km from the epicentral region. Reports exist of felt tremors from this region in 1962, 1967, 1983, and 1984. The epicentral area lies on the fringes of Deccan volcanic province of Peninsular India, and the thickness of volcanic rock is estimated to be between 100 and 200 m. There were no foreshocks of this earthquake large enough to be recorded at Hyderabad Observatory.

Macroseismic surveys and a suite of geophysical investigations are being undertaken in the vicinity of the Latur earthquake by the scientists of the National Geophysical Research Institute in Hyderabad. The aftershock activity consists of several tremors, the largest being of magnitude 4.4 on 30 September 1993 itself. The aftershock activity decreased rapidly in the days to follow. However, there was an aftershock exceeding magnitude 4 on 12 November 1993. There is no major visible continuous fracture on surface associated with this earthquake. There are a few discontinuous ruptures that continue intermittently for a kilometer or so. A maximum upthrow of 0.5 m along a plane dipping 40° northeast has been seen. Soil gas studies carried out in the vicinity of some of the cracks in the rupture zone near Killari have shown very high helium concentration in the range of 1000 parts per billion (ppb), as compared with background values of 200 ppb or less. Repeat measurements are being made. There are reports of smoke or gas emanation from a widespread area to a distance of 200 km from the epicenter as well as reports of ground-water changes 2 to 3 months before and after this earthquake. These reports are being authenticated. There were also reports of elevated surface temperature for the meizoseismal area in the vicinity of Killari. Ground temperatures were measured at a depth of 1 m with a thermistor probe at 16 sites from where smoke emanation was reported. With the exception of a couple of sites, temperatures were found to be normal.

Johnston (*2*) has prepared a list of the 100 largest stable, continent region earthquakes for the entire globe. Eight of them fall within the stable continent region of India (see map). However, all of them are associated with rifts or continent-ocean transition zones, or both. Unlike these events, the Latur earthquake is far removed from any known rift. The closest is a postulated Khurdwadi rift, which is more than 70 km from the epicenter.

As such, it is difficult to assign a definitive explanation for the Latur earthquake. Johnston and Kanter (*1*) have pointed out the rarity of stable earthquakes in continental crust, and the fact that the largest of them occurred long before the modern instruments were developed really makes us very poorly equipped to understand their mechanism. It is hoped that aftershock data collected through the operation of a number of seismic stations, which is under different stages of processing, and other geophysical, geological, and geochemical investigations being conducted in the region will provide much needed insight into the puzzling Latur earthquake.

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Cancer, Catenins, and Cuticle Pattern: A Complex Connection

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Society's investment in basic biological research is often justified by the claim that scientists may discover unexpected connections to problems important to human health and welfare. A spectacular example of such a connection is provided by two reports in this issue of *Science* (*1*), which establish a link between human colon cancer, epithelial cell adhesion molecules, and pattern formation in the fruit fly *Drosophila*.

Colon cancer, one of the most common forms of cancer in the Western world, results from an accumulation of mutations in oncogenes and tumor suppressor genes. Mutations in the tumor suppressor gene *APC* are thought to occur early in tumorigenesis. Although originally identified in families with familial adenomatous polyposis, who are predisposed to colon cancer, the *APC* gene is now known to be altered in many sporadic colon cancers as well. The cellular function of the APC protein has remained elusive because APC has little sequence similarity to other proteins (*2*). In this issue, two research groups use a biochemical approach to cellular function and find that APC associates with an adherens junction protein called β-catenin (*1*).

Adherens junctions (AJs; also called the zonula adherens) are critical for the establishment and maintenance of epithelial layers, such as those lining organ surfaces. AJs mediate adhesion between cells, communicate a signal that neighboring cells are present, and anchor the actin cytoskeleton. In serving these roles, AJs regulate normal cell growth and behavior. Certain stages of embryogenesis, wound healing, and tumor cell metastasis require that cells form and leave epithelia. This process, which involves the disruption and reestablishment of epithelial cell-cell contacts, may be regulated by the disassembly and assembly of AJs. Several lines of evidence have suggested that Src-mediated tyrosine phosphorylation of AJ proteins influences AJ assembly and cell adhesion (*3*), and there is evidence that down-regulation of AJ components often precedes metastasis (*4*). AJs may also function in the transmission of the "contact inhibition" signal, which instructs cells to stop dividing once an epithelial sheet is complete. Faulty transmission of this signal could easily lead to growth deregulation.

The AJ is a multiprotein complex (*5*) assembled around calcium-regulated cell adhesion molecules called cadherins. Cadherins are transmembrane proteins: the extracellular domain mediates homotypic adhesion with cadherins on neighboring cells, and the intracellular domain interacts with cytoplasmic proteins that transmit the adhesion signal and anchor the AJ to the actin cytoskeleton. These cytoplasmic proteins include the α-, β-, and γ-catenins. The genes for the α- and β-catenins have been cloned (*6*, *7*) and are unrelated in sequence. The γ-catenin protein, first identified as a band on an SDS gel, may in fact be a mixture of two proteins—a β-catenin relative called plakoglobin that is found in desmosomes (another type of intercellular junction) and an unidentified protein (*8*).

Although the stoichiometry and stability of the AJ protein complex have been well characterized, the biochemical roles of the individual proteins remain mysterious. Several clues have emerged from sequence analysis. The α-catenin protein shares slight but significant amino acid identity

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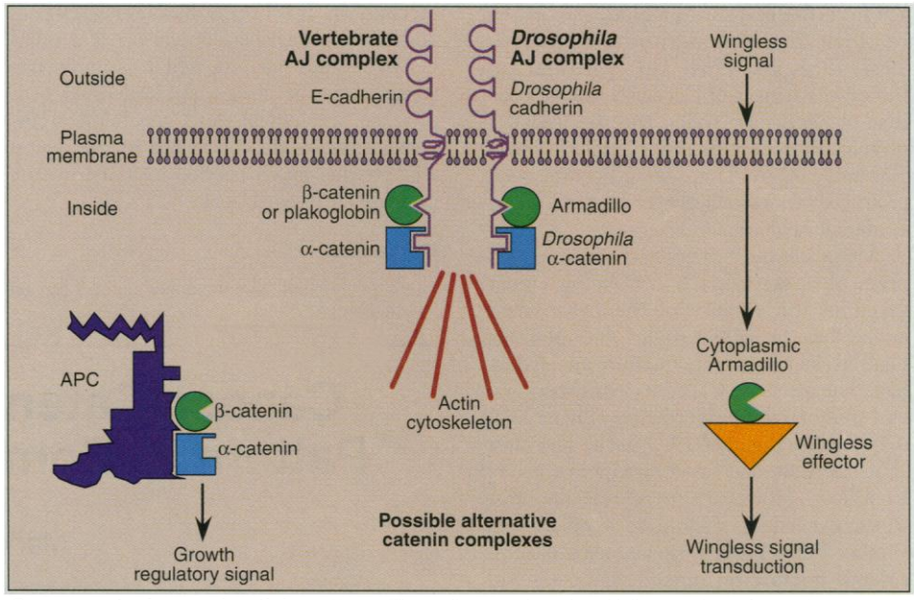
with vinculin (6), suggesting that it may help link the AJ to the actin cytoskeleton. The β-catenin protein shares 70% amino acid identity with both plakoglobin and the product of the *Drosophila* segment polarity gene *armadillo* (7). The Armadillo protein has structural and functional properties consistent with its sequence similarity to β-catenin. Biochemical studies have shown that Armadillo is part of a multiprotein AJ complex in *Drosophila* that also includes homologs of α-catenin and cadherin, and genetic studies indicate that it is required for cell adhesion and cytoskeletal integrity (9).

The *armadillo* gene was originally identified as one of a group of segment polarity genes that regulate pattern formation of the *Drosophila* embryonic cuticle (*10*). Many of these genes are thought to encode components of the signal transduction pathway for the cell-cell signaling protein Wingless, a *Drosophila* homolog of the mouse oncoprotein Wnt-1; both Wingless and Wnt-1 act as signals that establish cell fates during embryogenesis. Armadillo is directly required for transduction of the Wingless signal, and cells accumulate high levels of cytoplasmic Armadillo in response to Wingless (*11*). This cytoplasmic Armadillo may activate effectors of Wingless. Such effectors (which remain to be identified) could include cytoplasmic signal transducers such as kinases, as well as the AJ itself (*11*). The functional connections between catenins and Wingless/Wnt signaling have been evolutionarily conserved. The vertebrate Wnt-1 has been shown to regulate expression of both plakoglobin (γ-catenin) and cadherins, thereby altering cellular adhesive properties (*12*), and β-catenin has been implicated in axis formation during *Xenopus* development (*13*), a process that may require Wnt signaling.

Given the diverse cellular roles of Armadillo/β-catenin, what is the likely significance of its interaction with APC? One possibility is that the APC-catenin complex regulates transmission of the contact inhibition signal into the cell. This hypothesis is consistent with the observation that APC mutations are associated with the development of hyperplasia, an early event in tumorigenesis. A second possibility is that the APC-catenin complex regulates adhesion. Although this idea is supported by evidence that loss of cadherin-mediated adhesion can contribute to metastasis, it is less consistent with the evidence that APC acts early in tumorigenesis. Finally, it is possible that APC regulates transmission of a Wnt or Wnt-related signal, and that such a signal plays an unexpected role in growth control in the colon.

These models may be easier to distinguish once the details of the APC-catenin interaction become clearer. A key question is whether APC and caherins compete for binding to β-catenin. The sites of interaction of the various proteins may provide some clues. The catenin-binding domain of APC has been localized to the central region of the protein and includes imperfect repeated motifs of 15 to 20 amino acids each. These repeated motifs do not appear to be present in E-cadherin (whose catenin-binding domain has not yet been mapped). The APC-binding domain of β-catenin, which can be broadly defined from the data in (*1*), includes a different repeated sequence—13 copies of a 42– to 44– amino acid motif first identified in Armadillo (*14*). Interestingly, the latter repeat is also present in the amino-terminal region of APC, which does not appear to be involved in β-catenin binding. It may be that specific repeats in Armadillo mediate the APC interaction in the same way that specific epidermal growth factor repeats mediate interactions of the Notch receptor with its ligands.

It will also be important to identify other proteins in the APC-catenin complex. Notably, neither research group has been able to detect E-cadherin in the complex. However, Su *et al.* (*1*) show that α-catenin is also present in the complex, and they see consistent recovery of a protein the approximate size of γ-catenin. One might expect the complex also to include proteins required for whatever signal it is transmitting.



Cancer, catenins, and cuticle pattern. The adherens junction (AJ) complex of vertebrates and *Drosophila* is organized around a transmembrane cadherin protein that organizes a complex of cytoplasmic proteins, including α-catenin and Armadillo/β-catenin. The cadherin-catenin complex mediates adhesion, cytoskeletal anchoring, and signaling. Catenins can also form a complex with APC, which may mediate transmission of a growth regulatory signal. Armadillo/β-catenin is important for pattern formation in the *Drosophila* embryonic cuticle and is required for transduction of the Wingless/Wnt cell-cell signal. This signaling may involve a third complex of Armadillo/β-catenin with an unknown effector molecule.

Although many questions remain, the discovery of this unexpected protein-protein interaction is bound to stimulate much activity in three, no longer disparate, fields of research.

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