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Published in:
Current Opinion in Cell Biology

DOI:
10.1016/j.ceb.2023.102282

Published: 01/02/2024

Document Version
Final published version

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Current Opinion in Cell Biology

The keratin-desmosome scaffold of internal epithelia in health and disease – The plot is thickening

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Abstract

Keratin (K) intermediate filaments are attached to desmosomes and constitute the orchestrators of epithelial cell and tissue architecture. While their relevance in the epidermis is well recognized, our review focuses on their emerging importance in internal epithelia. The significance of keratin-desmosome scaffolds (KDSs) in the intestine is highlighted by transgenic mouse models and individuals with inflammatory bowel disease who display profound KDS alterations. In lung, high K8 expression defines a transitional cell subset during regeneration, and K8 variants are associated with idiopathic pulmonary fibrosis. Inherited variants in desmosomal proteins are overrepresented in idiopathic lung fibrosis, and familiar eosinophilic esophagitis. K18 serum fragments are established hepatocellular injury markers that correlate with the extent of histological inflammation. K17 expression is modified in multiple tumors, and K17 levels might be of prognostic relevance. These data should spur further studies on biological roles of these versatile tissue protectors and efforts on their therapeutic targeting.

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Current Opinion in Cell Biology 2024, **86**:102282

This review comes from a themed issue on **Cell Architecture (2023)**

Edited by **John Eriksson** and **Patrick Lusk**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.ceb.2023.102282

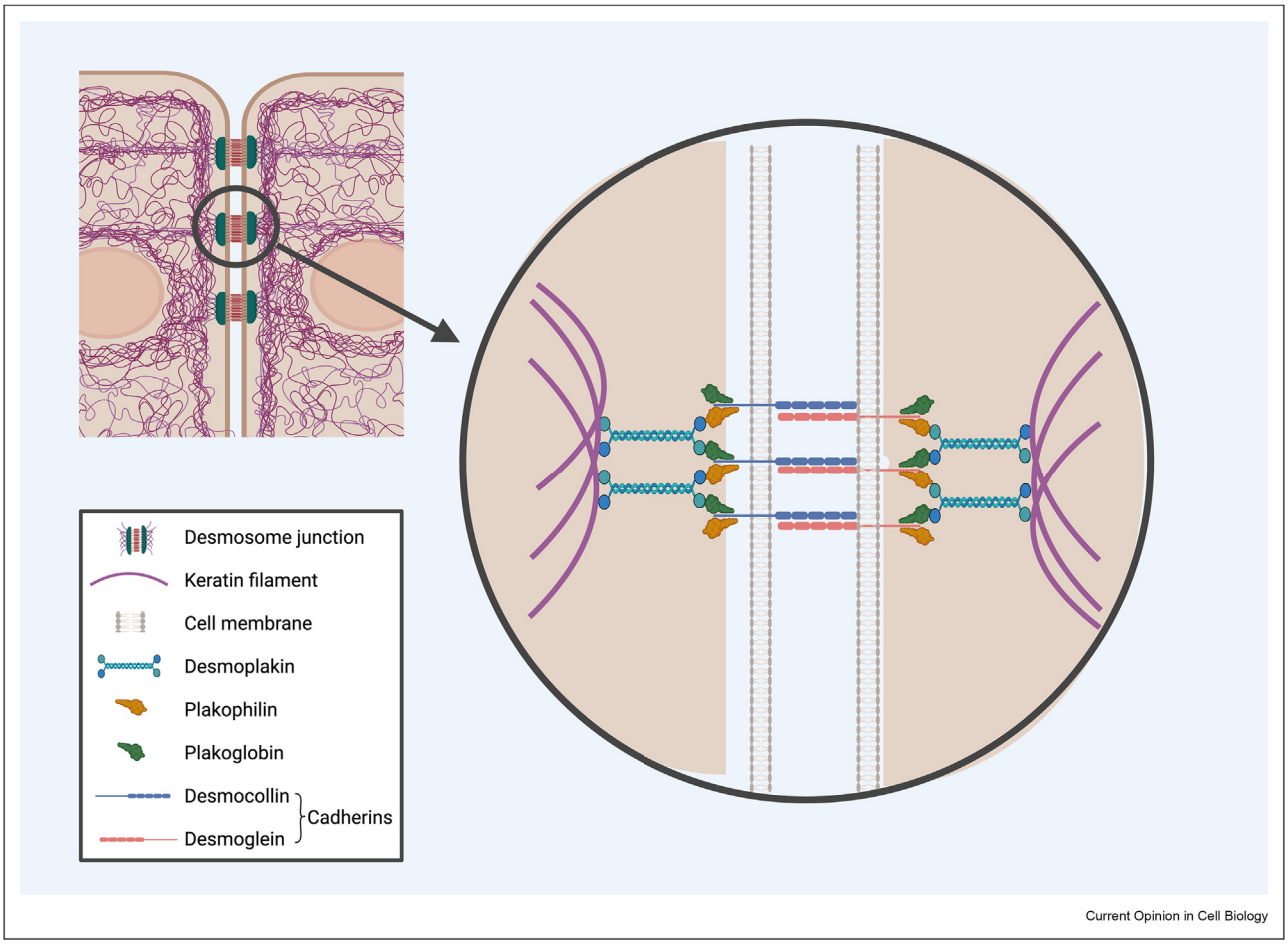
Introduction

The aim of this article is to discuss the emerging role of the keratin-desmosome scaffold (KDS) in internal epithelia. Keratins are cytoplasmic intermediate filaments produced primarily in epithelial tissues and skin appendages [1]. They are expressed in a tissue-dependent manner and subdivided into type I (K9–K20, K23–K28, K31–K40) and type II keratins (K1–K8, K71–K86). A member of each subfamily is needed to form obligate heteropolymers, which are the basic building blocks of keratin filaments. To fulfill their cytoprotective function, keratins are connected to desmosomes, thereby forming a transcellular scaffold [2]. Within desmosomes, the intercellular connection is mediated by cadherins of the desmoglein (DSG) and desmocollin (DSC) types. On the cytoplasmic side, they are connected to linker armadillo proteins plakophilin and plakoglobin, which, together with desmoplakin (DSP), facilitate attachment to keratin intermediate filaments [2,3] (Figure 1). At the basal side of the cell, linker proteins, such as plectin, mediate their connection to integrins [3].

The KDS is a versatile stress absorber that evolved to accommodate the contrasting requirements of different tissues [4]. Consequently, mechanically challenged structures, such as the epidermis or hair, produce polypeptides with unique amino acid compositions (i.e., more cysteine that forms disulfide bridges, etc.) [5], and their mutations lead to disorders that are exacerbated upon mechanical stress, such as the blistering skin disorder epidermolysis bullosa simplex [6]. While epidermolysis bullosa simplex became a hallmark of disorders with skin fragility [6], the human relevance of the less mechanically challenged KDS of simple epithelia was less obvious. KDS consists of K8/K18 as the major simple epithelial keratin (SEK) pair with various amounts of K7, K19, K20 and K23 [4]. Desmosomes in simple epithelia are made of the desmosomal cadherins DSG2 and DSC2 and the armadillo proteins plakophilin 2/3/4 together with the ubiquitous DSP and plakoglobin [2].

Approximately 30 years ago, the generation of K8 knockout mice and the fact that they displayed embryonic lethality, spontaneous colitis and hepatic alterations demonstrated for the first time the biological relevance of the KDS in the simple epithelia [4]. Later, K8/K18 mutations were found in patients with various liver disorders [4], while genome-wide association studies

Figure 1



The components of the keratin-desmosome scaffold (KDS) in epithelial cells. The schematic presents the overall KDS architecture, the assembly of the desmosomal components between two epithelial cells, and the connection between the desmosome and the cytoplasmic keratin filaments. Created with BioRender.com.

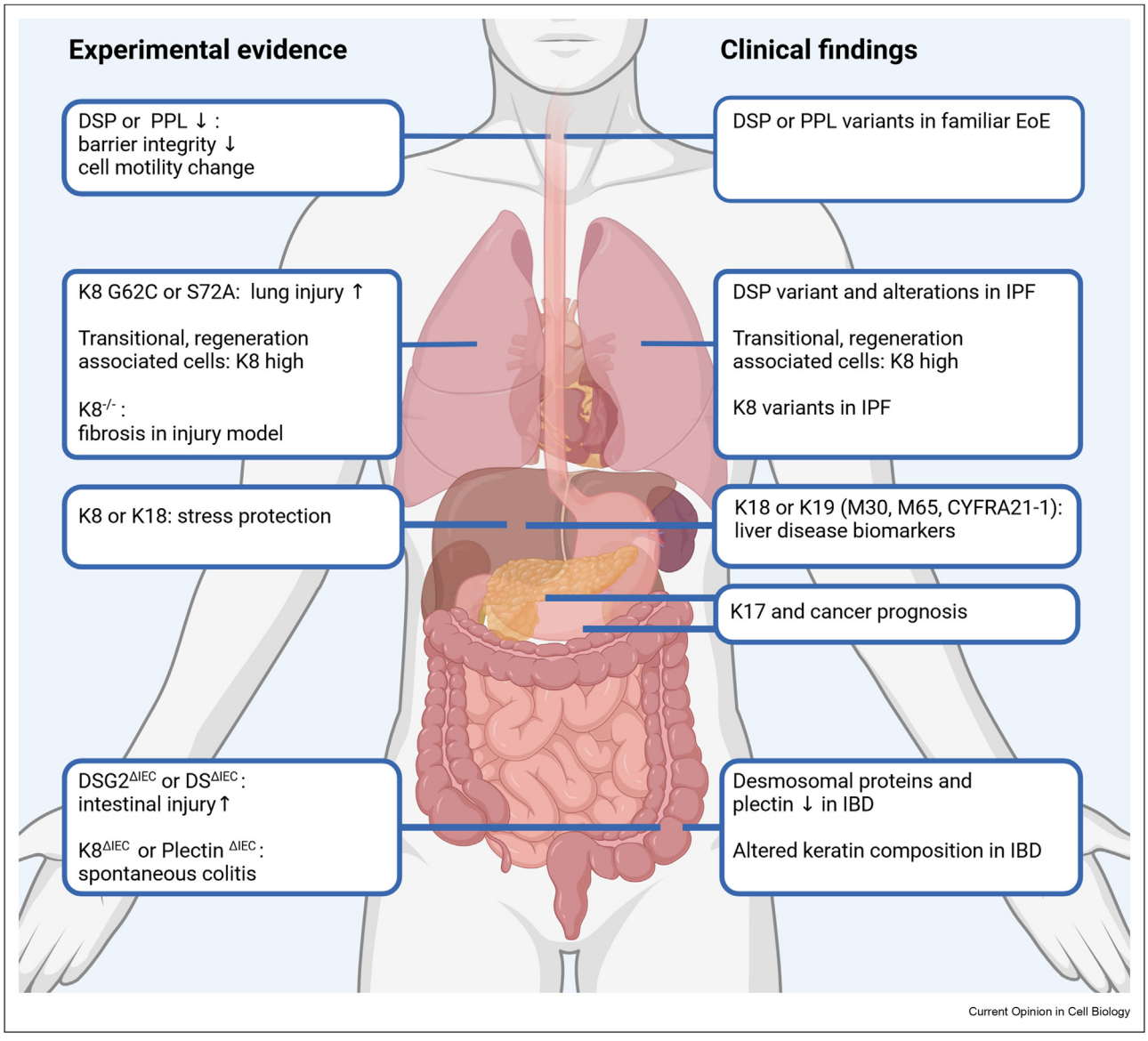
revealed a DSP variant in pulmonary fibrosis [7]. Moreover, studies from *C. elegans* demonstrated the evolutionary relevance of this scaffold [8,9]. Given their tissue-specific expression as well as their release into the bloodstream during stress situations, SEKs are well-established biomarkers that evolved from tumor markers to general indicators of tissue injury [10]. Desmosomes were decreased under conditions of intestinal inflammation in humans, and several tissue-specific animal models confirmed that the loss of desmosomal proteins leads to increased susceptibility of the gut barrier when challenged with proinflammatory stimuli (reviewed in Ref. [11]). In the current article, we will review the biological relevance of the KDS in internal epithelia that is now supported by multiple transgenic mouse lines as well as their importance in human medicine (see Figure 2) both as biomarkers and disease-causing or disease-modifying agents.

KDS as biomarker and protector in the liver

The biological relevance of K8/K18 in the liver is evidenced by multiple transgenic mouse lines and inherited K8/K18 variants that are associated with adverse outcomes of various hepatic disorders [4]. Notably, these K8/K18 variants were never convincingly tied to disease development in non-alcoholic/alcoholic liver disease, although their genetic modifiers are becoming increasingly well characterized [12,13]. This is somewhat surprising since both disorders display a redistribution of hepatocellular K8/K18 to protein inclusions termed Mallory-Denk bodies [4].

The abundance of SEKs together with their tissue-specific expression led to the recognition that they may serve as useful biomarkers. In particular, K8/K18/K19 fragments are components of tissue polypeptide antigen (TPA), tissue polypeptide-specific antigen

Figure 2



Keratin and desmosome changes associated with human diseases of internal epithelia or observed in the corresponding experimental disease models. The right side summarizes the inherited keratin and desmosomal alterations seen in human disorders as well as disease-induced/associated findings (Clinical findings), while the left panels depict experimental evidence based on both murine models and in vitro-based results with a focus on recent observations. DSP = desmoplakin, PPL = periplakin, EoE = eosinophilic esophagitis, K = keratin, IPF = idiopathic pulmonary fibrosis, DSG = desmoglein, IEC = intestinal epithelial cell, IBD = inflammatory bowel disease, Δ = deletion; -/- = knockout. Created with BioRender.com.

(TPS) and keratin fragment 21-1 (CYFRA 21-1), i.e., established tumor markers [10]. Later, M30 and M65 ELISAs were developed and were demonstrated to reflect a broad range of simple epithelial injuries. The attractiveness of these biomarkers is supported by the fact that M30 recognizes an apoptotic K18 fragment, while M65 constitutes an etiology-unspecific cell death marker [10]. The usefulness of M30 and M65 was extensively studied in subjects with non-alcoholic steatohepatitis (NASH), where they seem to be more sensitive than the widely used transaminases. In line with that, M30/M65 were included as exploratory outcome markers in recent high-profile NASH clinical trials [14,15]. In subjects with alcoholic hepatitis, a life-threatening, acute form of alcoholic liver disease, M30 detects a subset of individuals with severe histological

inflammation. Therefore, increased M30 levels might be useful to identify a subgroup of patients who may benefit from anti-inflammatory agents [16,17].

Recent data also demonstrated the potential usefulness of CYFRA21-1 in individuals with advanced liver disease. While K19, which is detected by CYFRA21-1, is not expressed in mature hepatocytes, it is produced by progenitor cells that become more numerous in advanced liver disorders. In line with that, serum CYFRA 21-1 levels are increased in subjects with advanced liver fibrosis and those with severe alcoholic hepatitis and, in both settings, are associated with poor survival [18,19].

Genetic KDS variants predispose to pulmonary diseases

The keratin composition of the lung, an organ exposed to constant mechanical stress, is complex [20]. While the lung KDS has not been studied in detail, recent research clearly highlights its importance. DSP has been identified to be expressed not only in airway bronchial epithelial cells but also in alveolar type 1 and 2 cells [21], which are thought to be the main cells affected in idiopathic pulmonary fibrosis (IPF). A non-coding DSP rs2076295 G-allele was identified in several genome-wide association studies as one of the top variants overrepresented in IPF [7,22,23]. This allele is also associated with chronic obstructive pulmonary disease, where it however, seems to be protective. While DSP is overexpressed in IPF patient lungs compared to control individuals, the DSP levels in the alveolar epithelial cells are decreased [7,21]. Deletion of the corresponding region in epithelial cells led to reduced epithelial characteristics and increased extracellular matrix gene expression [21], further strengthening its pathogenic relevance in IPF. The relevance is likely mediated by mechanosensing, as a stiffer matrix increases DSP gene expression in lung cells [24]. Mechanical stress on lung adenocarcinoma cells also induces K8/K18 phosphorylation, and affects keratin tensile properties while widening the DSG region in the desmosomes [25]. In fact, airway K8 phosphorylation is important for tissue function, since transgenic mice overexpressing the phosphorylation-deficient K8 S74A mutation were susceptible to acute and chronic lung injury in two models [26]. Similar susceptibility was observed in mice expressing the human liver disease-associated mutation K8 G62C [26].

Recently, using single-cell RNA sequencing, a new transitional cell population with high K8 expression was identified in injury-induced regeneration processes in lung epithelial cells [27,28]. These K8-high cells have unique morphological and signaling features and persist when type 2 alveolar cells in the regeneration process do not fully differentiate into type 1 after injury (e.g., IPF or lung disease models) [28,29]. K8-deficient mice develop less fibrosis and transitional alveolar cells in a lung fibrosis model, highlighting that K8 promotes the accumulation of transitional cells and fibrosis formation [30]. In addition to K8, K7, K18, K19, and K17 are also upregulated in these transitional cells [30]. Interestingly, a genome-wide meta-association analysis recently identified several K8 variants (but not K7 or K17-19 variants) in IPF, suggesting that K8 variants may be pathogenic [30].

The integrity of the keratin-desmosome scaffold is critical to maintain intestinal epithelial homeostasis

The contribution of the KDS to intestinal homeostasis is supported by multiple lines of evidence [31]. Data from patients with severe intestinal inflammation in inflammatory bowel diseases (IBDs) show a loss of DSG2 and DSC2 and increased phosphorylation of K8 and K18 [11,32]. Interestingly, the loss of DSG2 and DSC2 is preserved when organoids from patients with IBD are cultivated in media lacking inflammatory cytokines [33]. Evidence from animal models suggests that such changes may contribute to the perpetuation of the disease. In particular, while the loss of DSG2, DSC2 or DSP did not lead to to spontaneous inflammation, it increased intestinal permeability and susceptibility to intestinal injury [34–36]. Plakophilin 2 is also likely involved in the stabilization of the junctional complex in the gut since in vitro knockdown of plakophilin 2 resulted in reduced DSP levels and loss of tight junction integrity [37].

A contribution of the plaque proteins plakophilin 3 and plakoglobin to intestinal barrier regulation and mucosal wound healing has not been reported thus far. However, it is known that the loss of plakophilin 3 leads to increased adenoma formation and rectal prolapse in APC^{min} mice [38]. The connections between desmosomes and the keratin network are crucial to maintain intestinal epithelial integrity. This is supported by a study using intestinal epithelial DSP-deficient mice ($DSP^{\Delta IEC}$) showing that DSP in the apical junctional complex is required to maintain the keratin network architecture [34]. While $DSP^{\Delta IEC}$ mice are susceptible to chemical colitis, their phenotype is less pronounced than that seen in animals with intestinal epithelial K8 ablation ($K8^{\Delta IEC}$) [34,39]. Furthermore, the cytolinker plectin, which integrates the keratin network with other cytoskeletal components and cell junctions, has a critical role in maintaining intestinal homeostasis since mice lacking plectin in intestinal epithelial cells exhibit spontaneous colitis. A disease relevance is likely since the loss of plectin expression was observed in patients with IBD [40].

Mechanistically, plectin is required to connect the keratin network to integrins and to organize the formation

of the circumferential keratin rim and desmosomal integrity [41]. In addition to these observations, it is well accepted that the keratin network to which desmosomes are connected is important for maintaining epithelial homeostasis [42]. Evidence from animal models shows that K8 is the most important keratin in the colonic epithelium since tissue-specific knockout of K8 from intestinal epithelial cells leads to a spontaneous colitis phenotype with hyperproliferation, epithelial damage, intestinal permeability, and increased susceptibility to induced colorectal cancer [39]. In patients with active IBD and in murine acute dextran sodium sulfate (DSS)-induced colitis, keratin retraction and increased phosphorylation of K8 and K18 together with reduced intestinal barrier function were observed. In murine DSS colitis, keratin changes and an altered intestinal barrier were reversed when phosphorylation was blocked with p38 MAPK inhibitors [32].

Despite the clear experimental evidence, the genetic data are unequivocal. However, older studies identified K8 variants in patients suffering from IBD [43,44]. With regard to other keratins, mice with knockout of K15 display impaired crypt regeneration [45], whereas deficiency of K7, K18 or K19 shows no obvious disease phenotype in the colon under basal conditions [46–48]. Recently, it was reported that K7 is neo-expressed selectively in IBD patients, especially in areas with increased pathology. Further studies are needed to delineate whether the detection of K7 in IBD patients may serve as a useful disease biomarker [49].

KDS in other organs

Effective epithelial barrier function is critical to prevent luminal contents from penetrating into subepithelial layers, which causes inflammation. Impaired epithelial integrity is found in eosinophilic esophagitis (EoE), a chronic immune-mediated inflammatory condition and leading cause of dysphagia and food impaction in teenagers and adults [50]. Desmosomal genes (e.g., DSP, periplakin (PPL), DSC2, DSG3) are highly expressed in the stratified esophageal epithelia. In active EoE, the number of desmosomes in the basal layer is decreased and normalizes upon treatment, suggesting that these changes occur secondarily to inflammation [51]. To further support the relevance of desmosomes in EoE, Shoda et al. identified a series of rare, heterozygous, missense variants in genes encoding the desmosome-associated proteins *DSP* and *PPL* in approximately one fifth of patients with familial EoE [52]. Functionally, *DSP* and *PPL* variants in familial EoE resulted in reduced esophageal epithelial expression and impaired epithelial barrier function, despite disease quiescence. This was in contrast to non-familial EoE, where *DSP* and *PPL* loss is only seen in active disease. Of note, the presence of rare *DSP* and *PPL* variants was associated with enhanced tissue expression of thymic stromal lymphopoietin (TSLP). TSLP is known to promote the development of adaptive type 2 T-cell immunity characterized by excessive production of interleukin 5 and 13. These findings suggest a potential link between desmosome variants and the observed type 2 immunologic/allergic responses that are a key feature of EoE [53].

While epithelial scaffolding is the most established function of keratins, multiple lines of evidence demonstrate their relevance in multiple other processes. As such, K17 constitutes the prototypic stress-inducible type I keratin that regulates cell proliferation, differentiation and growth as well as inflammatory responses and carcinogenesis [54]. High K17 expression levels correlate with poor prognoses in several human epithelial cancers, such as breast, pancreatic, cervical and gastric cancers [54]. DNA damage and concomitant cell stress result in increased nuclear translocation of K17, which alters chromatin architecture and gene expression, thereby possibly contributing to tumor initiation [55]. In cervical cancer, K17 promotes tumorigenesis, and the genetic loss of K17 attenuates tumor growth through the induction of cell differentiation and differential regulation of cytokines in the tumor environment [56]. Using murine papillomavirus as a model of human papillomavirus (HPV) infection, Wang W et al. demonstrated that virus-induced K17 expression, in cooperation with estrogen, supports virus persistence and disease progression of papillomavirus-induced dysplastic cervicovaginal lesions due to modulation of the inflammatory milieu [57]. However, the role of K17 may be carcinoma specific. In particular, K17 expression in diffuse gastric cancer (DGC) is significantly lower than that in other major intestinal gastric carcinoma (IGC) subtypes, and low K17 expression in DGC is associated with poor prognosis [58]. Mechanistically, loss of K17 induces the activation of the YAP-IL6 axis. This contributes to E-cadherin loss and the epithelial-to-mesenchymal transition and enhances metastasis of DGC cells [58]. Interestingly, in differentiating keratinocytes, K17 expression decreases desmosomal components and prevents the formation of stable and hyperadhesive desmosomes, highlighting the importance and bidirectionality of the KDS in the contexts of cell and tissue function and architecture [59].

Conclusion and outlook

While the association between KDS and multiple inherited epidermal diseases is well established, recent findings clearly demonstrate their relevance in internal epithelia, which has long been underestimated. Among them, data from IPF and EoE that emerged from unbiased genetic searches are particularly striking and should spur additional studies to better characterize the KDS in these tissues. These data also demonstrate the versatility of keratins with various well-established functions, such as the maintenance of the epithelial

barrier, as well as several complex roles, such as the regulation of the inflammatory milieu. Keratins also have scaffolding functions in the cells, and they contribute to the homeostasis of internal epithelia for example through many organelle-related functions, such as those of mitochondria, the nucleus and ER [60,61]. To make the issue even more complex, both keratins and some desmosomal components are expressed in a tissue-specific or stress-induced manner, and some of the family members seem to have unique functions and properties. This is particularly true for K17, a highly stress-inducible keratin that is differentially expressed in multiple tumor entities and seems to modulate tumor biology. Similar findings have been made for additional keratins. For example, K19 is associated with poor prognosis and aggressive behavior in hepatocellular and breast cancer, and K7 is neo-expressed in the colon specifically in IBD patients. Another complex and somewhat underappreciated topic is the disease-related changes in KDS components that may perpetuate the pathogenic process but also serve as useful biomarkers. However, further studies are needed to determine which KDS changes reflect only the disease course and which ones actively drive it. To accomplish that, an iterative approach combining patient material with experimental studies is needed.

CRediT author statement

Diana M. Toivola, **Lauri Polari**, **Tobias Schwerd**, **Nicolas Schlegel**, **Pavel Strnad** contributed to: Conceptualization, Writing, Original draft preparation, Reviewing and Editing. **Lauri Polari:** Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

We thank everyone who contributed to the field and apologize for the references that had to be left out due to space restrictions. DMT is supported by the Academy of Finland (315139 and 332582), including the InFLAMES Flagship (337531 and 357911), Novo Nordisk Foundation (NNF20OC0063889), Åbo Akademi University Foundation/Åbo Akademi University Center of Excellence in Mechanostasis and Medicinska Understödsföreningen Liv och Hälsa Foundation. PS is supported by the Deutsche Forschungsgemeinschaft (DFG) grants SFB 1382 (ID 403224013) and STR 1095/6-1. NS is supported by DFG grants SCHL1962/8-1 and SCHL1962/5-2. TS is supported by DFG through the Collaborative Research Center 1371 (project number 395357507) and by the Munich Medical & Clinician Scientist Program (MCSP).

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