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The expanding significance of keratin intermediate filaments in normal and diseased epithelia

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Intermediate filaments are assembled from a diverse group of evolutionary conserved proteins and are specified in a tissue-dependent, cell type-dependent, and context-dependent fashion in the body. Genetic mutations in intermediate filament proteins account for a large number of diseases, ranging from skin fragility conditions to cardiomyopathies and premature aging. Keratins, the epithelial-specific intermediate filaments, are now recognized as multi-faceted effectors in their native context. In this review, we emphasize the recent progress made in defining the role of keratins towards the regulation of cytoarchitecture, cell growth and proliferation, apoptosis, and cell motility during embryonic development, in normal adult tissues, and in select diseases such as cancer.

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Keratins are the epithelial-specific members of the superfamily of intermediate filament (IF) genes and proteins. As many as 28 type I and 26 type II keratin genes are tightly regulated in a pairwise fashion, reflecting the heteromeric nature of the 10 nm filaments they form, as well as in a tissue-specific and differentiation-dependent manner in body epithelia [1–3] (Box 1). Rapid pace progress in recent years has set forth the notion that keratin IFs fulfill two fundamental roles in epithelial cells: (1) structural support, without which incident physical trauma exposes an inherent fragility and leads to loss of integrity, and (2) regulation of metabolic processes and of pathways governing their growth, proliferation, migration and apoptosis. These two roles involve regulated interactions with a diverse group of cellular proteins [4,5].

Substantive progress has been achieved in spatially mapping, in living epithelial cells, the initiation of keratin assembly, and the growth, maturation and turnover of the keratin IF network. These advances (Figure 1) have been covered in recent reviews [6•,7•]. Likewise, the mechanisms responsible for attachment of keratin filaments at sites of cell–cell and cell–matrix adhesion, and at the nuclear surface, are better understood and have been recently reviewed (Figure 1; see [8•–10•]). The role of keratin mutation as causative agents in inherited epithelial disorders continues to receive much attention, and have been commented upon as well [11•–13•,14]. For this review, we chose to focus on recent progress made in characterizing the role of keratin proteins in regulating cytoarchitecture, protein synthesis and growth, apoptosis, and epithelial cell motility in a myriad of contexts including embryonic development, normal adult tissues, and in select diseases such as cancer.

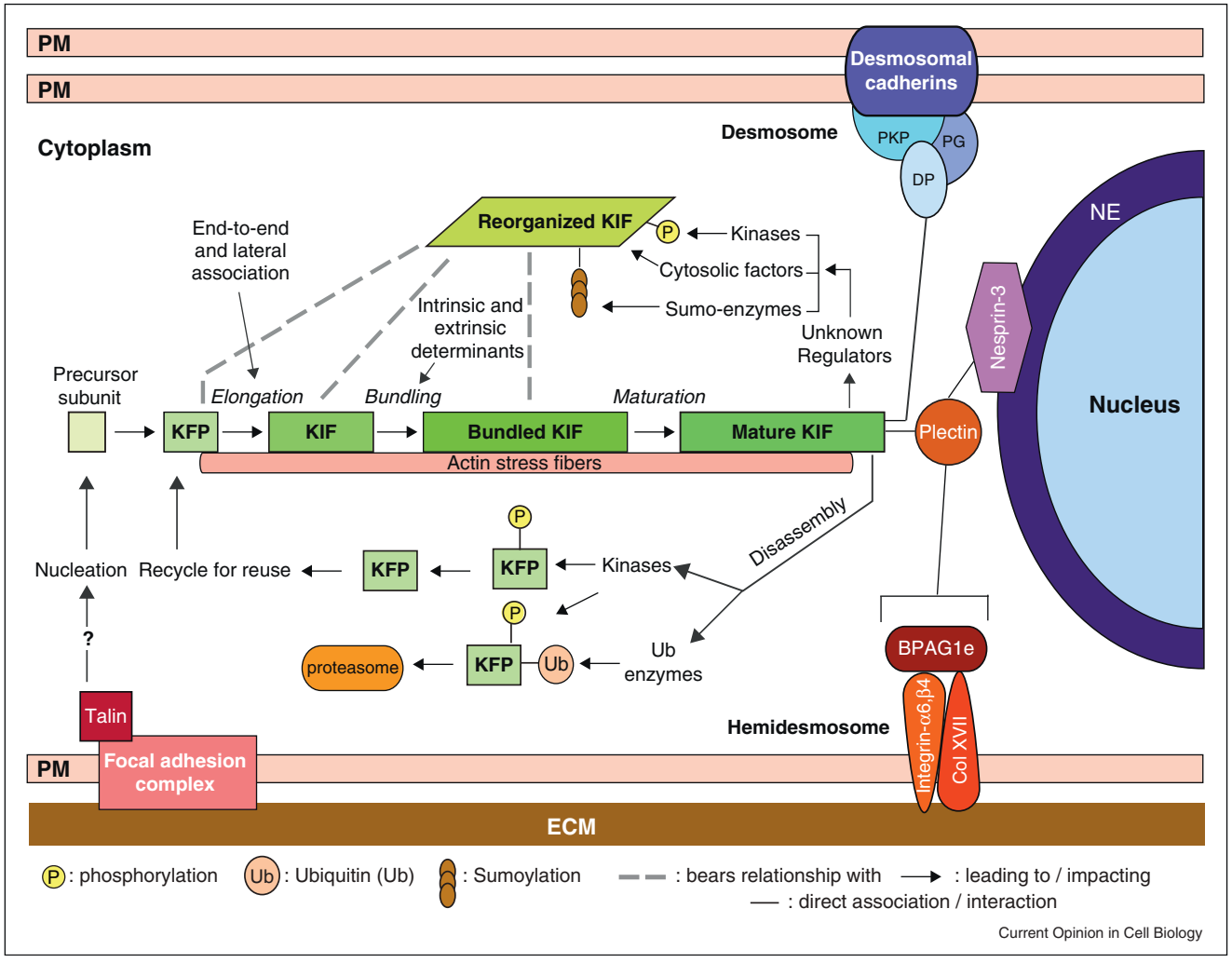
Building upon the already known: structural support, response to stress, and cytoarchitecture

Body surfaces and several internal organs are lined by polarized epithelial sheets. Among their multiple roles, these tissues protect us from environmental stresses that encompass many forms, including mechanical, cytotoxic, oxidative, and metabolic insults. Interference with these protective roles underlies many diseases [11•,15,16]. Accordingly, significant efforts continue to be devoted to determining when, where and how the protective roles of keratin are manifested.

Structural support

The structural support function of keratins is brought to the fore in skin fragility disorders involving mutations in epidermal keratins [11•,15,16]. Epidermolysis bullosa simplex (EBS) and epidermolytic hyperkeratosis (EHK) are examples of genetic conditions caused by mutations in K5/K14 and K1/K10, the keratin pairs expressed in the basal and suprabasal layers of epidermis, respectively, and are characterized by cytolysis of keratinocytes and loss of structural integrity in the relevant epidermal layers [11•,13•,14]. Several key aspects of the human EBS phenotype are manifested in transgenic mice expressing dominantly-acting deletion mutants in K14 [17–19] and in mice null for *K14* [20] or *K5* [21]. Likewise, transgenic mice expressing a truncated, dominant negative K10 mutant protein [22] or the K10 R154C mutant [23] exhibit lesions that resemble EHK. By contrast, inactivating *K10* triggers hyperproliferation as is seen in

Figure 1



Assembly, organization, and regulation of keratin intermediate filaments (KIFs). Live imaging studies in epithelial cells in culture show that keratin filament assembly is initiated at the periphery of the cell, near focal adhesions, and that newly formed filaments and their maturation into an organized network takes place in the context of a continuous centripetal flow with disassembly and turnover steps taking place near the nuclear envelope. The resulting 'keratin cycle' is highly dependent on interactions with F-actin, with additional proteins, and on several types of post-translational modifications including phosphorylation, ubiquitination, sumoylation and (though not shown here) O-GlcNAcylation. Most probably, the biological context dictates the rate of flow through this cycle. The figure also conveys that KIFs are attached at the surface of the nucleus (via a plectin/Nesprin-3 complex), at desmosome cell–cell adhesion sites, (via desmoplakin (DP), among other proteins), and at hemidesmosome cell–matrix adhesions (via plectin and BPAG1e). Not shown here are the interactions with F-actin and microtubules. The structural support role of KIFs depends upon their organization as a crosslinked network that is fully integrated with other structural elements within and between epithelial cells. NE: nuclear envelope; PM: plasma membrane; ECM: extracellular matrix; DP: desmoplakin; PKP: plakophilin; KFP: keratin filament precursor; KIF: keratin intermediate filament.

EHK but no obvious cell fragility in the epidermis [24,25]. This difference is probably related, at least partly, to the upregulation of K5 and K14 proteins, and their co-polymerization with K1, in differentiating suprabasal keratinocytes of *K10* null mouse epidermis [24]. A recent study supports that notion, as it reports that mice doubly null for *K10* and *K1* exhibit a lethal neonatal phenotype along with extensive skin lesions and cytolysis of suprabasal epidermal keratinocytes [26•]. The *K1*/*K10* double-null mouse phenotype also hints at the involvement of keratins in regulating the integrity of the nucleus as well as desmosome-based adhesion, as further discussed below.

Keratin mutation-based fragility phenotypes closely correlate with alteration in the micro-mechanical properties of the cytoskeleton [11•,12•,27,28]. A role for keratin filaments in providing structural support [28–30,31••,32] is promoted by their unique intrinsic properties – for instance, their ability to self-organize into crosslinked