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Cell and Developmental Biology— A Shared Past, an Intertwined Future

Commentary

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Cell and developmental biology are distinct disciplines with clear differences in emphasis and domains of interest, yet they also share a common historic origin and benefit from an increasingly productive exchange of insights and influences. Our goal in this commentary is to examine the common origin of cell and developmental biology, to explore ways in which they currently interact, and to consider the connections and differences that exist between these two fields.

A Shared History

Cell and developmental biology share a common ancestry and an intertwined history, and this is reflected by the number of forefathers that they share (e.g., E.B. Wilson, Theodor Boveri, Ross Harrison). Interest in embryology can be traced back to the times of Aristotle, but it was really the invention of the microscope in the mid-seventeenth century that launched the fields of modern cell and developmental biology. Investigation of the cellular basis of plants and animals led in the 1830s to Schleiden and Schwan's "Cell Theory," and this was followed by observations of fertilization and the understanding that both egg and sperm are cells (reviewed by Gall, 1996; Gilbert, 1994). These conceptual breakthroughs provided the foundation for both cell and developmental biology, and initially the two fields were almost indistinguishable. At that time, if you wanted to study cells you had to do so in the context of a living organism, and frequently the organism of choice was an egg or early embryo. The large size, abundance, and availability of these cells made them ideal material for the early biologist. In fact, in Joseph Gall's pictorial anthology of microscopy and cell biology, the vast majority of the specimens in question are from embryos and developing organisms (with protozoa making up most of the remainder) (Gall, 1996).

In the latter half of the nineteenth century, cell and developmental biology began to separate into two distinct fields, referred to as cytology and embryology, respectively. Cytology was concerned with the investigation of subcellular structure. Progress in this area paralleled the invention of progressively more powerful microscopic techniques. Embryologists, on the other hand, were grappling with the concepts of differentiation, the origins of complexity, and the eventual disproof of preformationism. Despite these differences, the two fields remained closely linked: both were concerned with the cellular basis of heredity, both were primarily descriptive, and both relied heavily on the use of embryos as the material of study. However, the development of tissue culture techniques (Figure 1), initiated by Ross Harrison in 1910, enabled biologists to study cells in vitro (Harrison, 1910). This further separated cytology from embryology and has remained an important difference between them.

Cytology and embryology were both greatly influenced by the discovery of DNA as the hereditary material and the resulting "molecular biology revolution." Around this time, the nature of cytology began to shift from a descriptive approach to a more experimental one. This was accompanied by the introduction of new techniques (such as genetics and radioisotope labeling) and a shift in interest from the structural composition of cells to the processes taking place within them and the molecular function of the components involved. For example, important experimental approaches were initiated to investigate mechanistic aspects of the cell cycle and these led to insights into the mechanism of chromosomal replication and to the partitioning of the eukaryotic cell cycle into S and M phases (reviewed by Nurse, 2000). With these changes in focus and approach, cytology grew into the field of cell biology, a field that was solidified in 1961 by the formation of the American Society for Cell Biology and the renaming of the *Journal of Biophysical and Biochemical Cytology* as the *Journal of Cell Biology*.

Embryology's own renaissance over the years that followed owed much to the blossoming fields of evolutionary biology and genetics, and the role of embryonic development in linking genotype to the phenotype selected during evolution. The success of genetic and molecular approaches coupled with a focus on the concepts of induction, patterning, and gene expression expanded embryology into the intellectual discipline of developmental biology (reviewed by Gilbert, 1994). Many aspects of developmental biology are now considered to be quite separate from those of cell biology, and the fundamental connection between these fields has become somewhat obscured by the differences that now exist between them.

Current Differences

The fields of cell and developmental biology now differ in many ways. Cell biology continues to concentrate on the study of subcellular processes and components, whereas developmental biology remains focused on the regulation and deployment of the processes that build the organism and drive its lifecycle. However, the differences extend beyond their general areas of focus and are to some extent reflected in the predominant experimental techniques used in the two fields.

Cell biology today is an umbrella term for a wide range of approaches and experimental systems. These range from the biochemistry performed on isolated tissues and cells through the study of cells kept in tissue culture to the primarily genetic procedures of yeast cell biology. Some of these methods, such as yeast genetics, overlap

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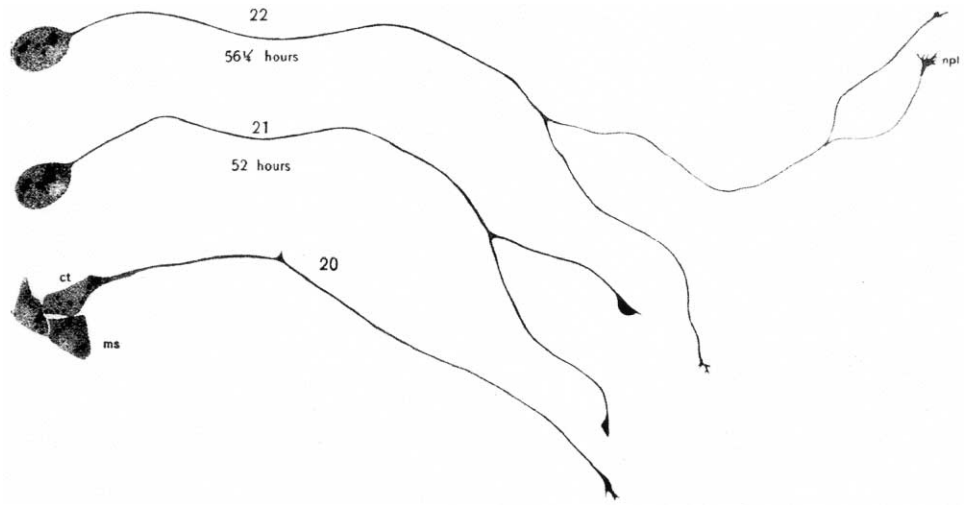

Figure 1. Ross Harrison's Sketches of the Elongation of Frog Nerve Fibers Grown in Culture
This work provided the foundation for modern tissue culturing techniques (Harrison, 1910).

significantly with methods used in developmental biology. However the study of cells in tissue culture is a powerful technique that has had particular impact on the field of cell biology. Tissue culture cells are, by definition, removed from their in vivo surroundings to one controlled by the experimenter. The controlled extracellular environment has allowed cell biologists to devise straightforward assays for activity and to produce large numbers of cells responding simultaneously to the same environmental cues. Tissue culture has therefore played an important role in elucidating components of many cell biological processes, ranging from signal transduction pathways to systems of cell adhesion and cytoarchitecture (reviewed by Alberts et al., 1994; Hunter, 2000). By removing cells from both their physical and temporal environments tissue culture offers the advantage of capturing a "snapshot" of a given cellular process. A continual challenge at the interface of cell and developmental biology is assessing how reliably these "snapshots" resemble particular in vivo situations. Nevertheless, tissue culture continues to provide a powerful means of studying the cell biology of a single population of cells away from the complicating environment of the entire organism.

Many of the experimental systems used in developmental biology bring approaches that differ in emphasis or method from those of cell biology. For example, the ease of embryonic manipulation provided by the large embryos of *Xenopus laevis* has enabled an exploration of cellular events that are unique to a multicellular environment or that occur over extended periods of time. Included among the resulting contributions are detailed investigations of the morphogenetic movements of cells (e.g., during gastrulation [reviewed by Keller and Winklbauer, 1992]) and insights into the role of cell interactions in cell fate determination (e.g., mechanisms whereby tissues organize and induce the patterning of other tissues and the "community effect" interactions between neighboring cells that are required for their continued and coordinated differentiation [reviewed by Gurdon, 1988; Lemaire and Kodjabachian, 1996]).

Other areas of developmental biology have been dominated by the genetic approaches provided by model systems including *Arabidopsis*, zebra fish, mouse, the fruit fly *Drosophila melanogaster*, and the nematode worm *Caenorhabditis elegans*. Genetic approaches have had a particular impact on questions of spatial patterning, which by its very nature lies at the heart of developmental biology. The often dramatic mutant phenotypes of many patterning genes have made them particularly amenable to this approach; the molecular basis of hundreds of patterning events in numerous different organisms can now be found in the literature. They involve many signaling cascades and combinations of transcription factor activity that ultimately control cellular differentiation (reviewed by Gilbert, 1994). Two surprises have been the extent to which patterning genes are conserved in a wide range of organisms and the way that the same patterning cascades are used repeatedly throughout the lifecycle of a single organism (reviewed by Patel, 1994). Elucidation of these pathways in genetically tractable model systems has therefore had far reaching implications that extend to aspects of cell biology and disease. However, many patterning events are so dependent on the correct spatial and temporal context (e.g., the use of cell lineage in cell fate determination [reviewed by Jan and Jan, 1995]) that in vivo methods remain the most feasible way to study them. So, just as in vitro techniques frequently offer the advantage of a controlled environment to study specific cell biological processes, the specific control and reproducibility provided by the developing organism is sometimes required to investigate certain other phenomena.

These differences in focus and approach have led to some different styles of successful research. Cell biologists are often concerned with distilling a process down to its constituent components and exploring function in terms of these components. By contrast, developmental biologists often paint with a broader brush, reducing a process down to only the essential components and exploring function in terms of regulation and variation. Although both approaches are reductionist in

nature, the end products are different. Developmental biology (particularly in the form of genetics) has proved very successful at defining the logic of a system without always knowing what the components do, only that they are important. Cell biology, on the other hand, has successfully characterized the function of components without always requiring an understanding of their relative importance in the overall process or their particular role in specific in vivo situations.

Despite these differences, interaction between the two fields enables each to use technology and insights from the other to obtain a better overall picture of how various processes operate. Mouse gene knockout technology provides an example of successful synergy of approaches from both fields. The derivation and propagation of embryonic stem cell lines was dependent upon tissue culturing techniques. Gene targeting strategies built upon a knowledge of homologous recombination that was gained from studies in yeast. However, to create mouse knockouts, these cell biological techniques had to be combined with embryological procedures and an understanding of mouse development. The resulting powerful technology has since been used extensively by both cell and developmental biologists. Developmentally important genes made up a large percentage of the early mouse knockouts (reviewed by Brandon et al., 1995). However, this reverse genetics approach has also proved an important tool in exploring the in vivo functions of many genes implicated in cell biological processes (reviewed by Muller, 1999). Culture of cells from knockout mice has also provided new insights into the cellular functions of a wide range of components. In the same vein, it is likely that *Drosophila* and *Caenorhabditis* will also provide increasingly more contributions to cell biological studies as a result of the recent introduction of the reverse genetic approaches of RNA interference and targeted knockout mutations, increasing use of cultured cell lines, and with the completion of genome sequencing that enables the systematic collection of mutants.

Interfacing Cell and Developmental Biology

Successfully combining cell and developmental biology will probably require that shared technologies be coupled with some shift in focus. Changes along these lines are in fact already becoming apparent. Developmental biology is becoming increasingly more defined and molecular, and cell biology has expanded out to incorporate broader aspects of function for the proteins of interest. This is well illustrated in areas where cell and developmental biology are already successfully interfacing and offers hope for the development of more such areas in the near future. In the following sections, we therefore consider examples of topics in which there is clear overlap between the fields.

The Growth Cone

Neurobiology provides a striking example of an area in which cell and developmental biology currently interface in the study of growth cones—the specialized, dynamic, and motile tips at the leading edges of extending axons (Figure 2). The basic understanding of cytoarchitecture derived from traditional cell biology has provided the foundation for understanding growth cone structure and

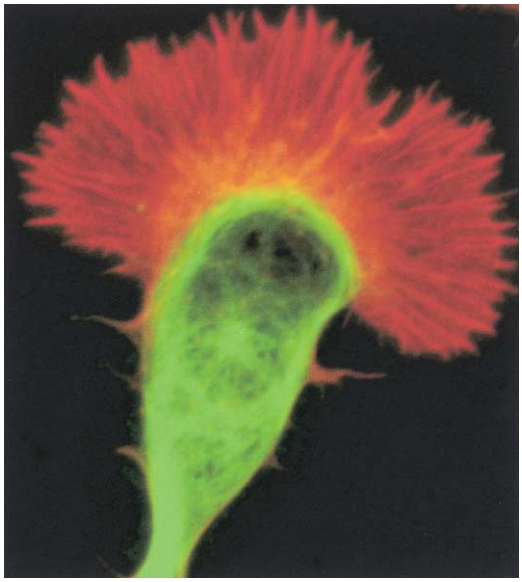

Figure 2. The Growth Cone of a Mouse Embryonic Hippocampal Neuron Grown in Culture

Filamentous actin is shown in red and microtubules are in green. Studies of how these cytoskeletal elements are regulated to guide the growth cone integrate aspects of both cell and developmental biology. Image kindly provided by Lorene Lanier and Frank Gertler.

mechanics. Further elegant in vitro studies have identified several mechanisms that may contribute to the forward extension of the growth cone. These include the assembly of actin filaments at the leading edge (through polymerization, nucleation, and/or annealing of short filaments), the retrograde flow of F-actin filaments in the extending growth cone and the recycling of F-actin behind the growth cone (reviewed by Suter and Forscher, 1998). It is now possible to begin to address the relative importance of these mechanisms in specific settings and how they are controlled in response to environmental cues (Mallavarapu and Mitchison, 1999). Investigations into the nature of these environmental cues have benefited from the biochemical purification of factors that promote cell adhesion and axon outgrowth (reviewed by Albright et al., 2000). For example, tissue culture assays in which antibodies were used to block the function of such molecules led to the identification of the neural cell adhesion molecule, NCAM (Rutishauser et al., 1982). Due to their often redundant effects and subtle phenotypes, many components of the adhesion and signal transduction pathways identified by these studies would have been more difficult to identify using genetic approaches in developmental systems. The fundamental understanding of the cell biology of the growth cone therefore provides the conceptual framework within which to investigate its regulation during development and the mechanism of action of axon guidance molecules.

Developmental biology's contributions have focused on higher levels of organization and mechanisms of growth cone guidance (reviewed by Albright et al., 2000). In fact, studies of the developing nervous system led to the important understanding that much of the neural specificity seen in adults comes from selective axonal

growth and synapse formation during the development of the organism. Similar observations also led to the theory that axons are guided in this selective outgrowth by a combination of short range and long range attractants and repellents. Many such guidance molecules have since been identified and developmental studies have played an important role in understanding how they may function (distinguishing between permissive and instructive signals, for instance) and how they may be used to achieve such precise wiring (reviewed by Tessier-Lavigne and Goodman, 1996). The ephrins, for example, were identified as ligands for the Eph family of receptors using in vitro studies. Subsequent developmental studies of their in vivo function, expression patterns, and manipulated misexpression have revealed the existence of gradients of the ligands and receptors in the target and originating tissues respectively (reviewed by Albright et al., 2000). These developmental studies have therefore led to an understanding of how these molecules are used in directing such precise topographic connections.

The complementary nature of cell and developmental biology is therefore often an important factor in successfully combining the two fields. However, these approaches also sometimes simply converge. An example in the field of growth cone guidance is the convergence of biochemical purification and developmental genetics in the identification of several important classes of guidance molecules (e.g., netrins, semapohorins, robo/slit family [reviewed by Albright et al., 2000; Tessier-Lavigne and Goodman, 1996]).

Signal Transduction Pathways

Convergence of cell and developmental biology is also seen in the study of signaling pathways. Many components of the Ras signal transduction pathway that were identified through cell biological studies have also been independently identified through genetic screens carried out by developmental biologists (e.g., Sos/CDC25, sem-5/Drk/Grb2, Dsor1/MAPKK, SUR-1/Rolled/MAPK [Simon et al., 1991; and reviewed by Kayne and Sternberg, 1995; Wassarman et al., 1995]). However, developmental biology has contributed more than a simple confirmation of the in vivo significance of these components. Analysis of the epistasis of the identified genes has enabled components to be ordered into a pathway. Furthermore, the genetic screens also extended this core pathway out in both directions (outward to the cell surface linking it to a variety of previously characterized receptor tyrosine kinases and inwards to the downstream targets in the cell nucleus [reviewed by Kayne and Sternberg, 1995; Wassarman et al., 1995]). In a somewhat converse situation, cell biological studies have contributed significantly to understanding the biochemical function and physical interactions of many components of the Wnt signal transduction cascade that had been previously assembled into a genetic pathway by developmental biologists (reviewed by Cadigan and Nusse, 1997; Peifer and Polakis, 2000; Thorpe et al., 2000). A powerful and complementary combination of both biochemical and genetic interactions continues to contribute to the understanding of many signal transduction pathways.

Tissue culture is particularly suited to the analysis of certain types of signal transduction pathways such as those controlled by growth factors. In fact, the discovery of the first peptide growth factor, NGF, was made using tissue culture of neuronal cells, which appropriately is the very cell type for which Ross Harrisson invented tissue culturing techniques (reviewed by Cowan, 2001; Hamburger, 1993). Subsequent work has shown that growth factors act predominantly not by promoting cell metabolism but by suppressing the "default" apoptotic death of the cell (Raff et al., 1993). The study of these signaling pathways in tissue culture has therefore contributed not only to our knowledge of signal transduction mechanisms but also to our understanding of the controlled balance of cell proliferation and cell death—phenomena for which tissue culture provides useful assays.

The study of cell signaling in the context of a developing organism has augmented cellular analyses in a number of ways. Disturbances in specific signaling pathways often produce distinct and easily recognizable phenotypes. This makes genetic approaches in model developmental systems particularly suited to the systematic (or sometimes serendipitous) identification of components of important pathways (e.g., Ras, Wnt, and TGF pathways in flies and worms [reviewed by Cadigan and Nusse, 1997; Kayne and Sternberg, 1995; Patterson and Padgett, 2000; Peifer and Polakis, 2000; Raftery and Sutherland, 1999; Thorpe et al., 2000; Wassarman et al., 1995]). In addition, the multicellular environment contains both the signaling cell and the responding cell populations. As a result, developmental biology has enabled the characterization of many signaling mechanisms and phenomena that are most clearly manifest within a multicellular context. An example is the allocation of different cell fates within a group of otherwise equivalent cell fate potentials through the process of lateral inhibition (e.g., the allocation of neuronal and epidermal cell fates from groups of equivalent neurectoderm cells [reviewed by Gilbert, 1994]). Studies of lateral inhibition have revealed the pivotal role of the Notch pathway in this type of signaling and have illuminated a mechanism whereby stochastic events can be amplified through autoregulation and used in making decisions of cell fate determination (reviewed by Baker, 2000; Greenwald, 1998). However, Notch signaling is rarely actually deployed in a stochastic manner, owing to underlying bias and additional inputs into the exquisitely sensitive system (e.g., fringe, wnt, numb, Barbu [Bray, 1998; Panin and Irvine, 1998; Zaffran and Frasch, 2000]).

The recently recognized overlap between signaling pathways and the cytoskeleton has also benefited from the combined approaches of cell and developmental biology. Components of integrin-cytoskeletal complexes provide a good example of this. These components have so far been best analyzed in the focal adhesion complexes that form in tissue culture cells in response to binding ligands in the extracellular matrix. Biochemical dissection of these aggregations of integrin receptors linked to actin stress fibers (Figure 3) has shown an association with both structural proteins (e.g., talin, vinculin, and filamin) and signaling molecules (e.g., RhoA, ILK, and src) (reviewed by Critchley, 2000; Ridley, 1999; Schoenwaelder and Burridge, 1999). Distinguishing structural from regulatory activities for these components, and those of many other pathways, is interesting

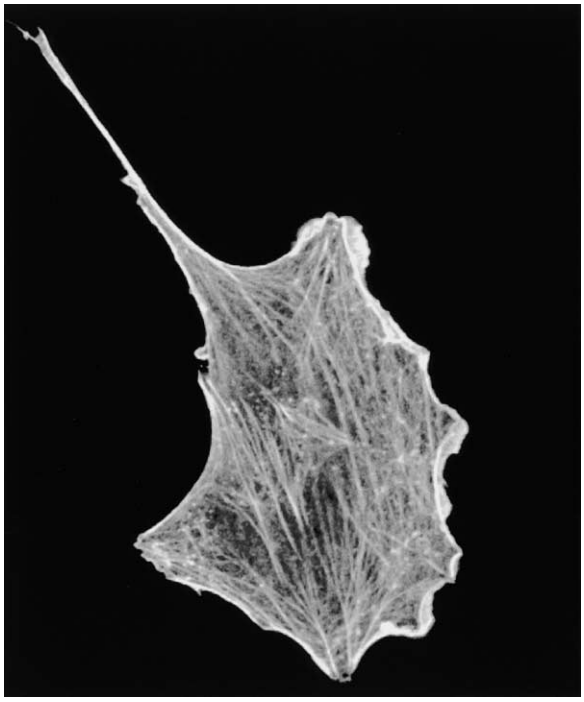

Figure 3. Swiss 3T3 Fibroblasts Caught in the Act of Moving, Showing the Actin-Rich Stress Fibers within the Cell and the Lamellipodia Extending at the Front of the Cell

Biochemical analysis of the complexes associated with stress fibers has revealed a striking association between structural and signaling proteins. Image kindly provided by Ritu Garg and Anne Ridley.

but complicated. Making such distinctions has benefited both from investigations of the biochemical characteristics of the components and from subtle genetic approaches in developmental systems (e.g., the surprising structural rather than signaling role for *Drosophila* ILK [Zervas et al., 2001]).

An Eye to the Future

Cell and developmental biology have already provided complementary information about areas of mutual interest. By extension, areas of biology that have been studied almost exclusively by developmental biologists may now benefit from cell biological approaches in order to identify missing components of pathways and to characterize biochemical functions. Likewise, areas that have been studied with great success using cell biological approaches are now making ideal candidates for study by developmental biologists interested in understanding the relative importance of different cell biological processes and how they are modulated and controlled in a multicellular setting. In the following section, we therefore consider examples that, from our perspective as developmental biologists, promise to benefit from such reciprocal interaction.

Cell Biology Meets Morphogenesis

Cell biological research has been hugely successful in investigating the internal workings of the cell. Investigations of this kind into the cytoarchitecture of cells and its links to cell adhesion are of particular relevance to biologists interested in studying cell movements during development. Cell biology has provided an understanding of the basic organization and dynamics of microfilaments, microtubules, and intermediate filaments in the cytoplasm and the identification of a myriad of associated proteins. In vitro assays for cell adhesion have enabled the biochemical purification of components of the extracellular matrix (e.g., collagens, fibronectrin, and laminins), the identification of their receptors and other adhesion molecules on the surface of cells (e.g., cadherin, integrin, selectin, and immunoglobulin-like adhesion molecules), and the characterization of the junctional complexes that link these with the internal cytoskeleton (e.g., adherens, desmosomal, and tight junctions) (reviewed by Alberts et al., 1994).

Related to this area of cell biology is the longstanding interest of developmental biologists in the visually striking morphogenetic events that remodel entire sheets of cells during development (Figure 4). Such rearrangements include infoldings (e.g., mesoderm invagination in flies and neurulation in vertebrates [reviewed by Leptin, 1999; Smith and Schoenwolf, 1997]), eversions (e.g., fly leg [reviewed by von Kalm et al., 1995]), convergent extensions (e.g., fly germ band extension and frog gastrulation [Irvine and Wieschaus, 1994; Keller et al., 1985]), and cell sheet spreading (such as dorsal closure in flies and ventral enclosure in nematodes [Kiehart et al., 2000; and reviewed by Simske and Hardin, 2001]). Interest in these morphogenetic movements has resulted in a detailed characterization of the underlying cell shape changes that drive them. For example, convergent extension can result from intercalation of neighboring cells, infoldings often involve constriction of the apices of cells, and cell sheet spreading often requires formation of a specialized leading edge (Irvine and Wieschaus, 1994; Keller et al., 1985; Kiehart et al., 2000; Sweeton et al., 1991).

Although these areas of cell and developmental biology are clearly related, it remains unclear how the particular changes in cell behavior are actually driven during development. Models to describe the creation and action of the forces that drive the changes in cell behavior draw on the wealth of cell biological studies on cell cytoarchitecture and mechanics. For example, the contractile "purse string" model of cell sheet spreading is based on the cell biology of cytokinesis and similar actin/myosin contractions have been proposed to drive apical constriction of cells (Young et al., 1991; Young et al., 1993). Proof of such models and the understanding of how individual cell shape changes interact within a sheet to drive these movements are best approached in the multicellular context offered by developmental biology. Unfortunately, the capacity of traditional genetic approaches has been compromised by the multiple pathways involved and the fact that the mechanisms are proving more complicated than the models put forward (e.g., multiple pathways driving fly mesoderm invagination, and multiple mechanisms driving fly dorsal closure [Kiehart et al., 2000; Leptin, 1999]). However, as we get better at discerning and separating the multiple mechanisms at work, and as our approaches become more sophisticated, this promises to be an exciting area. In addition, progress will be aided by combing the detailed analyses of specific forces and cell shape changes with investigations into their control by the recently discovered WASP, Arp2/3, and Rho families of regulators

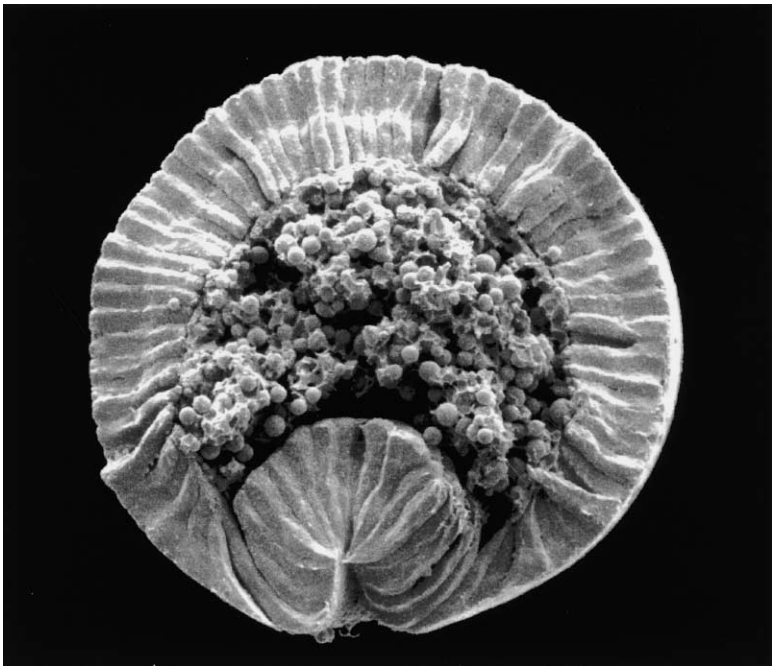

Figure 4. A Scanning Electron Micrograph of a Gastrulating *Drosophila* Embryo

Infolding of the prospective mesoderm, as seen in this cross-section, provides an example of the types of morphogenesis that occur to entire sheets of cells during development. Image obtained by Darri Sweeton.

(reviewed by Hall and Nobes, 2000; Welch, 1999). Morphogenesis therefore promises to be an area of research where cell and developmental biology will hopefully come together to reveal and explain the complex mechanisms and interactions that drive specific changes in cell dynamics and behavior in distinct in vivo settings.

Tissue Polarity

Tissue polarity is the term used to describe polarity coordinated across a field of cells. It often involves the imposition of polarity in an axis orthogonal to the cell's apical basal polarity (planar polarity) and is exemplified by the ordered orientation of hairs seen in an epithelium. In *Drosophila*, for example, the hairs of the wing are all oriented in essentially the same direction, pointing distally (reviewed by Adler, 1992). Studies in developmental systems have shown that this type of patterning requires cell-cell communication and can be traced to a specific signal transduction pathway (reviewed by Shulman et al., 1998; and see also Feiguin et al., 2001 [this issue of *Developmental Cell*]). This pathway enables neighboring cells in the tissue to polarize themselves with respect to one another. The molecular components of this pathway include the Frizzled seven-pass transmembrane receptor and the signal transduction protein Dishevelled, although the polarizing signal itself remains elusive (reviewed by Bray, 2000; Shulman et al., 1998). These proteins are also components of the Wnt signal transduction pathway, but there are additional components that are so far unique to either tissue polarity (e.g., Rho A) or Wnt signaling (e.g., Zw3). In *Drosophila* these two pathways also differ in their use of the multiple Frizzled receptors in that FZ mutants show tissue polarity defects whereas Wnt signaling involves some redundancy between FZ and FZ2. However, there are instances in both *C. elegans* and *Drosophila* where both Wnt signaling and the tissue polarity pathway are involved in patterning or polarizing the same cell. Further establishing the individual contribution of these two pathways and the extent to which they overlap in different developmental settings promises to be very interesting.

This type of patterning can only be recognized in an intact field of cells, and it appears to be established as the tissue forms. This and the genetic tractability of the process have made it well suited to the approaches of developmental biology that have provided the basic characterization of the process and the identification of pathway components. In addition, studies in developmental systems have revealed links between tissue polarity and other cell biological phenomena. For example, characterization of the *Xenopus* Dishevelled homolog has identified a link between tissue polarity and morphogenesis by demonstrating a requirement for planar polarity in the convergent extension movement of cells during gastrulation (Wallingford et al., 2000).

Developmental biology has therefore successfully revealed the basic logic of this tissue polarity pathway and highlighted its interactions with other processes. However, the future incorporation of cell biological approaches offers a powerful means to investigate many aspects of tissue polarity that are so far poorly understood. For example, cell biological approaches may help provide a molecular understanding of how this pathway operates and identify currently missing components. Combining the development of a tissue culture system for this pathway, with reverse genetic approaches such as RNAi (recently made available in mammalian tissue culture [Elbashir et al., 2001]) would also provide a means to investigate the extent and molecular basis of differences in Frizzled signaling between the Wnt and tissue polarity pathways. Furthermore, cell biological approaches will play an important role in understanding how this pathway feeds into and modifies the cytoskeleton to control the orientation of cell polarization.

Asymmetric Cell Division during Development

An asymmetric cell division is defined as a division that results in the production of two cells of different developmental potentials (reviewed by Horvitz and Herskowitz, 1992). This specialized form of cell division plays an important role in the spatial patterning of a range of organisms through the production of cell diversity. Diversity is achieved by the asymmetric allocation of cell fate determinants, formation of cells of different sizes, and/or by physically placing the daughter cells in differing environments. Asymmetric cell divisions have been shown to be dependent upon two related cell biological processes: the polarized localization of gene products within the cell and the orientation of the mitotic spindle (reviewed by Jan and Jan, 1998; Matsuzaki, 2000). These processes are interrelated in that the correct segregation of localized gene products to the daughter cells is dependant on the orientation of the mitotic spindle, which is itself determined by the asymmetric localization of additional gene products.

During *Drosophila* neurogenesis, the asymmetric segregation of Numb and Prospero cell fate determinants, and their anchoring proteins Pon and Miranda, plays an important role in establishing cell diversity (Figure 5) (reviewed by Knoblich, 1997; Matsuzaki, 2000). The mitotic spindle rotates 90° to correctly segregate these determinants and then itself becomes asymmetric to produce daughter cells of different sizes (Kaltschmidt et al., 2000). In *C. elegans*, the first embryonic cell divisions produce six unique founder cells, and many of the differences between these cells result from asymmetric partitioning of determinants and regulators (including P-granules, SKN-1, PIE-1, MEX-1, PAL-1, MEX-3, and POP-1) (reviewed by Guo and Kemphues, 1996; Lu et al., 1998). Investigations into mitotic spindle rotation during these divisions has led to identification of a number of important regulators, such as PAR-2/PAR-3 in the germline and the *mom* genes in the somatic founder cells. Asymmetric cell division, in both *Drosophila* and *C. elegans* development, is also associated with a number of important signaling pathways. Numb protein is a repressor of Notch activity and is often partitioned into daughter cells to bias Notch mediated decisions to be made in a certain direction and with greater speed (reviewed by Greenwald, 1998; Jan and Jan, 1995). Members of the Wnt pathway have been identified as regulators of spindle orientation in *C. elegans*, and both tissue and cell polarity pathways have been implicated in asymmetric cell divisions in *Drosophila* (Gho and Schweisguth, 1998; Whangbo et al., 2000; and reviewed by Lu et al., 1998).

The cell biology of asymmetric cell division has been successfully investigated in a wide range of organisms, including yeast and bacteria (reviewed by Horvitz and Herskowitz, 1992), and increasing use of cell biological approaches will also be required to understand many aspects of asymmetric cell division during development. For example, a number of genes controlling spindle orientation have been identified in developmental systems (e.g., Inscutable in flies and members of the Par-3/ASIP/Bazooka family in a range of organisms [Kraut et al., 1996; and reviewed by Matsuzaki, 2000]), but understanding the molecular basis of their action and the machinery that actually rotates the spindle is likely to require combined approaches from both cell and developmental biology. Furthermore, investigating the cell biology of asymmetric cell divisions in specific developmental settings promises insight into the diversity, dynamics, and biochemical nature of the links between a variety of processes, including mitosis, RNA/protein localization, and cell polarity.

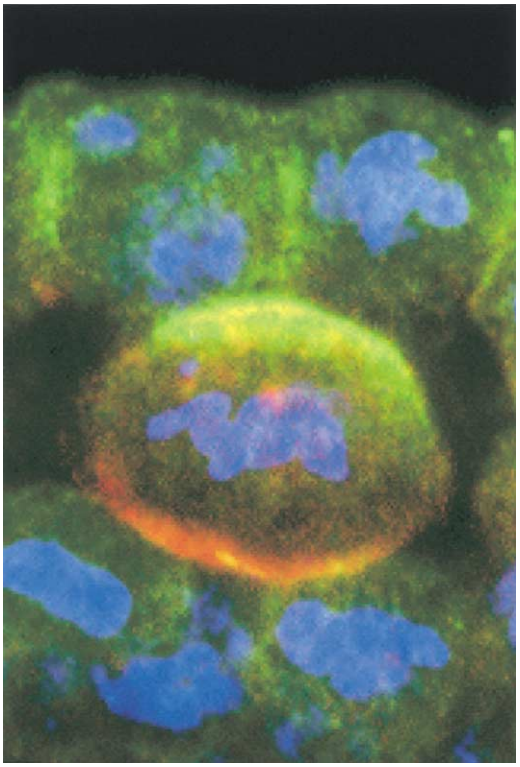

Figure 5. Asymmetric Cell Division of a *Drosophila* Neuroblast (the Large Cell in the Center of the Image with DNA Stained in Blue)

The Pins protein (in green) is asymmetrically localized in the neuroblast revealing a polarity that is lacking from the overlying symmetrically dividing epithelial cells (where Pins, in green, is unlocalized). The outcome of this polarity in the neuroblast is the asymmetric localization of Miranda (in red), which will result in its segregation to only one of the daughter cells and will make the daughter cells different from one another. The cell biological processes of asymmetric cell division are often used in this way to create cellular diversity during development. Image kindly provided by Matthias Schaefer and Juergen Knoblich.

Discussion

Will the increasing overlap between cell and developmental biology necessarily merge aspects of one field into the other, or are there some fundamental differences that will continue to distinguish the two disciplines? Cell biology involves investigation of the molecular basis of how cells work, whereas developmental biology is often concerned with understanding how processes are integrated to make the organism. Can we view developmental biology as simply the assembly of cell biological units in spatial and temporal patterns or are there cases where the way something works differs from the way it is made? Cell adhesion provides such

an example. Studies of static populations of cells, both in tissue culture and developmental systems, has led to a detailed understanding of the junctional complexes and families of adhesion molecules involved in the adhesive interactions of these cell types. However, during development it appears that cell movement and migration, studied both in developmental systems and in vitro, often involve the integration of multiple adhesion systems and are mediated through different types of cell contacts, i.e., the ways in which cells employ and regulate adhesive systems may be different in forming a tissue than in holding a tissue together (reviewed by Alberts et al., 1994). Differences like this may become more significant factors in defining different areas of research in situations where experimental approaches from cell and developmental biology continue to merge.

The analysis of how cell biological units are indeed assembled into a developing organism may also reveal novel higher order levels of mechanism and regulation. These could include the production and transmission of forces within sheets of cells, the self-organizing properties of tissues, the dynamic links and balances between many cell biological processes or cell states, and the plasticity of developmental events that provides the remarkable buffering against variable or perturbed inputs (reviewed by Kirschner et al., 2000; Steinberg, 1998). These higher levels of organization are found in the context of developing organisms, and developmental biology is therefore likely to play a central role in their elucidation. Indeed, encouraging progress has already been made in understanding how multiple signaling pathways interact, how cellular processes such as mitosis or membrane trafficking and morphogenesis affect one another and in which forces operate during specific morphogenetic events (Berset et al., 2001; Grosshans and Wieschaus, 2000; Kiehart et al., 2000). These areas of developmental biology all promise to be very exciting to cell and developmental biologists alike. However, the success of developmental biology has traditionally relied on the use of limited vision—seeing the whole but not all the parts. Will the approaches that have served developmental biologists well in providing stripped down versions of cell biological phenomena now limit attempts to reveal and elucidate higher order mechanisms? It is likely that the elucidation of these types of mechanisms will require a synergy of approaches from multiple fields.

Successful interaction between cell and developmental biology is sometimes complicated by differences in the prevailing styles and strengths of these two fields. A strength of developmental biology is the ability to paint a broad overall picture, as a result of the methods and assays used. The emphasis of such assays is often on end states that can be easily recognized and analyzed (e.g., the patterns of hairs on the larval fly cuticle as a read out of a signal transduction pathway). As a result, entire processes can be reduced to a few relevant aspects or components. This approach is very effective in revealing the rationale of a system but it necessarily requires that many components are left out of the picture. This can sometimes put it at odds with the powerful biochemical approaches of cell biology in which potential molecular interactions between many components can be simultaneously and more extensively explored, but the relative degrees of importance for these interactions are often difficult to determine. However, we have entered an era in which the limitations of both approaches are becoming increasingly apparent as studies are pushed further and further. For example, the traditional approaches of developmental biology face serious obstacles when it comes to investigating increasingly common redundant mechanisms or parallel pathways, and cell biological discoveries made using in vitro systems are often compromised by the lack of understanding of their in vivo significance. In attempting to overcome such problems scientists are more often finding ways to successfully combine approaches from both disciplines.

Thus, as developmental biology gets more sophisticated and the phenotypes studied become less dramatic, the boundaries between cell and developmental biology are once again beginning to blur. The intricate complexity that has emerged from cell biological studies is ultimately likely to prove important in understanding so far intractable developmental phenomena. Developmental biology in turn is likely to move beyond being an inferior arena for questions of cell biology to, paradoxically, providing both an additional layer of complexity to many of these questions as well as a means by which to navigate some of their growing complexity. Furthermore, there is an increased blending of experimental approaches as cell biological studies move into developmental systems to address questions of regulation and multicellular behavior, and developmental biologists incorporate techniques from cell biology to learn more about how proteins function in their cellular context. However, differences do still exist between cell and developmental biology and the complementary nature of these differences in fact benefits investigations into areas of mutual interest. In addition, progress has been made into characterizing phenomena that arise from considering the organism as a whole and not just as individual cells. Hence, we have not returned to a situation in which cell and developmental biology completely overlap. Nevertheless, the recent shifts in these two fields offer much promise to benefit them both in the way that E.B. Wilson foresaw: "The key to every biological problem must finally be sought in the cell, for every living organism is, or at some time has been, a cell" (Wilson, 1925).

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