonizes the effects of bFGF. This effect is probably mediated by production of PA, since antibodies to bFGF repress PA production and inhibition of PA activity stops migration.

26. •• CHEN W-T: **Proteolytic activity of specialized surface protrusions formed at rosette contact sites of transformed cells.** *J Exp Zool* 1989, 251:167–185.

Transformed chicken embryo fibroblasts form special rosette-shaped contacts with the substratum that are sites of protease release and matrix degradation. Transmission electron microscopy shows that these sites contain membrane protrusions that look very much like lamellipodia. These 'invadopodia' are hypothesized to mediate the invasive movements of transformed cells.

27. • MENOUD PA, DEBROT S, SCHOWING J: **Mouse neural crest cells secrete both urokinase-type and tissue-type plasminogen activators *in vitro*.** *Development* 1989, 106:685–690.

Mouse neural crest cells produce PA as revealed by electrophoresis and zymography.

28. • ERICKSON CA, ISSEROFF RR: **Plasminogen activator activity is associated with neural crest cell motility in tissue culture.** *J Exp Zool* 1989, 259:123–133.

Quail neural crest cells produce PA in culture, which increases with time. This increase is shown to be associated not with time in culture or differentiation, but with motility. Inhibitors of PA or plasmin also inhibit or reduce cell movement. These results suggest that the movement of neural crest cells during embryogenesis is dependent upon PA production.

29. •• FISHER SJ, CUI T-Y, ZHANG L, HARTMAN L, GRAHL K, GUO-YANG Z, TARPEY J, DAMSKY CH: **Adhesive and degradative properties of human placental cytotrophoblast cells *in vitro*.** *J Cell Biol* 1989, 109:891–902.

Cytotrophoblast cells were isolated from human placentas of different ages. Their ability to degrade extracellular matrix in culture corresponded to their invasive capabilities *in vivo*. Inhibiting metalloproteinases abolished all matrix-degradative capabilities of the cytotrophoblast.

30. •• MIGNATTI P, TSUBOI R, ROBBINS E, RIFKIN DB: ***In vitro* angiogenesis on the human amniotic membrane: requirement for basic fibroblast growth factor-induced proteinases.** *J Cell Biol* 1989, 108:671–682.

Invasion of the human amnion by endothelial cells is induced by bFGF. bFGF induces protease production including PA/plasmin and collage-

nases. Invasion is inhibited when the proteases are inhibited. Protease production is not only important for endothelial cell movement, but also for invasion during the angiogenic process.

31. • GHERARDI E, GRAY J, STOKER M, PERRYMAN M, FURLONG R: **Purification of scatter factor, a fibroblast-derived basic protein that modulates epithelial interactions and movement.** *Proc Natl Acad Sci USA* 1989, 86:5844–5848.

Scatter factor has been purified to a single 62 kD polypeptide. This purified material causes increased movement of single epithelial cells and disruption of epithelial junctions from preformed sheets.

32. • GREY A-M, SCHOR AM, RUSHTON G, ELLIS I, SCHOR SL: **Purification of the migration stimulating factor produced by fetal and breast cancer patient fibroblasts.** *Proc Natl Acad Sci USA* 1989, 86:2438–2442.

A purification scheme for migration-stimulating factor has important implications for screening cancer patients and developing therapies for treatment of cancer patients.