Networking galore: intermediate filaments and cell migration
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Intermediate filaments (IFs) are assembled from a diverse group of evolutionarily conserved proteins and are specified in a tissue-dependent, cell type-dependent, and context-dependent fashion in the body. IFs are involved in multiple cellular processes that are crucial for the maintenance of cell and tissue integrity and the response and adaptation to various stresses, as conveyed by the broad array of crippling clinical disorders caused by inherited mutations in IF coding sequences. Accordingly, the expression, assembly, and organization of IFs are tightly regulated. Migration is a fitting example of a cell-based phenomenon in which IFs participate as both effectors and regulators. With a particular focus on vimentin and keratin, we here review how the contributions of IFs to the cell’s mechanical properties, cytoarchitecture and adhesion, and to regulatory pathways collectively exert a significant impact on cell migration.

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Ten nanometer wide intermediate filaments (IFs), first described as such in muscle by Holtzer and colleagues [1], are assembled from the most diverse and heterogeneous group of proteins among intracellular cytoskeletal fibers. There are ~70 genes that code for IF-forming proteins in the human genome, with 54 of them coding for keratin proteins that occur primarily in epithelia [2,3]. IFs can be partitioned into six major subtypes based on gene substructure or sequence homology within their signature central rod domain (Figure 1a). All IF proteins share the property of self-assembly into ~10-nm wide filaments (Figure 1b), which they do as obligatory or facultative heteropolymers, along with a defining tripartite domain structure consisting of a central α-helical rod domain featuring long range, coiled-coil forming heptad repeats that is flanked by variable end domains located at their N-termini and C-termini (Figure 1c). Collectively, IF proteins exhibit pronounced heterogeneity — for instance, their molecular mass ranges from 40 kDa (type I keratin 19) to 240 kDa (type IV nestin) — though individually their primary structure is evolutionarily well-conserved. IF systems are present across multi-cellular eukaryotes [4]. The evidence in hand suggests that they appeared as nuclear proteins related to the current-day lamins in lower eukaryotes such as Dictyostelium [5]. The presence of the IF-like crescentin in Caulobacter crescenti [6] raises the intriguing prospect that IFs might have been born earlier, in prokaryotes.

Another remarkable signature feature of the IF superfamily of genes and proteins is the tissue type-dependent, differentiation program-dependent, and context-dependent nature of their regulation (Figure 1a). Consistent with this, the list of functions fulfilled by IFs in their natural biological setting is growing rapidly — by now all major facets of cell biology, including cell motility, have been linked to IFs and their associated elements (see [3,7,8]). Given their status as abundant fibrous elements within cells, IFs can impact cellular migration from mechanical and cytoarchitectural perspectives. IFs also impact migration from a regulatory perspective, owing to their ability to interact with and regulate various cellular effectors including signaling molecules [3].

As it should become clear from this text, there are IF proteins, for example, vimentin (Figure 2b), that consistently stimulate cell migration and invasion independent of the setting while others, for example, various keratins, exert a more variable, nuanced, and at first sight complicated, impact on these processes. Beyond the type of IF protein, additional determinants such as the level at which it is expressed, its associated partners, intracellular organization and covalent modifications (e.g. phosphorylation) are acting in concert to define the overall impact on intricate processes such as cell migration. Further, cellular and biological context is crucially important. The expression ‘networking galore’ (cf. title for this review) is meant to convey the recurring notion that the nature and impact of various IFs during migration in normal as well as disease settings reflects their pervasive integration, in a context-dependent manner, within the broader fabric of the cell.

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Introduction to intermediate filaments (IFs). (a) Classification of IF genes and proteins by type, according to gene substructure and sequence homology, and cell type-specificity of their distribution in the body (note: the latter list is partial). (b) Visualization of assembled 10-nm wide IFs reconstituted from purified recombinant proteins (the type II K5 and type I K14; human) by negative staining and transmission electron microscopy. Bar equals 100 nm. (c) Schematic representation of the common tripartite domain structure shared by all IF proteins. A central rod domain, comprised of heptad repeat-containing α-helical coils 1A, 1B, 2A, and 2B and separated by non-heptad repeat-containing linkers L1, L12, and L2, is flanked by ‘head’ and ‘tail’ domains of variable length and primary structure at the N-termini and C-termini, respectively. The boundaries of the rod domain (see blue bars) are highly conserved in primary structure among IF proteins.

Basic attributes of IFs relevant to their properties and function in vivo

As is the case for F-actin and microtubules, IFs depend on an array of partner proteins for their assembly, organization, function, and regulation. In particular, plakin family proteins are ‘cytoskeletal organizers’ that anchor IFs, microtubules and actin at several strategic locations within cells [9]. Beyond their signature plakin domain, plakin family members tend to be large and exhibit a modular substructure that enables them to act as versatile organizers of the cytoskeleton [10]. Plakins proteins mediate IF attachment to the cytoplasmic ‘plaque’ domain in cell–cell desmosome adhesions and cell–matrix hemidesmosome adhesions, to other elements of the cytoskeleton (F-actin, microtubules), and to the surface of the nucleus [9–11].

IF proteins are regulated by several types of post-translational modifications including phosphorylation, O-glycosylation, ubiquitination, sumoylation, and acetylation [12–14]. Such modifications are site-specific within the IF protein backbone, are typically reversible (and often dynamic), and regulate virtually all aspects of their assembly, organization, properties, and function [3,15,16]. In combination, associated proteins and post-translational modifications help define the polymerization status and intracellular organization of IFs in their natural setting. Actively migrating, polarized cells tend to have their IF system reorganized around the nucleus or at their rear, trailing end, in natural settings [17,18,19**] and under conditions of mutant IF protein expression [20].

Interplay between intermediate filaments, adhesion, and other cytoskeletal elements

Desmosomes are comprised of transmembrane cadherins, armadillo proteins such as plakoglobin and plakophilins, and plakin proteins such as desmoplakin that link desmosomal plaques to IFs intracellularly [11] (Figure 2a). Desmosomes maintain tissue integrity under mechanical stress [11] beginning at an early stage during mouse embryogenesis [21]. Potent pro-migratory cues such as epidermal growth factor (EGF) regulate the assembly and functional state of desmosomes (and hemidesmosomes) and IF network architecture [22*,23*,24*,25*]. Stimulation of cell migration is generally coupled to weaker desmosome-dependent cell–cell adhesion [26]. Indeed, enhanced desmosome turnover and their reduced colocalization with keratin have been observed in migrating oral squamous cell carcinoma cells [27*].