JCI The Journal of Clinical Investigation

"IF-pathies": a broad spectrum of intermediate filament–associated diseases

M. Bishr Omary

J Clin Invest. 2009;119(7):1756-1762. https://doi.org/10.1172/JCI39894.

Review Series

Intermediate filaments (IFs) are encoded by the largest gene family among the three major cytoskeletal protein groups. Unique IF compliments are expressed in selective cell types, and this expression is reflected in their involvement, upon mutation, as a cause of or predisposition to more than 80 human tissue-specific diseases. This Review Series covers diseases and functional and structural aspects pertaining to IFs and highlights the molecular and functional consequences of IF-associated diseases (IF-pathies). Exciting challenges and opportunities face the IF field, including developing both a better understanding of the pathogenesis of IF-pathies and targeted therapeutic approaches.

"IF-pathies": a broad spectrum of intermediate filament–associated diseases

M. Bishr Omary

Department of Molecular & Integrative Physiology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

Intermediate filaments (IFs) are encoded by the largest gene family among the three major cytoskeletal protein groups. Unique IF compliments are expressed in selective cell types, and this expression is reflected in their involvement, upon mutation, as a cause of or predisposition to more than 80 human tissue-specific diseases. This Review Series covers diseases and functional and structural aspects pertaining to IFs and highlights the molecular and functional consequences of IF-associated diseases (IF-pathies). Exciting challenges and opportunities face the IF field, including developing both a better understanding of the pathogenesis of IF-pathies and targeted therapeutic approaches.

Intermediate filaments

Intermediate filaments (IFs), microfilaments (MFs), and microtubules (MTs) are the major fibrillar cytoplasmic elements that make up what is referred to as the cytoskeleton. IFs consist of a large protein family that includes 73 unique gene products, which places the genes encoding them among the 100 largest gene families in humans (1). The IF proteins are grouped into six types (types I–VI): those in types I–IV are found in the cytoplasm, the type V IF proteins are found in the nucleus, and those classified as type VI are found exclusively in the lens (Table 1). Several features distinguish IFs (2–4) from MFs and MTs, including IF structural diversity, tissue- and cell-selective expression, unique subcellular compartment distribution (lamins are found in the nucleus, whereas the remaining IFs are in the cytoplasm), relative insolubility, nucleotide-independent assembly, restricted expression to higher eukaryotes, and, most relevant, their involvement in more than 80 human diseases (Human Intermediate Filament Database, http://www.interfil.org/index.php) (5). Another distinguishing feature of IFs is their regulation (primarily but not exclusively) by phosphorylation, whereas MFs and MTs are regulated preferentially but not exclusively by their associated proteins and posttranslational modifications other than phosphorylation (6). Furthermore, IFs are characteristically resistant to breakage when mechanically stressed, whereas MFs and MTs are far less compliant (7).

In addition to the unique and complex cell and tissue distribution of IFs (Figure 1), the expression of some IF proteins is highly regulated during development and cell differentiation and can be markedly induced in cells and tissues undergoing an injury response. For example, keratin 5 and 14 (K5/K14) are found in basal keratinocytes, whereas K1/K10 are found in the differentiating layers of suprabasal epidermis (8); K19 is found in fetal but not normal adult hepatocytes (9); K19/K20 (10) and K6/K16 (11) are highly induced in response to pancreatic acinar cell and skin injury, respectively; and glial fibrillary acidic protein (GFAP) is upregulated during reactive gliosis (12).

The Review Series

The Review Series herein includes eight state-of-the-art treatises by leaders in the field. The first article, by John Eriksson, Robert Goldman, and colleagues, sets the stage by providing a historical perspective of IFs and their classification (13). It also provides several functional perspectives with an emphasis on the paradigm shifting notion that IFs are not only structural proteins but also play essential roles as signaling organizers and buffers of cellular stress (13). The second Review, by Harald Herrmann, Sergei Strelkov, Peter Burkhard, and Ueli Aebi, highlights some of the structural features of IFs versus MFs and MTs and describes the current understanding of the assembly properties of IFs and how IF mutations affect IF structure and assembly properties (14). The remaining six articles cover specific members of the IF protein family in the sequential order of IF types I–VI. The type I and type II keratins are covered in the third and fourth reviews (15, 16). Pierre Coulombe, Michelle Kerns, and Elaine Fuchs discuss K5 and K14 and how mutations in the genes encoding these proteins are responsible for epidermolysis bullosa simplex (EBS), the first human disease known to be linked to an IF gene (15). Nam-On Ku, Pavel Strnad, Shinichiro Hanada, and Bishr Omary discuss the simple epithelial keratins and how mutations in the genes encoding K8, K18, and K19 serve as liver-disease modifiers (16). These authors also summarize the role of K8 and K18 in the hepatocyte inclusions, termed Mallory-Denk bodies, that are seen in several human liver diseases (16). In the fifth review, Lev Goldfarb and Marinos Dalakas discuss the type III IF protein desmin and its role in skeletal and cardiac myopathies (17). Ronald Liem and Albee Messing discuss, in the sixth review, the IF proteins found in glial cells and neurons, which include both type III and type IV IF proteins, and their involvement in several neurodegenerative disorders and inclusion formation (18). In the seventh review, Harold Worman, Stephen Young, and colleagues tackle laminopathies, the diseases caused by mutations in the genes encoding the type V IF proteins, the lamins, and discuss how cell biology and physiology efforts are providing unique therapeutic approaches to the highly complex disorders caused by lamin A/C gene mutations (19). Finally, Roy Quinlan and colleagues discuss the type VI beaded filament proteins of the eye lens and how their mutation leads to cataract formation in animal models and humans (20).

Conflict of interest: The author has declared that no conflict of interest exists.

Nonstandard abbreviations used: EBS, epidermolysis bullosa simplex; GFAP, glial fibrillary acidic protein; IF, intermediate filament; IF-pathy, IF-associated disease; K, keratin; MF, microfilament; MT, microtubule.

Citation for this article: *J. Clin. Invest.* **119**:1756–1762 (2009). doi:10.1172/JCI39894.

Table 1
Summary of IF-pathy categories and IFs not yet linked to a human disorder

IF protein type	Proteins	Primary cell/tissue	Diseases
Cytoplasmic			
I and II (including hair keratins)	K1–K28, K31–K40, and K71–K86	Epithelia and epidermal appendages	A broad range of skin and nail disorders (epidermal keratins), eye (ocular keratins), liver (simple epithelial keratins), and hair (hair keratins) disorders
I and II	K7, K15, K20, some hair keratins	Epithelia and epidermal appendages	?
III	Vimentin	Mesenchymal cells and lens	Cataract
	GFAP	Astrocytes	Alexander disease
	Desmin	Muscle	Cardiomyopathies
	Syncoilin	Muscle (mainly skeletal/cardiac)	?
	Peripherin	Peripheral nervous system	ALS
IV	Neurofilaments	Central nervous system	ALS and CMT
	α-Internexin	Central nervous system	?
	Nestin	Neuroepithelial cells	?
	Synemin	Muscle	?
Nuclear			
V	Lamins	Nuclear lamina	More than 12 laminopathies (lipodystrophy, muscular dystrophy, progeria, cardiomyopathy, restrictive dermatopathy, mandibuloacral dysplasia, CMT2B1, leukodystrophy).
Lens			
VI	Bfsp1 and Bfsp2	Fiber cells	Cataract

ALS, amyotrophic lateral sclerosis; Bfsp, beaded filament structural protein; CMT, Charcot-Marie-Tooth.

Clinically relevant contexts of IFs

IFs are involved in human disease in several contexts (Figure 2). First, mutations in genes encoding IF proteins either cause or predispose to human disease. Essentially all IF proteins, except for a few that, to date, have not been linked to a particular human disease, involve well-defined diseases (Tables 1 and 2). Second, mutation-independent or -dependent involvement of IF proteins in human disease results in the formation of characteristic cytoplasmic inclusions (Figure 2). It is unclear whether the formation of such inclusions protects or perpetuates the underlying disease, but these inclusions are histopathologic and diagnostic hallmarks for the diseases they associate with (16–18). The IF protein–containing inclusions may form as a consequence of specific diseases that are associated with IF overexpression in the absence of a mutated IF protein (e.g., Mallory-Denk bodies in alcoholic and nonalcoholic steatohepatitis; ref 16). In humans, the inclusions termed Rosenthal fibers (characteristic of Alexander disease) are found in the context of *GFAP* mutation, while similar inclusions are found in mice overexpressing wild-type GFAP, which phenocopy human Alexander disease (18). This suggests that IF inclusion formation, at least in some cases, is related to IF overexpression coupled with an appropriate stress milieu, rather than IF mutations per se (16, 18). Last, additional clinically relevant contexts are related to the detection of IF proteins as surrogates of disease activity and as diagnostic markers for disease. Here, IFs have utility as tumor or tissue markers (16), as apoptosis or necrosis markers (16, 18), or as autoantigens (16).

Overview of the IF-associated diseases

The IF-associated diseases (IF-pathies) involve a broad range of tissues and reflect the wide tissue and cell-type expression of IFs (Table 1). The first IF to be directly linked to any human disease was K14 (21, 22), which led to the rapid realization that a wide spectrum of human Mendelian-inherited diseases are caused by mutations in IF protein–encoding genes (Table 2) (3, 23). Most of the mutations act in a dominant fashion because of the normal oligomeric state of IFs. For example, the simplest unit of an IF protein in cells is a tetramer that consists of either homopolymers (as is seen for desmin and several other IF proteins) or obligate heteropolymers (as is seen for type I and type II keratins). The location of a mutation within the IF protein backbone plays an important role in determining the severity of a given IF-pathy (15). The cause of IF-pathies covers the whole spectrum of genetic alterations, including missense and nonsense mutations, deletions, and gene duplications. The vast majority of mutations are represented by missense alleles that involve individual amino acids on the IF protein backbone. Although there are some mutation "hot spots" for different IFs, the mutations in general involve many amino acids that cover the entire molecule. Lamin A has the most number of variants, and more than 30% of the 664 lamin A amino acids are involved in a disease (5). Some genetic variants appear to have a near 100% association with specific ethnic backgrounds; for example, the K8 Gly434Ser variant is found exclusively in those of African descent (16). Furthermore, there are increasing cases of pleiotropy, whereby identical mutations result in two different diseases in different families or in a range of phenotypes within the same family (23, 24). For example, the same lamin A/C gene mutations can cause dilated cardiomyopathy type 1A, Emery-Dreifuss muscular dystrophy, and limb-girdle muscular dystrophy type 1B (25), and the K17 Arg94Cys mutation causes

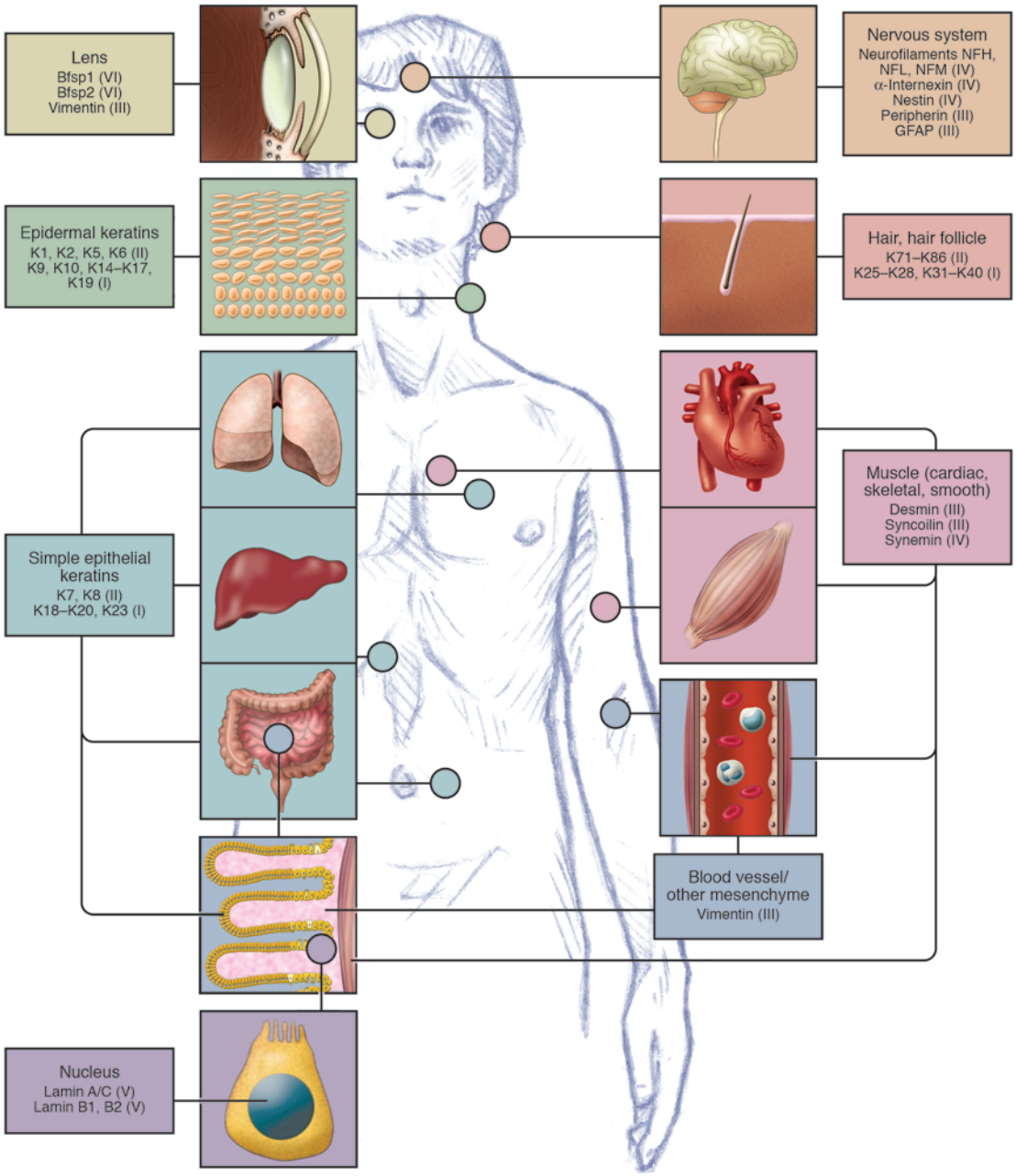

Figure 1
The broad and complex distribution of IFs in human tissues. The six types of IFs (types I–VI) are shown. To simplify the schematic, not all epithelial and nonepithelial tissues are displayed. Different keratin pairs are found primarily in unique epithelial cell types in a differentiation state–selective and/or cell type–specific distribution (e.g., K4/K13 in the esophagus, K20 in suprabasal but not in basal crypt enterocytes). The complexity of IF expression in tissues is exemplified in the intestine, in which epithelial cells express different compliments of simple epithelial keratins, the vasculature and other resident mesenchymal cells express vimentin, the smooth muscle layer expresses desmin, and neural elements of the enteric nervous system express neurofilaments. Numbers in parentheses indicate the type of IF. Bfsp1, beaded filament structural protein 1 (previously known as CP115 and filensin); Bfsp2 was previously known as CP49 and phakinin. NFH, high-molecular-weight neurofilament subunit; NFL, low-molecular-weight neurofilament subunit; NFM, middle-molecular-weight neurofilament subunit. This figure was adapted from *Trends in cell biology* (34).

steatocystoma multiplex and pachyonychia congenita type 2 (26). Hence, genetic modifiers are likely to play an important role in disease manifestation.

Most of the IF-pathies are rare or orphan diseases, which are defined by the Office of Rare Diseases Research of the National Institutes of Health as diseases with a prevalence of fewer than 200,000 affected individuals in the United States (Office of Rare Diseases Research, http://rarediseases.info.nih.gov/RareDiseaseList.aspx). Potential exceptions include the mutations that predispose to common diseases, as exemplified by the mutations

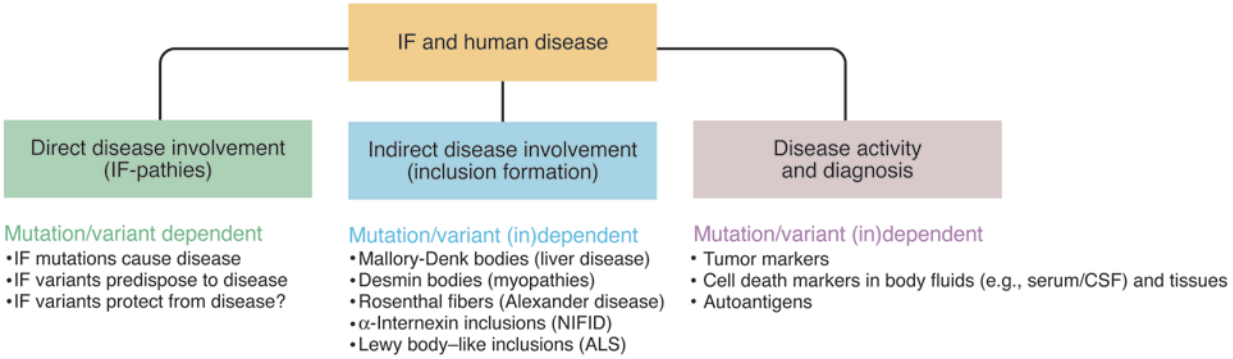

Figure 2
IFs and human disease. The involvement of IFs with human disease occurs at several levels. First, mutations in genes encoding IF proteins may either precipitate or predispose to a wide range of human diseases. It is also possible that natural selection has favored unique variants that may serve a protective role (16), although this hypothesis remains to be tested. Second, IF proteins, as a group, are essential for the formation of a variety of cell-specific inclusions that represent hallmarks of various diseases. Formation of these inclusions is generally independent of the presence of an IF mutation but does occur in the context of *GFAP* mutation in Alexander disease (18). Third, antibodies specific for IF proteins are routinely used in pathology laboratories across the world to help identify the origin of poorly differentiated tumors and are beginning to be used to assess tissue injury (directly in tissues, in blood, or in cerebrospinal fluid [CSF]) (16, 18). In addition, antibodies specific for IF proteins have been observed in the context of some autoimmune disease (16). ALS, amyotrophic lateral sclerosis; NIFID, neuronal IF inclusion disease.

in the genes encoding K8, K18, and K19 that predispose to progression of common chronic liver diseases such as infection with HCV (16). In addition, it remains to be determined whether specific IF-protein variants may predispose to other common complex diseases or idiosyncratic drug toxicities that one would not necessarily consider to be related to IF genes (16). Candidate IF proteins and potential mutations that may be analyzed to test this hypothesis include IF proteins that when mutated serve to predispose rather than cause disease per se (e.g., simple epithelial keratins) (16), IFs that have not yet been linked to a human

Table 2
Chronology of the discovery of IF-pathies, as related to specific IF proteins[A]

Year	IF protein	Disease	References
1991	K14	EBS	21, 22
1992	K5	EBS	36
	K1, K10	Epidermolytic hyperkeratosis	37, 38
1994	K2	Ichthyosis bullosa of Siemens	39
	K9	Epidermolytic palmoplantar keratoderma	40
	NFH	ALS (predisposition)	41
1995	K4, K13	White-sponge nevus	42, 43
	K6, K16, K17	Pachyonychia congenita	44, 45
1997	K3, K12	Meesmann corneal dystrophy	46
	K18	Liver disease (predisposition)	47
	K86 (hair keratin)[B]	Monilethrix	48
1998	Desmin	Severe generalized myopathy; familial cardiac and skeletal myopathy	49,50
1999	Lamin A/C	Emery-Dreifuss muscular dystrophy; dilated cardiomyopathy	51, 52
2000	NFL	CMT type 2	53
	BFSP2	Autosomal dominant cataract	54, 55
2001	K8	Liver disease (predisposition)	56
	GFAP	Alexander disease	57
2004	Peripherin[C]	ALS (predisposition)	58
2006	K85 (hair keratin)[B]	Ectodermal dysplasia, pure hair-nail type	59
	Lamin B1	Autosomal dominant leukodystrophy	60
	Lamin B2	Acquired partial lipodystrophy	61
2007	BFSP1	Autosomal recessive juvenile cataract	62
2009	K19	Primary biliary cirrhosis (predisposition)	63
	Vimentin	Cataract	29

[A]The first description of a human disease that is linked with each listed IF is shown. Several of the listed IF proteins (e.g., the lamins and several of the keratins) are associated with multiple human diseases that are not included in the table, as they were linked to the IF proteins in subsequent years. [B]K86 and K85 were originally termed Hb6 and Hb5, respectively. [C]The truncated peripherin protein in one reported patient may have been a cause of ALS. NFH, high-molecular-weight neurofilament subunit; NFL, low-molecular-weight neurofilament subunit.

Table 3
Challenges and opportunities related to IFs and IF-pathies

Challenges/opportunities	Comments	References
Development of targeted therapies	Animal studies provide important model systems, as exemplified by the laminopathies and blistering skin diseases models.	15, 19
How many more IF-pathies remain to be identified, and what are the genetic modifiers?	Some "orphan" IFs remain to be linked to human disease. IFs as disease modifiers are poorly understood, and little is known regarding ethnic background associations.	16
Phenomics of IF-pathies	A systematic analysis of the phenotype and genotypes of IF-pathies is essential, particularly for the laminopathies.	30
Development of cost-efficient diagnostic tests	This can be involved, since IF mutations for a given IF are numerous and tend to be scattered throughout the protein backbone.	64
Use of IFs as disease activity and diagnostic markers	The abundance and tissue specificity of IF proteins and the changes they undergo during apoptosis render them useful potential targets for disease diagnosis and prognosis assessment.	16
Pathogenesis and significance of IF inclusions	Therapeutic intervention at the level of inclusion formation may become an option.	16, 18, 65
The fundamentals: IF structure	A better understanding of the structural determinants will help elucidate the function of IFs and the potential consequences of specific IF mutations.	14, 66
The fundamentals: IF regulation	A better understanding of IF posttranslational modifications and associated proteins will help clarify additional IF functions. Understanding IF regulation may also relate to mutations in IF-associated proteins that can phenocopy IF mutations.	6, 67, 68
The fundamentals: IF functions	A better understanding is needed of how IF mechanical function is transmitted. The list of nonmechanical functions is continuing to grow.	4, 6, 15–20, 34, 69, 70

disease (Table 1), and mutations in IF protein–encoding genes that are known to cause well-defined diseases (e.g., those that cause the multisystem laminopathies or the epidermal keratin diseases), in particular those mutations that affect amino acids that are not usually involved in the high penetrance diseases or that involve more subtle amino acid alterations.

Numerous opportunities and challenges in the IF field

Several recent and long-standing challenges continue to create excellent areas of basic and translational research opportunities in the IF field (Table 3). The number and breadth of multi-system diseases associated with IFs is staggering, which brings to focus the need to develop targeted therapies for IF-pathies, as these are sorely lacking at present. Most, if not all, currently available therapies are palliative and preventative in nature and include standard measures such as limiting skin trauma in individuals with EBS (e.g., minimizing even rubbing of the skin in individuals with the severe Dowling-Meara type of EBS) and close clinical monitoring of individuals with cardiomyopathies (e.g., through implantation of a pacemaker or defibrillator). Gene therapy approaches remain a viable option, but the technology for this type of therapy, in general, remains under development and is even more challenging for many of the IF-pathies, as they tend to be dominantly inherited or acquired genetic disorders. However, the availability of many animal IF-pathy models has afforded exciting new potential therapies. For example, isothiocyanate sulforaphane, which is a natural product found at high levels in a precursor form in broccoli sprouts and other vegetables, induces K16 and K17 expression in epidermal keratinocytes and prolongs survival of K14-deficient mice (27). In addition, administration of the compound PD98059, an inhibitor of ERK signaling, to mice with a knockin of the lamin A His222Pro mutation (which causes Emery-Dreifuss muscular dystrophy) prevented the cardiomyopathy that is seen in untreated animals (28). These studies offer an exciting hope that pharmacologic targeting of mutation-triggered aberrant pathways can provide meaningful compensation for the detrimental effects of an IF mutation.

Other disease-related areas (Table 3) that remain to be explored are potential links between the IFs that so far have not been associated with any human disease or human clinical condition (Table 1) and the potential association of new diseases to IFs that already have been tied to one or more disorder. An example of the latter is vimentin, which has recently been associated with cataract formation (29). The broad distribution of vimentin in mesenchymal cells raises the intriguing possibility, which remains to be tested, that disorders involving other cell types (e.g., endothelial and hematopoietic cells) could be modified by vimentin variants. In addition, as appreciation of the complexity of phenotype-genotype correlations of IF-pathies (30) is accumulating, systematic approaches coupled with the characterization of other genetic modifiers are clearly warranted. Such efforts also mesh well with the development of cost-efficient genetic tests that can provide prognostic and diagnostic needs. However, clinical testing for IF mutations is complicated, since IF mutations for a given IF protein are numerous. For example, more than 200 amino acids are involved in lamin A/C mutations (5), and of the 432 amino acids of human GFAP, 91 mutations, involving 62 amino acids, have been described (18) (Waisman Center, http://www.waisman.wisc.edu/alexander).

The potential utility of IFs as "disease activity" and diagnostic markers (Figure 2) is likely to grow significantly as their usefulness in this area becomes increasingly appreciated (16, 18). Although IF inclusions could be categorized as diagnostic markers, given their current clinical utility as histopathological features of several IF-pathies, IF inclusions represent a unique category because of their shared properties (e.g., cytoplasmic deposits that are ubiquitinylated but resistant to proteosomal degradation) but more importantly because they can be manipulated pharmacologically (31).

In addition to the above challenges, there are fundamental and exciting opportunities remaining that pertain to IF structure, regulation, and function. Understanding IF-protein structure has been difficult, in part because it has not been possible so far to obtain a crystal structure (although "divide-and-concur" approaches of crystallizing subdomains of IFs have been fruitful [ref. 14]) and NMR approaches are difficult due to the relative limited solubility of IFs. Developing cell-free systems that mimic the in vivo situation is warranted, because IFs self-assemble in vitro, but in vivo assembly is likely to be highly regulated. In terms of IF regulation, advances in understanding phosphorylation have been made. For example, a common human K8 variant (Gly62Cys) that predisposes its carriers to liver disease progression does so by inhibiting K8 in vivo phosphorylation by the stress-activated p38 kinase at the adjacent K8 Ser74, as demonstrated using transgenic mice that express K8 Gly62Cys or K8 Ser74Ala (32). However, IFs contain numerous phosphorylation sites, and the function of their in vivo phosphorylation and their hierarchal regulation (including dephosphorylation) is poorly understood. In addition, relatively few IF-associated proteins have been identified, but the list of these proteins is ever growing (4, 33), and there are several examples of IF-pathies that are caused by mutations in genes encoding either IF proteins or their associated proteins (19, 20).

With regard to IF function, there are several established and emerging functions, many of which are highlighted in the articles in this Review Series. These functions include cell-specific roles, such as (a) the role of neurofilaments in axonal transport, as demonstrated by the Charcot-Marie-Tooth phenotype due to low-molecular-weight neurofilament subunit mutations (18); (b) generalized functions, particularly cytoprotection from mechanical (e.g., skin rubbing in patients with EBS) and nonmechanical forms of stress (e.g., oxidative or other apoptosis-triggering stresses) (15, 16, 23); (c) compartment-specific actions related to organelle functions, including those pertaining to mitochondria (that likely relates to the importance of IFs in protecting from apoptosis), nuclei (as clearly evidenced by the pleiotropic effects of lamin mutations and the interaction of lamins with chromatin and transcription factors), protein targeting, and protein synthesis (4, 19, 34); (d) cell signaling organization (6, 13); and (e) cell migration (35).

Summary

If MTs, MFs, and IFs are considered to be the three major branches of the cytoskeleton (the legislative, executive, and judicial branches of cell government), then IFs are involved in all three aspects of cell oversight, including legislating the phenotype of many diseases, executing multiple functions, and deciding the fate of cells. The broad and multisystem involvement of IF-pathies interfaces with many other non-IF diseases that either phenocopy the IF-pathies or share some of their manifestations. It is anticipated that this interface will attract new investigators to the field and fuel unanticipated advancements. Hence, the intended goal of the authors of the articles in this Review Series is to disseminate information about the broad spectrum of IF-related diseases and the exciting challenges and opportunities of the IF field to the widest audience possible. We welcome with open arms all those interested in extending their work to this exciting field.

Acknowledgments

I would like to acknowledge Werner Franke, Howard Green, Peter Steinert, and Klaus Weber, who have mentored some of the authors of the enclosed reviews and/or are considered, together with some of the authors of the current reviews, as founders of the IF field and its disease relevance. The Review Series was made possible because of the hard work by all the authors of the eight accompanying Reviews. The author thanks Pierre Coulombe and Howard Worman for their insightful comments pertaining to this overview and Kris Morrow for assistance with figure preparation. The author's work is supported by NIH grants DK47918 and DK52951 and a Department of Veterans Affairs Merit Review Award.

Address correspondence to: Bishr Omary, University of Michigan Medical School, Department of Molecular & Integrative Physiology, 7744 Medical Science II, 1301 E. Catherine Street, Ann Arbor, Michigan 48109-5622, USA. Fax: (734) 936-8813; E-mail: mbishr@umich.edu.

1. Hesse, M., Magin, T.M., and Weber, K. 2009. Genes for intermediate filament proteins and the draft sequence of the human genome: novel keratin genes and a surprisingly high number of pseudogenes related to keratin genes 8 and 18. *J. Cell Sci.* **114**:2569–2575.
2. Ku, N.-O., Zhou, X., Toivola, D.M., and Omary, M.B. 1999. The cytoskeleton of digestive epithelia in health and disease. *Am. J. Physiol.* **277**:G1108–G1137.
3. Fuchs, E., and Cleveland, D.W. 1998. A structural scaffolding of intermediate filaments in health and disease. *Science.* **279**:514–519.
4. Kim, S., and Coulombe, P.A. 2007. Intermediate filament scaffolds fulfill mechanical, organizational, and signaling functions in the cytoplasm. *Genes Dev.* **21**:1581–1597.
5. Szeverenyi, I., et al. 2008. The human intermediate filament database: comprehensive information on a gene family involved in many human diseases. *Hum. Mutat.* **29**:351–360.
6. Omary, M.B., Ku, N.-O., Tao, G.Z., Toivola, D.M., and Liao, J. 2006. "Heads and tails" of intermediate filament phosphorylation: multiple sites and functional insights. *Trends Biochem. Sci.* **31**:383–394.
7. Wagner, O.I., et al. 2007. Softness, strength and self-repair in intermediate filament networks. *Exp. Cell Res.* **313**:2228–2235.
8. Coulombe, P.A., and Omary, M.B. 2002. "Hard" and "soft" principles defining the structure, function and regulation of keratin intermediate filaments. *Curr. Opin. Cell Biol.* **14**:110–122.
9. Ku, N.-O., Strnad, P., Zhong, B., Tao, G.Z., and Omary, M.B. 2007. Keratins let liver live: mutations predispose to liver disease and crosslinking generates Mallory-Denk bodies. *Hepatology.* **46**:1639–1649.
10. Zhong, B., et al. 2004. Organ-specific stress induces mouse pancreatic keratin overexpression in association with NF-κB activation. *J. Cell Sci.* **117**:1709–1719.
11. Paladini, R.D., Takahashi, K., Bravo, N.S., and Coulombe, P.A. 1996. Onset of re-epithelialization after skin injury correlates with a reorganization of keratin filaments in wound edge keratinocytes: defining a potential role for keratin 16. *J. Cell Biol.* **132**:381–397.
12. Pekny, M., and Pekna, M. 2004. Astrocyte intermediate filaments in CNS pathologies and regeneration. *J. Pathol.* **204**:428–437.
13. Eriksson, J.E., et al. 2009. Introducing intermediate filaments: from discovery to disease. *J. Clin. Invest.* **119**:1763–1771.
14. Herrmann, H., Strelkov, S.V., Burkhard, P., and Aebi, U. 2009. Intermediate filaments: primary determinants of cell architecture and plasticity. *J. Clin. Invest.* **119**:1772–1783.
15. Coulombe, P.A., Kerns, M.L., and Fuchs, E. 2009. Epidermolysis bullosa simplex: a paradigm for disorders of tissue fragility. *J. Clin. Invest.* **119**:1784–1793.
16. Omary, M.B., Ku, N.-O., Strnad, P., and Hanada, S. 2009. Toward unraveling the complexity of simple epithelial keratins in human disease. *J. Clin. Invest.* **119**:1794–1805.
17. Goldfarb, L.G., and Dalakas, M.C. 2009. Tragedy in a heartbeat: malfunctioning desmin causes skeletal and cardiac muscle disease. *J. Clin. Invest.* **119**:1806–1813.
18. Liem, R.K.H., and Messing, A. 2009. Dysfunctions of neuronal and glial intermediate filaments in disease. *J. Clin. Invest.* **119**:1814–1824.
19. Worman, H.J., Fong, L.G., Muchir, A., and Young, S.G. 2009. Laminopathies and the long strange trip from basic cell biology to therapy. *J. Clin. Invest.* **119**:1825–1836.
20. Song, S., et al. 2009. Functions of the intermediate filament cytoskeleton in the eye lens. *J. Clin. Invest.* **119**:1837–1848.
21. Coulombe, P.A., et al. 1991. Point mutations in human keratin 14 genes of epidermolysis bullosa simplex patients: genetic and functional analysis.

Cell. **66**:1301–1311.
22. Bonifas, J.M., Rothman, A.L., and Epstein, E.H., Jr. 2009. Epidermolysis bullosa simples: evidence in two families for keratin gene abnormalities. *Science.* **254**:1202–1205.
23. Omary, M.B., Coulombe, P.A., and McLean, W.H. 2004. Intermediate filament proteins and their associated diseases. *N. Engl. J. Med.* **351**:2087–2100.
24. Jacob, K.N., and Garg, A. 2006. Laminopathies: multisystem dystrophy syndromes. *Mol. Genet. Metab.* **87**:289–302.
25. Brodsky, G.L., et al. 2000. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation.* **101**:473–476.
26. Irvine, A.D., and McLean, W.H.I. 1999. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype-genotype correlation. *Br. J. Dermatol.* **140**:815–828.
27. Kerns, M.D., DePianto, D., Dinkova-Kostova, A.T., Talalay, P., and Coulombe, P.A. 2007. Reprogramming of keratin biosynthesis by sulforaphane restores skin integrity in epidermolysis bullosa simplex. *Proc. Natl. Acad. Sci. U. S. A.* **104**:14460–14465.
28. Muchir, A., Shan, J., Bonne, G., Lehnart, S.E., and Worman, H.J. 2009. Inhibition of extracellular signal-regulated kinase signaling to prevent cardiomyopathy caused by mutation in the gene encoding A-type lamins. *Hum. Mol. Genet.* **18**:241–247.
29. Müller, M., et al. 2009. Dominant cataract formation in association with a vimentin assembly disrupting mutation. *Hum. Mol. Genet.* **18**:1052–1057.
30. Hegele, R.A., and Oshima, J. 2007. Phenomics and lamins: from disease to therapy. *Exp. Cell Res.* **313**:2134–2143.
31. Harada, M., et al. 2008. Autophagy activation by rapamycin eliminates mouse Mallory-Denk bodies and blocks their proteasome inhibitor-mediated formation. *Hepatology.* **47**:2026–2035.
32. Ku, N.-O., and Omary, M.B. 2006. A disease and phosphorylation related non-mechanical function for keratin 8. *J. Cell Biol.* **174**:115–125.
33. Green, K.J., Böhringer, M., Gocken, T., and Jones, J.C. 2005. Intermediate filament associated proteins. *Adv. Protein Chem.* **70**:143–202.
34. Toivola, D.M., Tao, G.Z., Habtezion, A., Liao, J., and Omary, M.B. 2005. Beyond cellular integrity: organelle-related and protein-targeting functions of intermediate filaments. *Trends Cell Biol.* **15**:608–617.
35. Nieminen, M., et al. 2006. Vimentin function in lymphocyte adhesion and transcellular migration. *Nat. Cell Biol.* **8**:105–107.
36. Lane, E.B., et al. 1992. A mutation in the conserved helix termination peptide of keratin 5 in hereditary skin blistering. *Nature.* **356**:244–246.
37. Cheng, J., et al. 1992. The genetic basis of epidermolytic hyperkeratosis: a disorder of differentiation-specific epidermal keratin genes. *Cell.* **70**:811–819.
38. Chipev, C.C., et al. 1992. A leucine-proline mutation in the H1 subdomain of keratin 1 causes epidermolytic hyperkeratosis. *Cell.* **70**:821–828.
39. Rothnagel, J.A., et al. 1994. Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens. *Nat. Genet.* **7**:485–490.
40. Reis, A., et al. 1994. Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). *Nat. Genet.* **6**:174–179.
41. Figlewicz, D.A., et al. 1994. Variants of the heavy neurofilament subunit are associated with the development of amyotrophic lateral sclerosis. *Hum. Mol. Genet.* **3**:1757–1761.
42. Rugg, E.L., et al. 1995. A mutation in the mucosal keratin K4 is associated with oral white sponge nevus. *Nat. Genet.* **11**:450–452.
43. Richard, G., De Laurenzi, V., Didona, B., Bale, S.J., and Compton, J.G. 1995. Keratin 13 point mutation underlies the hereditary mucosal epithelia disorder white sponge nevus. *Nat. Genet.* **11**:453–455.
44. Bowden, P.E., et al. 1995. Mutation of a type II keratin gene (K6a) in pachyonychia congenita. *Nat. Genet.* **10**:363–365.
45. McLean, W.H.I., et al. 1995. Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat. Genet.* **9**:273–278.
46. Irvine, A.D., et al. 1997. Mutations in cornea-specific keratin K3 or K12 genes cause Meesmann's corneal dystrophy. *Nat. Genet.* **16**:184–187.
47. Ku, N.-O., Wright, T.L., Terrault, N.A., Gish, R., and Omary, M.B. 1997. Mutation of human keratin 18 in association with cryptogenic cirrhosis. *J. Clin. Invest.* **99**:19–23.
48. Winter, H., et al. 1997. Mutations in the hair cortex keratin hHb6 cause the inherited hair disease monilethrix. *Nat. Genet.* **16**:372–374.
49. Goldfarb, L.G., et al. 1998. Missense mutations in desmin associated with familial cardiac and skeletal myopathy. *Nat. Genet.* **19**:402–403.
50. Munoz-Marmol, A.M., et al. 1998. A dysfunctional desmin mutation in a patient with severe generalized myopathy. *Proc. Natl. Acad. Sci. U. S. A.* **95**:11312–11317.
51. Bonne, G., et al. 1999. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat. Genet.* **21**:285–288.
52. Fatkin, D., et al. 1999. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N. Engl. J. Med.* **341**:1715–1724.
53. Mersiyanova, I.V., et al. 2000. A new variant of Charcot-Marie-Tooth disease type 2 is probably the result of a mutation in the neurofilament-light gene. *Am. J. Hum. Genet.* **67**:37–46.
54. Jakobs, P.M., et al. 2000. Autosomal-dominant congenital cataract associated with a deletion mutation in the human beaded filament protein gene BFSP2. *Am. J. Hum. Genet.* **66**:1432–1436.
55. Conley, Y.P., et al. 2000. A juvenile-onset, progressive cataract locus on chromosome 3q21-q22 is associated with a missense mutation in the beaded filament structural protein-2. *Am. J. Hum. Genet.* **66**:1426–1431.
56. Ku, N.-O., Gish, R., Wright, T.L., and Omary, M.B. 2001. Keratin 8 mutations in patients with cryptogenic liver disease. *N. Engl. J. Med.* **344**:1580–1587.
57. Brenner, M., et al. 2001. Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease. *Nat. Genet.* **27**:117–120.
58. Gros-Louis, F., et al. 2004. A frameshift deletion in peripherin gene associated with amyotrophic lateral sclerosis. *J. Biol. Chem.* **279**:45951–45956.
59. Naeem, M., Wajid, M., Lee, K., Leal, S.M., and Ahmad, W. 2006. A mutation in the hair matrix and cuticle keratin KRTHB5 gene causes ectodermal dysplasia of hair and nail type [letter]. *J. Med. Genet.* **43**:274–279.
60. Padiath, Q.S., et al. 2007. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat. Genet.* **38**:1114–1123, 2006. Erratum: *Nat. Genet.* **39**:276.
61. Hegele, R.A., et al. 2006. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. *Am. J. Hum. Genet.* **79**:383–389.
62. Ramachandran, R.D., Perumalsamy, V., and Hejtmancik, J.F. 2007. Autosomal recessive juvenile onset cataract associated with mutation in BFSP1. *Hum. Genet.* **121**:475–482.
63. Zhong, B., et al. 2009. Keratin variants are overrepresented in primary biliary cirrhosis and associate with disease severity. *Hepatology.* doi:10.1002/hep.23041.
64. Fine, J.D., et al. 2008. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J. Am. Acad. Dermatol.* **58**:931–950.
65. Zatloukal, K., et al. 2007. From Mallory to Mallory-Denk bodies: What, how and why? *Exp. Cell Res.* **313**:2033–2049.
66. Herrmann, H., Bär, H., Kreplak, L., Strelkov, S.V., and Aebi, U. 2007. Intermediate filaments: from cell architecture to nanomechanics. *Nat. Rev. Mol. Cell Biol.* **8**:562–573.
67. Sihag, R.K., Inagaki, M., Yamaguchi, T., Shea, T.B., and Pant, H.C. 2007. Role of phosphorylation on the structural dynamics and function of types III and IV intermediate filaments. *Exp. Cell Res.* **313**:2098–2109.
68. Hyder, C.L., Pallari, H.M., Kochin, V., and Eriksson, J.E. 2008. Providing cellular signposts--post-translational modifications of intermediate filaments. *FEBS Lett.* **582**:2140–2148.
69. Perrot, R., Berges, R., Bocquet, A., and Eyer, J. 2008. Review of the multiple aspects of neurofilament functions, and their possible contribution to neurodegeneration. *Mol. Neurobiol.* **38**:27–65.
70. Dechat, T., et al. 2008. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev.* **22**:832–853.