ship is required with a long-term vision and with a willingness to learn from the successes and failures of others.

It is difficult to predict how the epidemic will develop in the future. We have seen unexpected successes, but also the dramatic spread of HIV to prevalence rates that few believed possible. Many of the countries where HIV prevalence is currently low have all of the ingredients for the extensive spread of HIV if no action is taken. In others, where significant spread has already occurred, prevalence may continue to rise until HIV endangers the entire society. The future course of the pandemic will depend largely on how the successes of today can fuel immediate action in many more countries and communities.

Research has provided a good scientific understanding of HIV and AIDS. Epidemiological and public health studies have provided clear guidance on what actions can control the pandemic. What remains is the political will to implement the programs necessary to stop HIV transmission, and the necessary resources to initiate and maintain an effective response. The international conference on AIDS in South Africa will bring together more than 10,000 researchers, public health specialists, activists, policy-makers, and decision-makers from governments and communities around the world. It is to be hoped that this exchange can at last bring a sense of real urgency to the need to respond to the disaster facing us from the AIDS pandemic. This response must be immediate, it must have a united political leadership from all governments, and it must be on a scale of resource allocation not seen before in the history of our fight against infectious disease.

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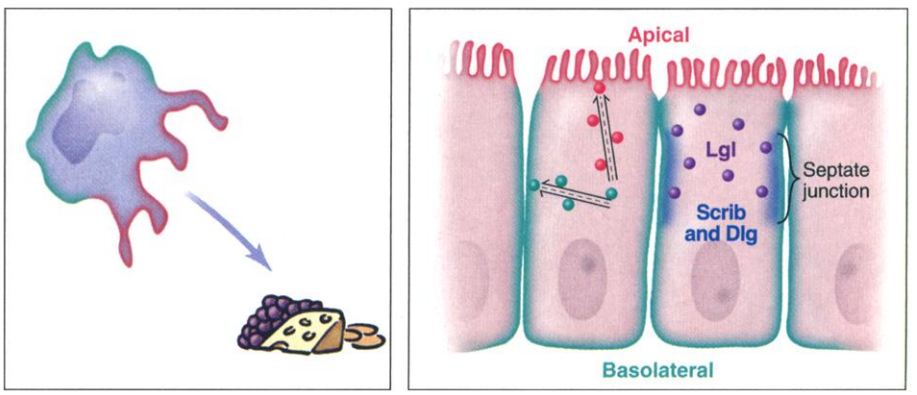
PERSPECTIVES: CELL BIOLOGY

Travel Bulletin—Traffic Jams Cause Tumors

Mark Peifer

As we depart on vacation, we're likely to get a crash course on what happens when traffic is not properly directed. The global transportation system is a marvel, carrying people and goods from Toledo to Timbuktu and all points between, but just try telling that to someone stuck in a traffic jam between Philadelphia and New York with three kids in a minivan. Just as the transportation system depends on the smooth operation of a complex mix of machinery and personnel, so the proper functioning of our bodies' cells—and ultimately of our bodies—depends on proper traffic direction. This travel advisory is well illustrated by the report from Bilder and colleagues on page 113 of this issue (*1*). The authors reveal surprising connections between three seemingly different cellular events: protein transport, cell polarity, and the regulation of cell proliferation.

Cells exist in an asymmetric environment, and their response to this environment requires that they are asymmetric as well. For example, even single cells must detect and move toward nutrients and away from predators. To achieve asymmetry cells are polarized, that is, different cellular machinery is deployed at distinct locations on the cell surface. Our understanding of the machinery that regulates cell polarity rests on twin experimental approaches: cell biology in cultured mammalian cells and genetics in the worm *Caenorhabditis elegans*, the fruit fly *Drosophila*, and yeast. Animal cell polarity has been most closely examined in epithelial cells, which have an apical-basal axis of polarity (that is, the top and bottom of the epithelial cells are different). The apical and basolateral domains of epithelial cells are arrayed with a different set of proteins; protein complexes at the lateral junctions between adjacent cells separate these two domains (see the figure). Although the establishment of cell polarity during development remains rather mysterious, the maintenance of cell polarity clearly depends on proper traffic direction—epithelial cells



Scribbling connections. All eukaryotic cells are polarized, with different proteins localized to distinct membrane domains. (**Right**) Epithelial cells accumulate different proteins on their apical (top) and basolateral (bottom) surfaces. Proteins are transported within the cell in vesicles that "move" along cytoskeletal highways. Different subsets of proteins are targeted to the apical and basolateral cell surfaces. Scrib and Dlg are localized at the septate junctions along the lateral cell surface, whereas Lgl coats vesicles that are found both in the cytoplasm and "docked" at the lateral surface of the cell.

The author is in the Department of Biology and Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599–3280, USA. E-mail: peifer@unc.edu

must target the delivery of an entire cast of proteins to the correct apical and basolateral destinations.

Bilder and Perrimon previously identified the *scribble* gene (*scrib*) in a screen for genes required for establishing epithelial cell polarity in *Drosophila* (*3*). In embryos lacking the Scrib protein, cells rapidly lose their initial polarity, with a striking disruption of the localization of apical proteins. In their new paper, Bilder *et al.* (*1*) identify Scrib's partners and suggest how they may be involved in establishing polarity. In the course of analyzing Scrib's role in other fly tissues, the authors noticed an unexpected similarity between the phenotype of the *scrib* mutant flies and the phenotypes of flies with mutations in two other genes, *lethal giant larvae* (*lgl*) (*4*), and *discs large* (*dlg*) (*5*). It was known that both the *lgl* and *dlg* fly mutants showed similar abnormalities in the brain, imaginal discs, and follicle cells. This led Bilder *et al.* to carefully compare the phenotypes of all three mutant flies in different epithelial tissues. In all cases, mutations in the three genes had identical consequences: cells rounded up, losing their epithelial character and the polarization of apical and junctional complex proteins. Furthermore, the three mutant genes exhibited striking genetic interactions that were strongly dose-sensitive—that is, a reduction in the amount of protein product encoded by one mutant gene strongly enhanced the aberrant phenotype caused by mutations in the other two genes. These genetic interactions suggest that the three wild-type proteins are involved in a common cell biological process. Finally, Dlg and Scrib proteins colocalize to the septate junctions, which form part of the junctional machinery that joins cells together along their lateral surfaces (see the figure). These two proteins depend upon one another for proper localization, consistent with the possibility that they physically interact.

The interactions of Dlg and Scrib with Lgl are more complex. Lgl protein (*1, 6*) is sequestered in dots that are found both in the cytoplasm and at the cell surface. Based on previous work (*7, 8*), these dots are likely to represent transport vesicles, the trucks that carry proteins to their proper cellular destinations (see the figure). Although these vesicles normally show only limited overlap (at septate junctions) with Dlg and Scrib, the intracellular localization of Lgl is dramatically altered in *scrib* or *dlg* mutants (the vesicles disappear) (*1*). Likewise, targeting Scrib and Dlg to their correct intracellular locations requires Lgl activity. Thus, Scrib, Dlg, and Lgl are components of the cellular machinery that maintains cell polarity. But what type of machinery is involved, and what does it do?

Recent revelations about the function of Lgl homologs in yeast (*8*) and mammals (*7*) provide a clue, directly implicating protein traffic direction in the maintenance of cell polarization. The maintenance of epithelial cell polarity depends on the asymmetric transport of transmembrane proteins to the cell's apical or basolateral domains (see the figure). Lgl's homologs are required to properly deliver vesicles containing secretory and transmembrane proteins to particular cellular locations—in yeast their absence results in a traffic jam, with secretory vesicles accumulating inside the cell (*8*). Lgl's homologs bind to different SNARE proteins (*7, 8*), which directly mediate targeting and docking of the vesicles with the plasma membrane. Thus, one model of cell polarity suggests that Lgl assists in the proper targeting of transport vesicles containing apical proteins. In the absence of Lgl and accurate protein targeting, cell polarity would gradually be lost.

The mechanistic connection between Lgl and the Dlg and Scrib pair of proteins is more speculative. Dlg and Scrib both contain PDZ domains, which often bind to the cytoplasmic tails of transmembrane proteins. Several models seem plausible. Dlg and Scrib might direct specific vesicle-targeting machinery such as the exocyst complex (a multiprotein machine important for vesicle targeting in yeast and animal cells) to septate junctions. Consistent with this finding, the exocyst is localized to tight junctions in mammalian cells (*9*). If this is so, it is mysterious why apical proteins stop off at septate junctions on their way to the apical surface, and why Scrib and its partners regulate apical protein localization whereas the mammalian exocyst shepherds basolateral proteins to their final destinations. Alternatively, Dlg or Scrib might bind to transmembrane proteins during vesicular transport, helping to facilitate interactions with the cytoskeletal highways along which the vesicles travel. This function is analogous to that of a distinct set of PDZ proteins that have been implicated in kinesin/microtubule-based transport of neuronal vesicles (*10*). It is possible that Lgl and its homologs use actin-based highways for vesicle transport because Lgl shows physical and genetic interactions with myosin (*11, 12*).

Additional excitement comes from another connection. Both *dlg* and *lgl* are tumor suppressor genes, that is, they encode proteins that regulate cell proliferation and so prevent tumor formation [reviewed in (*13*)]. Fly larvae that carry mutations in either gene have a similar phenotype—rather than differentiating, the imaginal discs and brain lose their normal cellular organization and form metastatic tumors. Bilder *et al.* now demonstrate that Scrib also functions as a tumor suppressor protein. This stands the usual view of cell transformation on its head by suggesting that disruption of protein traffic removes the normal limits placed on cell proliferation. Changes in cell architecture are often viewed as a downstream consequence of the genetic changes that occur during tumor formation. However, here it seems highly likely that the change in architecture is the primary defect, resulting in loss of growth regulation and tumor development.

How might alterations in cell polarity affect the regulation of cell proliferation? Several models have been proposed. First, the junctional complex (disrupted by mutations in *scrib* and partners) is the location of much of the cell's signal transduction apparatus. Mislocalization of receptors might alter signaling, although altered signaling would seem more likely to disrupt rather than to activate proliferative signals. A second scenario may be more attractive. In this model, *scrib* mutations would disrupt "contact inhibition," a mysterious process that decreases the proliferative rate of epithelial cells when they are in contact with neighboring cells on all sides. Consistent with this, the cadherins and catenins, junctional proteins that are thought to contribute to contact inhibition, are mislocalized in *scrib* mutants.

Genetic analysis has thus provided the cast of characters required for coordinating protein transport, cell polarity, and proliferation. We now await the results of biochemical and cell biological studies, which will tell us if these proteins act as truck drivers, air traffic controllers, or baggage handlers in the complex process of assembling a polarized cell.

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