the Himalayan plate boundary (see the inset in the figure). It may therefore be classified as an intraplate earthquake. Such earthquakes are rare, accounting for less than 0.5% of global seismicity (*4*). However, the proximity to the triple junction (see the inset in the figure) formed by the Indian, Arabian, and African plates complicates the tectonics of the Kutch region and influences the local tectonic processes considerably. The presence of several faults in this region may be related to previous episodes of rifting associated with plume activity as the Indian plate traversed active hotspots since its breakup from Gondwanaland 120 million years ago.

The surface geology of the 2001 earthquake epicentral region comprises Mesozoic (245 to 65 million years old) sediments overlying an uplifted granitic basement. The region lies outside the basalt-covered areas of southern Kutch, which are part of the 65- to 60-million-year-old Deccan traps, one of the largest volcanic provinces in the world. Erosion of the younger sedimentary layers and the Deccan traps in the uplifted region may have left an isostatic imbalance (a gravitational instability of landmass). The focal mechanisms of Kutch earthquakes such as the 1956 Anjar earthquake (*5*), the 1819 Rann of Kutch earthquake, and a few others indicate reverse faulting, where two blocks of a fault slide over one another. Hence, under the prevailing compressional stress field caused by the northward collision of the Indian tectonic plate with Eurasia, preexisting normal faults associated with the possible plume-related Early Mesozoic rifting (*6*), may be getting reactivated as reverse faults.

On the Seismic Zoning Map of India (*7*), prepared by the Indian Standards Institution (*8*), the Kutch region lies in zone V—the zone of highest seismic potential, on par with the plate boundary regions adjoining the Himalayan belt and northeast India. The seismic hazard map of the Indian region (*9*) indicates a 10% probability that ground acceleration in the Kutch region will exceed 0.25 times the gravitational acceleration in a period of 50 years. Nonadherence to the high-risk zone building codes is chiefly responsible for the damage to many recently constructed multistoried buildings during the recent earthquake. The damage potential could be reduced substantially by strict implementation of building codes, retrofitting of important buildings particularly in zones IV and V, popularization of simple, inexpensive methods to strengthen old buildings and rural dwellings, and microzonation studies (as undertaken by the government for Jabalpur in central India) to prepare risk maps of important cities.

If these steps are implemented in a timely manner, India will be much better prepared to deal with major earthquakes. Other earthquake-prone developing countries should adapt a similar approach to reduce earthquake-related hazards.

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PERSPECTIVES: TRANSDUCTION

When Worlds Collide—Trafficking in JNK

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Components of intracellular signal transduction pathways are often organized into signaling modules. As these complexes get larger, however, they face the increasingly difficult problem of how to move within the cell to their sites of action. This problem is particularly acute, for example, in neurons of the human peripheral nervous system—the anatomical separation of the neuronal cell body (where signaling molecules are synthesized) and neuronal termini (where many of them are needed) may span a meter or more. A possible solution has emerged from a number of recent experiments capped by the elegant studies of Verhey *et al.* published in the *Journal of Cell Biology* (*1*). These studies unite the two formerly disparate intracellular worlds of signaling and vesicle transport driven by motor proteins. The intriguing implication is that signaling complexes associated with transport vesicles are moved along microtubules to their distant cellular sites of action by motor proteins such as kinesin-I (see the figure). Furthermore, kinesin motors are attached to the transmembrane proteins of cargo vesicles through specific scaffold molecules that also bind to the signaling complexes.

A key problem in understanding how molecular motors direct intracellular transport has been to identify the molecules that connect the motors to cargo vesicles and other organelles. With a yeast two-hybrid screening assay, Verhey *et al.* searched for proteins that bound to the light-chain subunit of kinesin-I. Surprisingly, they identified three known proteins—the JNK interacting proteins JIP-1, JIP-2, and JIP-3—that bound to the putative cargo-binding tetratricopeptide repeat domains in the kinesin-I light chain (*2–5*). JIPs are scaffold proteins that bind to the three kinase components of the JNK signaling pathway: JNK itself [c-Jun NH_2-terminal kinase, a mitogen-activated protein (MAP) kinase], a kinase that phosphorylates JNK such as MKK7 or MKK4 (MAP kinase kinase), and a kinase that phosphorylates MKK7 or MKK4 (MAP kinase kinase kinase). JIP-1 and JIP-2 are related proteins that share 50% amino acid identity. JIP-3 is related to JIP-1 and JIP-2 in name and potential activity only—its sequence and predicted domain organization are completely different.

JIP proteins are thought to organize components of JNK signaling pathways into functional modules that respond to specific signal inputs. Intriguingly, previous work suggests that JIP-1 and JIP-2 may interact with cargo vesicles by binding directly to the cytoplasmic domain of transmembrane low density lipoprotein (LDL) receptors such as ApoER2 (also called reelin), the LDL receptor–related protein (LRP), and megalin (see the figure) (*6*, *7*). Indeed, Verhey *et al.* demonstrate, with coimmunoprecipitation and microtubule-binding assays, that kinesin-I, JIP-1, ApoER2, and a JNK kinase (DLK) can all be found in the same complex. They also show that localization of JIP-1, JIP-2, and DLK to the tips of long processes in cultured neuronlike cells can be perturbed by overexpression of the JIP-binding regions of kinesin light chain. Thus, kinesin-I may be linked to certain transport vesicles through the JIP-1 and JIP-2 scaffold proteins, which bind to transmembrane receptors of the LDL family. This suggestion provides a mechanism

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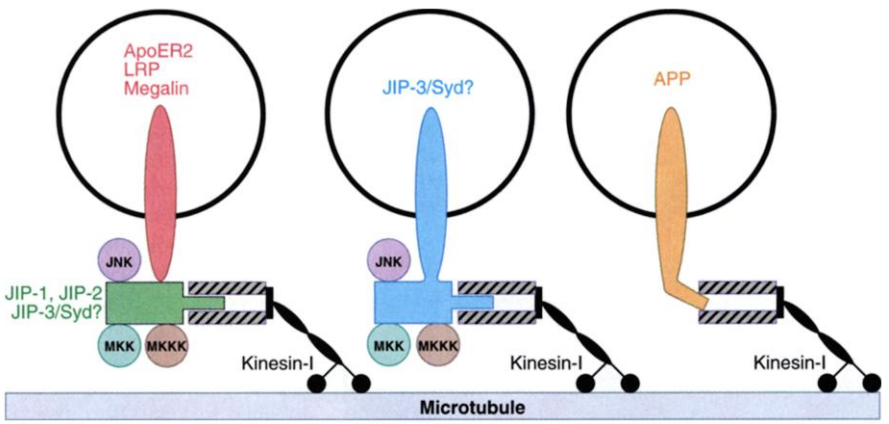
whereby JNK signaling modules that are bound to JIP scaffold proteins are simultaneously moved along with the transport vesicles to cellular surfaces and neuronal termini (see the figure).

The situation with JIP-3 is more complex, but equally intriguing. Like JIP-1 and JIP-2, JIP-3 can bind to the three components of a JNK signaling module, can be coimmunoprecipitated with kinesin-I, and has a cellular location that is perturbed by overexpression of the JIP-binding regions of kinesin light chain. The mechanism by which JIP-3 interacts with transport vesicles, however, is controversial. Although Verhey *et al.* suggest that JIP-3 is linked to cargo vesicles by binding to ApoER2, there is no evidence to support this view. Independent studies (*8*) of JIP-3, known to be encoded by the *sunday driver* (*syd*) gene in *Drosophila*, have identified an alternative possibility. Mutations in the gene encoding Syd/JIP-3 appear to disturb kinesin-I–based axonal transport and are lethal. In addition, biochemical experiments suggest that the Syd/JIP-3 protein binds directly to kinesin light chain. A number of lines of evidence have led to the proposal that Syd/JIP-3 is itself a membrane-associated protein, perhaps a transmembrane receptor, that directly links kinesin-I to axonal transport vesicles (see the figure). Thus, perhaps all three JIP proteins (with their associated JNK signaling complexes) are involved in attaching motor proteins to vesicles and transporting the vesicles to distant cellular sites. It will be intriguing to discover whether JIP-1, JIP-2, and JIP-3 are restricted to different vesicular transport and signaling pathways, whether other "cargo" molecules are "hitchhiking" in transport vesicles, and whether their transport is also controlled by JNK signaling.

These experiments contribute to the growing literature on the interactions between molecular motors and transport vesicles. Several other studies report on interactions between motor proteins and cargo vesicles that are mediated by scaffold (or adaptor) proteins. The KIF17 motor binds to the scaffold protein mlin-10, which is connected to a membrane protein complex that includes the glutamate receptor, *N*-methyl-D-aspartate (*9*). The KIF13 kinesin motor binds to adaptin, which interacts with the mannose-6-phosphate receptor (*10*), and the dynein motor binds to vesicles in neuronal axons through spectrin (*11*). In addition to indirect motor attachment to vesicles through a scaffold protein, there is also evidence that motors interact directly with the transmembrane receptor cargo of vesicles. Recent examples of this type of interaction include direct binding of dynein to the cytoplasmic carboxyl terminus of the retinal protein opsin (*12*), and binding of kinesin light chain to the cytoplasmic domain of amyloid precursor protein (APP), proteolysis of which has been implicated in Alzheimer's disease (*13*). Together these findings suggest two general ways in which motors bind to vesicles (see the figure). Whether these mechanisms reflect different regulatory strategies or are simply divergent solutions to a common problem remains unclear.



Motoring along microtubules. Different ways in which kinesin-I could be connected to transport vesicles containing cargo. **(Left)** The JIP proteins—JIP-1, JIP-2, JIP-3 (green)—are scaffold proteins that may connect the motor protein kinesin-I (black) to a transport vesicle by binding to a transmembrane lipoprotein receptor such as ApoER2, LRP, or megalin (pink) in the vesicle membrane. JNK pathway signaling components that interact with the JIPs are transported along with the vesicles to distant cellular sites **(Middle)** It is also possible that JIP-3 (called Syd in the fly), rather than being an independent scaffold protein, is itself a vesicle transmembrane receptor (blue) that contains scaffold domains. **(Right)** Kinesin-I can bind directly to the transport vesicle without the help of a scaffolding protein by interacting directly with the transmembrane protein APP (yellow).

An interesting implication of these investigations is the possibility that JNK signaling could directly influence motor-dependent transport. If so, then JNK signaling components may control their own transport to and from cell surfaces and neuronal termini by directly regulating kinesin-I activity. An additional exciting possibility is that vesicular transport may be crucial for connecting JNK signaling in neuronal cell bodies with that in distant neuronal termini. Recent work suggests that a similar arrangement regulates neurotrophic signaling: Activated neurotrophin-receptor complexes are thought to be ferried to the cell body by dynein (*14*, *15*). Could JNK pathway components transmit long-range signals in neurons by hitching a ride on the transport system running between cell bodies and neuronal termini and mediated by the dyneins and kinesins? Could such a system be implicated in the apoptotic, neuronal damage, and stress responses directed by JNK signaling?

Finally, it is striking that this recent work adds to the growing list of proteins implicated in Alzheimer's disease that also have links to intracellular transport. Tau protein, a prominent component of the neurofibrillary tangles found in Alzheimer brains and directly implicated in some forms of dementia, also binds to microtubules and has been suggested to modulate kinesin-I–based transport (*16*). APP, a transmembrane component of certain transport vesicles, may be a receptor for kinesin-I (see the figure) (*13*). ApoER2, LRP, and megalin—which may be linked to kinesin-I through JIP-1 and JIP-2—are receptors for ApoE, whose allelic status is a major risk factor for Alzheimer's disease (*17*). Further work in this unfolding area will hopefully reveal whether components of the cell's molecular transport machinery are indeed key players in Alzheimer's disease and other neurodegenerative disorders.

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