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# A Structural Scaffolding of Intermediate Filaments in Health and Disease

Elaine Fuchs and Don W. Cleveland*

The cytoplasm of animal cells is structured by a scaffolding composed of actin microfilaments, microtubules, and intermediate filaments. Intermediate filaments, so named because their 10-nanometer diameter is intermediate between that of microfilaments (6 nanometers) and microtubules (23 nanometers), assemble into an anastomosed network within the cytoplasm. In combination with a recently identified class of cross-linking proteins that mediate interactions between intermediate filaments and the other cytoskeletal networks, evidence is reviewed here that intermediate filaments provide a flexible intracellular scaffolding whose function is to structure cytoplasm and to resist stresses externally applied to the cell. Mutations that weaken this structural framework increase the risk of cell rupture and cause a variety of human disorders.

In contrast to microfilaments and microtubules, whose components are highly evolutionarily conserved and very similar within cells of a particular species, intermediate filaments (IFs) display much diversity in their numbers, sequences, and abundance (*1*). In humans, there are more than 50 different IF genes, which are differentially expressed in nearly all cells of the body. Intermediate filaments generally constitute approximately 1% of total protein, although in some cells, such as epidermal keratinocytes and neurons, IFs are especially abundant, accounting for up to 85% of the total protein of fully differentiated cells. Thus, IF cytoskeletons seem to be tailored to suit specific structural needs of each higher eukaryotic cell.

Despite their diversity, members of the IF superfamily share a common structure: a dimer composed of two α-helical chains oriented in parallel and intertwined in a coiled-coil rod. First discovered in the 1950s in the keratins constituting hair (*2*), this mechanism of dimerization through coiled-coil interaction is now universally found throughout biology. The highly conserved ends of the IF rod associate in a head-to-tail fashion, and mutations in these rod ends have deleterious consequences for the assembly process of most if not all IF proteins (*3*, *4*). The association of dimers results in linear arrays, four of which associate in an antiparallel, half-staggered manner to produce protofibrils; and three to four protofibrils intertwine to produce an apolar intermediate filament 10 nm in diameter (Fig. 1). Generally, the assembly equilibrium is heavily in favor of IF polymer.

Although IFs share similar structures, their properties can be quite unique. Keratin IFs of hair and epidermal cells are highly insoluble, and even their noncovalently linked dimer subunits do not fully dissociate in 9 M urea (*5*). In contrast, nuclear lamin IFs that line the inner surface of the nuclear membrane and vimentin IFs of fibroblasts are dynamic, dissociating and reforming in a cell cycle–dependent manner (*6*). Indeed, despite very small intracellular pools of unassembled subunits, both recovery after photobleaching of fluorescently labeled IFs (*7*) and introduction of small peptide inhibitors of IF assembly (*8*) have demonstrated that individual IFs apparently have in vivo

E. Fuchs is at the Howard Hughes Medical Institute and Department of Molecular Genetics and Cell Biology, University of Chicago, Chicago, IL 60637, USA. D. W. Cleveland is at the Ludwig Institute for Cancer Research and the Departments of Medicine and Neuroscience, University of California at San Diego, La Jolla, CA 92093, USA.
*To whom correspondence should be addressed.

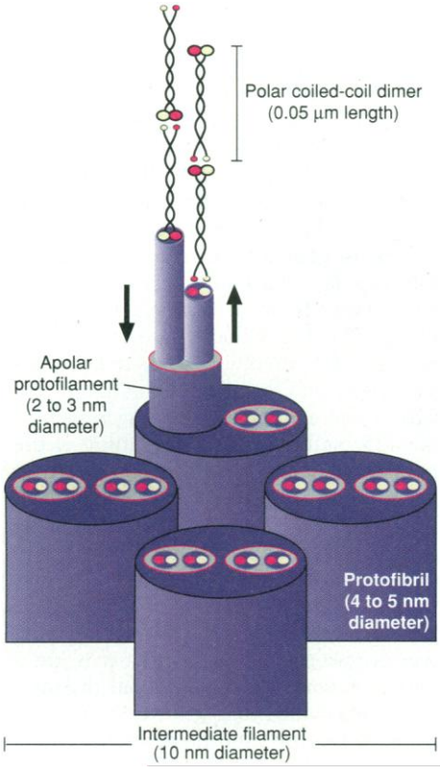


**Fig. 1.** Structural model of an IF. Polar dimers of IF subunits form staggered antiparallel tetramers that associate longitudinally and laterally into apolar protofilaments 2 to 3 nm in diameter and protofibrils 4 to 5 nm in diameter. Two to four protofibrils (four are drawn here) associate to yield a coiled-coil lattice composed of approximately 16 to 32 polypeptides in cross section. For more detail, see (*1*, *16*).

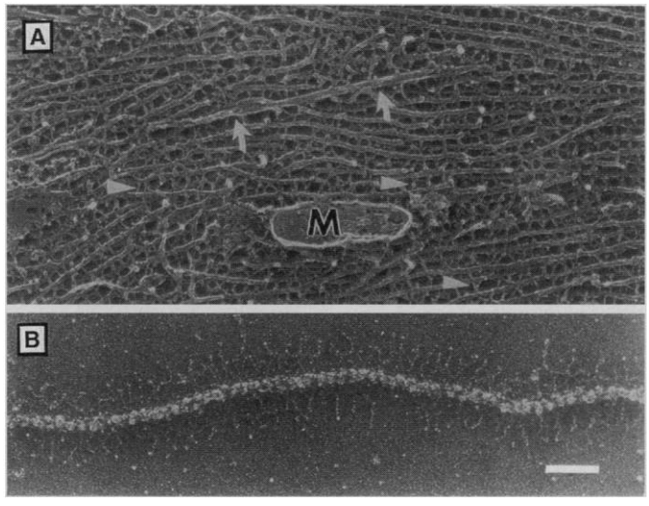


**Fig. 2.** Neurofilaments as determinants of axoplasmic structure. (**A**) Quick-freeze deep-etch view of the cytoplasm of a myelinated axon from a rabbit sciatic nerve. A single (25 nm in diameter) microtubule is denoted by curved arrows. All remaining filaments are neurofilaments 10 nm in diameter, which are extensively cross-bridged to each other (arrowheads) and to microtubules. M, a mitochondrion. [Micrograph reproduced with permission from Hirokawa *et al.* (*64*).] (**B**) Rotary-shadowed view of a native neurofilament showing the tail domains of NF-M and NF-H extending from the core of the filament. Scale bar, 100 μm. (Micrograph kindly provided by U. Aebi.)

half-lives of an hour or less.

Intermediate filaments also show dramatic individuality in the company they keep. This is largely, but not solely, due to fact that the coiled-coil rod domains of IF polypeptides are flanked by nonhelical head and tail segments that vary enormously in size and sequence. Although the importance of head and tail segments in IF structure is dependent on the individual IF protein, at least a portion of these segments is likely to protrude along the surface of the IF, imparting different cloaks to each filament and enabling diversity in the proteins that associate with them (*1*). The most extreme instance is the neurofilament (NF) proteins NF-L (67 kD), NF-M (150 kD), and NF-H (200 kD), whose size variation is due to dramatic differences in the lengths of their COOH-termini: Although NF-L forms the backbone of the neurofilament, NF-M and NF-H integrate in the peripheral dimer arrays, which leaves their tails protruding up to 30 nm away from the filament backbone (Fig. 2B) and enables them to associate with other NFs and microtubules in the axoplasm (Fig. 2A).

Hair-specific keratins also have unusual nonhelical sequences that are rich in cysteine residues, enabling IFs to covalently cross-link with each other and with IF-associated proteins. During terminal differentiation, the cells of the hair shaft acquire a very rigid cytoskeleton; and through making and breaking the cysteine bonds between keratin IFs and their associated proteins, the hair shafts can change shape, in a process analogous to what happens in a permanent wave (*1*).

## Intermediate Filament Functions and Their Relation to Genetic Disease

Although the abundance of IFs in keratinocytes and neurons indicated that they play important roles, for many years this speculation seemed firmer than any of the experimental evidence supporting it. However, once the key residues for IF assembly had been uncovered, the behavior of mutant IF proteins could then be tested in transgenic mice to address questions of IF function and their possible relation to genetic disease. The paradigm was set with K5 and K14, the keratins expressed in the innermost, mitotically active layer of the epidermis (Fig. 3). When Vassar *et al.* (9) expressed levels comparable to wild-type levels of a filament-disrupting, truncated human K14 gene in transgenic animals, newborn mice exhibited skin blistering upon mild mechanical trauma. When different K14 mutations were tested, mice displayed a good correlation between the severity of skin blistering and the degree to which a particular keratin mutant perturbed filament assembly. Examination of cross sections of skin revealed that the blistering arose from cell degeneration and cytolysis within the basal epidermal layer (Fig. 3). In severe cases, aggregates of insoluble keratin accumulated in the cytoplasm, concomitant with the absence of a normal keratin network.

Discovery of natural K14 null mutations in humans and of engineered K14 gene disruptions in mice provided definitive evidence that the normal function of the keratin network is to impart mechanical integrity to epidermal cells (*10*). When the structural framework for the cell is disorganized, the cells become fragile and prone to rupture when stressed. In the absence of K14, its dimerization partner K5 was unstable, leaving no trace of the extensive K14-K5 keratin network that normally constitutes 20 to 25% of the basal epidermal cell. In the limited number of human K14 null cases examined thus far, and in the K14 null mice, the blistering has been somewhat milder than seen with many dominant mutations. If these observations hold as more cases are analyzed, it could be an indication that aggregates of protein exacerbate the degenerative process, presumably because insoluble debris provides an additional insult (Fig. 3).

The phenotype and pathology of transgenic animals expressing severely disrupting K14 mutant genes (9) bore a striking resemblance to epidermolysis bullosa simplex (EBS), a human skin disorder of then-unknown etiology. Less than a year after the first transgenic mouse report, two groups discovered point mutations in the K14 gene of patients with human EBS (*11*, *12*). Soon a K5 point mutation was identified in affected members of a small family with EBS

(*13*), and more precise genetic mapping with larger EBS families revealed chromosomal locations now consistent with the known locations for the functional K14 and K5 genes (*12*, *14*, *15*). As additional cases were characterized, the location of mutations correlated well with disease severity and with the degree to which randomly engineered mutations in similar locations were known to perturb filament assembly (*4*). Often, and especially in severe cases of EBS, the mutations resided in the highly conserved ends of the coiled-coil rod domain. Such a mutation seen in numerous severe EBS cases is a cysteine or histidine substitution for a particular arginine that is important for the filament elongation process (*11*, *16*, *17*).

To date, most severe EBS cases can be accounted for by K5 and K14 mutations. However, there are a number of cases, often the mildest ones, in which the K5 and K14 genes have been analyzed but no mutations were identified. Thus, for some incidences of EBS, the defect in these patients may reside outside the K5 or K14 genes, perhaps in associated proteins that interact with the basal keratin network. The possibility of genetic heterogeneity in EBS is attractive in light of recent studies involving keratin network perturbations by nonkeratin mutations (see below).

The discovery of the genetic basis of EBS set the paradigm for a keratin disorder, revealing that a severe filament-disrupting keratin mutation can cause disorganization or aggregates of IF protein in cells where the protein is expressed, leading to mechanically induced degeneration. It was inevitable that additional disorders of keratin would surface, given that the human genome contains more than 30 different keratin genes, which are differentially expressed in epithelial cells of the body. Electron microscopy studies had noted parallels between EBS and another blistering skin disorder, epidermolytic hyperkeratosis (EH), in which basal cells appear normal, but degeneration and accumulation of keratin aggregates occur in spinous cells (*18*). Given that epidermal cells switch from K5 and K14 expression to K1 and K10 expression as they leave the basal layer and move outward toward the skin surface (*19*, *20*) (Fig. 3), it was soon demonstrated that EH was a disorder of K1 and K10 (*21*). Many EH patients display mutations in the exact corresponding residues of K10 or K1 that when mutated in K14 or K5 give rise to EBS. Thus, the same mutation in a highly conserved residue of two genes can give rise to two distinct genetic diseases because of differential expression patterns. Genes from many additional EH patients have now been sequenced, and overall the K1, K10, and (more suprabasally) K2e mutations fall into patterns that are similar to those seen in EBS (*1*, *17*).

Another disorder caused by keratin mutations is epidermolytic palmoplantar peratoderma (EPPK), in which patients exhibit palmoplantar skin blistering due to keratin filament clumping and cytolysis in suprabasal layers (*22*). K9 is a keratin that has previously been shown to be restricted to the spinous layers (see Fig. 3) of the especially protective thick skin on the hands and the feet (*19*, *20*), and indeed mutations in the gene encoding K9 are the basis of some EPPK cases (*23*). One family with a noncytolytic form of this disorder has a mutation that was recently mapped to the region of chromosome 18 where the desmosomal cadherin genes reside (*24*), which suggests that some disorders similar to EBS may arise from perturbations in the specialized cell-cell junction proteins that connect the keratin filament network to the periphery of epidermal cells.

The list of genetically characterized keratin disorders continues to grow and now encompasses 14 of the known keratins (Table 1). This list includes autosomal dominant disorders involving stress-induced degeneration and keratin clumping in the cells of the epidermal appendages such as hair (*25*) and nails (*26*), the lining of the mouth and esophagus (*27*), and the corneal covering of the eye (*28*). Additionally, defects in intestinal cell proliferation have been detected in mice lacking K8 (*29*), and although as yet untested functionally, mutations in a simple epithelial keratin have been detected in a patient with chronic liver disease (*30*). It seems that it is just a matter of time before additional disorders will be uncovered that will extend to most if not all keratins and the epithelial tissues that express them.

## Neurofilament Function and Relation to Genetic Disease

Since their initial visualization by the great neuroanatomists of the 19th century, mounting evidence has pointed to the importance of neurofilaments in structuring axons, the long thin nerve processes that are the conduits for electrical signaling. In

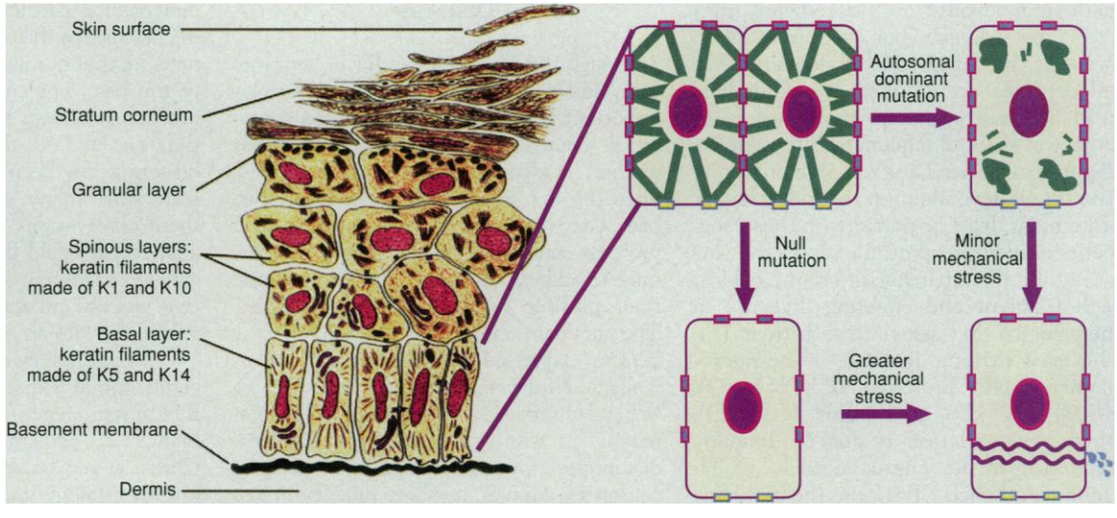


**Fig. 3.** The role of the IF network in the mitotically active keratinocytes of the epidermis. The epidermis is a stratified epithelium, composed of an inner layer of dividing cells and outer layers of terminally differentiating cells. All of these layers display extensive keratin filament networks. The dividing cells produce ~20 to 25% of their protein as K5 and K14; the differentiating cells shut off expression of these keratins and switch to expressing K1 and K10 (and later K2e), which ultimately will constitute up to 85% of the protein of the fully differentiated cell (squame) that is sloughed from the skin surface. The keratin filaments provide a cellular framework that reaches from the nucleus to the specialized cell-cell junctions called desmosomes (blue boxes) and to the specialized cell-substratum junctions called hemidesmosomes (yellow boxes) [for review, see (*65*)]. When the K5-K14 network is missing in null mutants, cells become fragile and prone to rupturing and degeneration upon mechanical trauma, resulting in a skin blister (jagged horizontal line). When the K5-K14 network is disrupted, insoluble aggregates of keratin exacerbate the situation, making the cell even more sensitive and resulting in more severe cell degeneration and skin blistering.

many neurons, once stable synapses have formed, neurofilaments accumulate robustly as axonal diameter increases. Outnumbered by an order of magnitude, microtubules are surrounded by a sea of neurofilaments that are cross-bridged to each other, to microtubules, and to actin (Fig. 2A).

The number of neurofilaments relative to axonal cross-sectional area does not change during development or after axonal injury, leading to the proposal that neurofilament density determines axonal diameter (*31*). This has been demonstrated unambiguously in genetically engineered animals that either contain enhanced levels of neurofilaments or lack axonal neurofilaments (*32*, *33*). Disruption of the NF-L gene in mice results in motor neuron axons that are only ~30% of their normal diameter. Although neurofilaments are not essential for survival, NF deficiency in quails causes a reduction in the velocity of electrical signal conduction in the axon (*34*) and uncontrollable quivering, as well as breeding and behavioral defects (*33*). Moreover, a 15% loss in motor axon survival early in life in neurofilament-free mice (*32*) most likely reflects a requirement for neurofilaments in maintaining the structural integrity of axons.

How might neurofilaments structure axoplasm to support and maintain a large increase in axoplasmic volume? Because the nearest-neighbor spacing between neurofilaments remains constant in axons of transgenic mice expressing altered numbers of neurofilaments and of neurofilaments assembled from NF-L and from varying proportions of NF-M and NF-H subunits (*31*), there must be short- and long-range interactions not only between neurofilaments themselves but with other components of the axonal cytoskeleton. Neurofilament connections most likely involve cross-bridging imparted by the long carboxy tails of NF-M and NF-H and also by plectin, BPAG1n, and their relatives (see below).

Abnormal accumulation and disorganization of neurofilaments is a hallmark of a collection of motor neuron diseases including familial and sporadic amyotrophic lateral sclerosis (ALS), infantile spinal muscular atrophy, and hereditary sensory motor neuropathy (*35*). In human ALS, the large motor neurons—those with the most neurofilaments—are most affected (*36*). Transgenic mice expressing either high levels of wild-type neurofilament genes or levels of a mutant neurofilament gene comparable to wild-type levels (*37*) develop motor neuron disease reminiscent of human ALS (*38*).

Although ~20% of familial ALS cases arise from mutations in the soluble enzyme superoxide dismutase (SOD) (*39*), most ALS cases are not due to SOD mutations. Neurofilament-disrupting mutations have thus far gone undetected in analyses of 100 familial ALS patients (*40*), although in sporadic ALS cases, deletions not found within the normal population have been detected in a repeated motif within the long NF-H tail (*41*). However, even in cases where the primary cause of disease lies in a toxic property arising from a SOD mutant (*42*), neurofilament misaccumulation remains a prominent pathologic feature (*43*). Thus, irrespective of genetic defect, the mechanism of disease may arise from disorganized neurofilaments choking the transport of components that would otherwise be delivered down the motor axons after synthesis (*44*).

## Proteins That Make Essential Connections Between IF Networks and Actin or Microtubules

Given the deleterious consequences of a disorganized IF cytoskeleton, it is not surprising that eukaryotic cells have evolved mechanisms for keeping IFs anchored. Such anchorage contributes to cell integrity by cross-linking within the cytoplasm and to the membrane skeleton. In stratified epithelia, IFs attach to sites of cell-cell adhesion, or desmosomes. Desmosomes contain a protein called desmoplakin, which localizes intracellularly to the region where keratin IFs interface with the electron-dense membranous plaque (*45*). The COOH tail domain of desmoplakin associates with keratin networks, whereas the $NH_2$-terminal head domain associates with desmosomes (*46*). Thus, desmoplakin is a cytoskeletal linker protein, mediating the association of IFs with desmosomes. A protein related to desmoplakin is envoplakin, which may be involved in linking desmosomes and keratin filaments to the cornified envelope, a structure underlying the plasma membrane of the terminally differentiating epidermal cell (*45*).

Not to be confused with these ultrastructurally similar cousins, hemidesmosomes are specialized integrin-mediated junctions that anchor IFs to the base of the inner layer of a stratified squamous epithelium. Two proteins associate on the cytoplasmic surface of the integrin and anchor the IF network to it. One of these is the epidermal form of the bullous pemphigoid 1 antigen, BPAG1e, a 230-kD protein so named because patients with the bullous pemphigoid autoimmune disorder fortuitously make antibodies against BPAG1e. The other is plectin, first discovered as a protein that can "decorate" IF networks in a number of cell types, including epidermal and muscle cells (*47*). BPAG1e and plectin are related in sequence to desmoplakin, and both have the capacity to bind IFs and to localize to hemidesmosomes.

The first hint that this group of IF-linker proteins might be physiologically important came from Guo *et al.* (*48*), who used gene targeting to ablate the *BPAG1* gene in mice. In the absence of BPAG1e, IFs were severed from the hemidesmosomes, generating an intracellular zone of mechanical fragility at the base of the stratified epithelium, and resulting in skin blistering. Disruption of the BPAG1 locus also resulted in gross degeneration of the sensory nervous system, apparently due to disorganization and large aggregates of neurofilaments (*48*). Reminiscent of the well-known mouse neurological mutant *dystonia musculorum* (*dt/dt*), mating revealed that the BPAG1 gene was allelic with the *dt* locus (*48*), a feature found independently by positional cloning of the *dt* gene (*49*).

**Table 1.** Genetic disorders of IFs and their cytoskeletal networks.

| Disorder | Cells involved | Species | Genes mutated | References |
|---|---|---|---|---|
| EBS | Basal epidermal | Human, mouse | *K5, K14* | (*11–13*) |
| EBS with muscular dystrophy | Basal epidermal | Human | *Plectin* | (*54*) |
| EBS with sensory neuron degeneration | Basal epidermal, dorsal root ganglia | Mouse | *BPAG1* | (*48, 49*) |
| EH, EPPK | Suprabasal, epidermal | Human, mouse | *K1, K10, K2e, K9* | (*21, 23*) |
| Pachyonychia congenita | Nails, hair | Human | *K6, K16, K17* | (*26*) |
| White sponge nevus | Esophagus, oral epithelia | Human | *K4, K13* | (*27*) |
| Meesmann's corneal dystrophy | Corneal epithelia | Human | *K3, K12* | (*28*) |
| Monilethrix | Hair | Human | *Keratin Hb6* | (*25*) |
| Chronic hepatitis, cryptogenic cirrhosis | Liver | Mouse human | *K18* | (*30*) |
| Colorectal hyperplasia | Colon | Mouse | *k8* (null) | (*29*) |
| Motor neuron disease | Motor neurons | Mouse | *NFL* | (*37*) |

The neural phenotype was puzzling until it was discovered that neural isoforms of the *BPAG1* gene exist (*49*, *50*). In these isoforms, exon 1 of the epidermal form is replaced by a new sequence containing an actin-binding domain with a binding affinity comparable to that seen in well-characterized actin-binding proteins such as α-actinin and β-spectrin; the remainder of the neural and epidermal polypeptides are shared, including an IF-binding domain in the COOH-terminal tail segment (*50*). That both putative actin and IF binding domains of BPAG1n are functional was demonstrated by forcing expressing of NF-L, NF-H, and BPAG1n in a non-neuronal cell; this resulted in coalignment of neurofilaments with the endogenous array of actin stress fibers (Fig. 4, A to C). This new cytoskeletal linkage uncovers a direct association between IFs and the actin cytoskeleton that appears to be crucial to the survival of sensory neurons. Given that mice lacking BPAG1n (*48*, *49*) are worse off than those lacking axonal neurofilaments (*32*), it would appear to be better not to have neurofilaments than to leave them unanchored.

Another protein harboring actin and IF-binding domains is plectin, an enormous ~500-kD protein (*51*). Plectin has long been known to decorate and associate with IFs (*52*). Direct visualization by immunoelectron microscopy has documented plectin cross-bridges between IFs and microtubules, IFs and actin filaments, and even IFs and myosin filaments (*53*) (Fig. 4D). That plectin is essential for mechanical resistance in cells has been demonstrated by null mutations in the plectin gene of both mice and humans (*54*): The phenotype is that of the rare complex genetic disorder of EBS with muscular dystrophy, typified by skin blistering and muscle weakness and degeneration. Thus, as underscored by the physiological importance of BPAG1n and plectin in skin, muscle, and the nervous system, cross-linking of cytoskeletons through IF-associated components (Fig. 4E) is likely to be a functionally important general feature of cells.

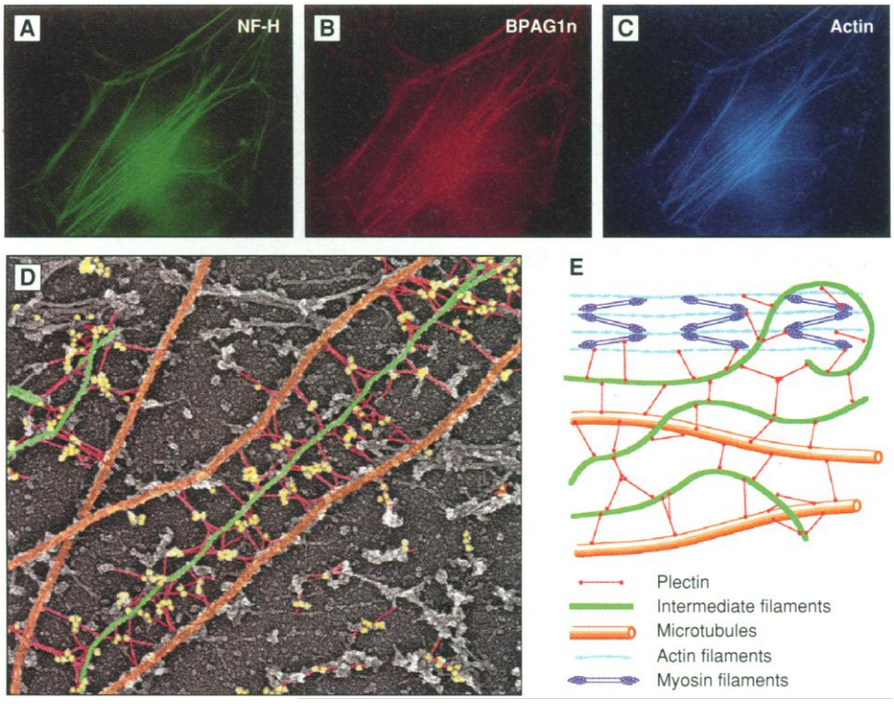


**Fig. 4.** IF-associated proteins provide flexible intracytoplasmic resilience in response to external stresses by reversibly cross-linking IFs to other cytoskeletal and membrane sites. (**A** through **C**) BPAG1n/dystonin, a 280-kD linker protein with actin- and neurofilament-binding domains, aligns neurofilaments along actin stress fibers when a cultured mammalian cell is triply transfected to express BPAG1n, NF-L, and NF-H. (A) Neurofilament; (B) BPAG1n/dystonin; (C) actin. [Reproduced with permission from Yang *et al.* (*50*).] (**D**) Electron micrograph of the residual cytoskeleton of a rat embryo fibroblast after dissolution of actin filaments with gelsolin. Linked to 10-nm gold particles, antibodies against the 500-kD cross-linker protein plectin reveal bridges between microtubules and IFs. Pseudocolored elements are microtubules (orange), IFs assembled from vimentin (green), plectin (red), and gold particles marking plectin (yellow). (**E**) Model suggesting that plectin mediates linking between IFs, microtubules, actin, myosin, and membrane-bound adhesion sites (focal contacts or plasma membrane components) (*51*, *53*). (Images kindly provided by T. Svitkina and G. Borisy.)

## Functions and Disruptions of Other IF Networks

Like keratinocytes and neurons, muscle cells have developed elaborate IF networks. Genetically engineered mice lacking the muscle-specific IF protein desmin exhibit cardiovascular lesions and skeletal muscle myopathy (*55*). The muscle fibers of these mice are more susceptible to damage during contraction, and myofibrillogenesis in regenerating fibers is often abortive. Whether desmin defects contribute to human disease has not been determined, although some cases of congenital distal myopathy have been associated with aberrations in the desmin IF network (*56*). At present, no linkage between any form of cardiomyopathy and mutations in the desmin locus on chromosome 2 has been found (*57*).

With the exception of keratins, neurofilaments, and desmin, the relation between most other IF genes and human pathology is still in its infancy. However, wherever tested, gross perturbations in IF networks seem to be incompatible with cell survival. In the lens of the eye, disruption of IFs leads to cataract formation in mice, apparently caused by the presence of insoluble protein aggregates (*58*). In contrast, mice lacking either vimentin (*59*) or glial fibrillary acidic protein (GFAP) (*60*) develop normally and without any obvious phenotypic abnormality in early life. By 18 months of age, however, GFAP null mice exhibit major defects in myelination of axons, leading to structural and functional defects in the white matter of the brain and in the blood-brain barrier and deficits in a form of memory for conditioned responses (called long-term depression) (*61*). Similarly, we now know that vimentin is essential for assembly of a GFAP network in astrocytes and also in the myelin-producing cells in the peripheral nervous system (*62*). Thus, although other IF networks may not be as essential as the epidermal or the desmin IF network in withstanding the daily rigors of life, IF cytoskeletons seem to have evolved to serve specialized roles that structure the cytoplasm to resist external stresses.

## Summary

The past decade has brought us answers about the elusive functions of IFs. It is quite remarkable that, as first suggested by Lazarides (*63*) many years ago, IFs seem to be mechanical integrators of the cytoplasm that function to resist mechanical stress. Key genetic evidence now supports this notion and strengthens the view that IFs are central to cytoarchitecture and structural

integrity. The recent discovery of linker proteins bridging between IFs and other cytoskeletal components and their importance to cell survival and genetic disease open a new field for understanding the functional interactions among the structural elements within the cytoplsm.

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# Kinesin and Dynein Superfamily Proteins and the Mechanism of Organelle Transport

Nobutaka Hirokawa

Cells transport and sort proteins and lipids, after their synthesis, to various destinations at appropriate velocities in membranous organelles and protein complexes. Intracellular transport is thus fundamental to cellular morphogenesis and functioning. Microtubules serve as a rail on which motor proteins, such as kinesin and dynein superfamily proteins, convey their cargoes. This review focuses on the molecular mechanism of organelle transport in cells and describes kinesin and dynein superfamily proteins.

Neurons and epithelial cells are among the many types of cells that develop polarized structures. The neuron is composed of a cell body, dendrites, and a long axon along the direction of impulse propagation. The axon lacks protein synthesis machinery, and thus all the proteins required in the axon and synaptic terminal must be transported down the axon after they are synthesized in the cell body. Most proteins are conveyed in membranous organelles or protein complexes. In this sense, organelle transport in the axon is fundamentally important for neuronal morphogenesis and functioning. Because similar mechanisms are observed in other cells, the neuron serves as a good model system to study the general mechanisms of organelle transport (*1*). Epithelial cells also develop polarized structures, that is, the apical and basolateral regions, to which certain proteins are specifically transported and sorted (*2*).

Microtubules are 25-nm tubule-like structures formed by α,β-tubulin heterodimers. Thirteen parallel protofilaments composed of linearly arranged heterodimers form the

The author is in the Department of Cell Biology and Anatomy, Graduate School of Medicine, University of Tokyo, Hongo 7-3-1, Tokyo, Japan. E-mail: hirokawa@m.u-tokyo.ac.jp