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REVIEW

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From structural resilience to cell specification — Intermediate filaments as regulators of cell fate

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Abstract

During the last decades intermediate filaments (IFs) have emerged as important regulators of cellular signaling events, ascribing IFs with functions beyond the structural support they provide. The organ and developmental stage-specific expression of IFs regulate cell differentiation within developing or remodeling tissues. Lack of IFs causes perturbed stem cell differentiation in vasculature, intestine, nervous system, and mammary gland, in transgenic mouse models. The aberrant cell fate decisions are caused by deregulation of different stem cell signaling pathways, such as Notch, Wnt, YAP/TAZ, and TGFβ. Mutations in genes coding for IFs cause an array of different diseases, many related to stem cell dysfunction, but the molecular mechanisms remain unresolved. Here, we provide a comprehensive overview of how IFs interact with and regulate the activity, localization and function of different signaling proteins in stem cells, and how the assembly state and PTM profile of IFs may affect these processes. Identifying when, where and how IFs and cell signaling congregate, will expand our understanding of IF-linked stem cell dysfunction during development and disease.

KEYWORDS

differentiation, stem cells, cytoskeleton, cell signaling, regeneration

1 | BACKGROUND

Cells, just like humans, contain a skeleton providing them with shape, support, and mechanical rigidity. The cellular skeleton, called the cytoskeleton, is made up of different types of fibers such as the actin filaments, microtubules, and intermediate filaments. This review focuses on the intermediate filaments and how they interact with developmental signaling pathways to regulate cell fate decisions. Intermediate filaments (IFs) have tissue-specific

Abbreviations: BEC, biliary epithelial cells; CNS, central nervous system; Dll, Delta-like ligand; EC, endothelial cell; ECM, extracellular matrix; EMDM, Emery-Dreifuss muscular dystrophy; EMT, epithelial-mesenchymal transition; GFAP, glial fibrillary acidic protein; HES, hairy and enhancer of split; HEY, hairy/E(spl)-related with YRPW motif; HGPS, Hutchinson-Gilford Progeria Syndrome; IBD, inflammatory bowel disease; IF, intermediate filaments; KO, knockout; MMEC, mouse mammary epithelial cell; MSC, mesenchymal stem cell; NF, neurofilament; NICD, Notch intracellular domain; NPC, neural progenitor cell; NSC, neural stem cell; PC, pachyonychia congenital; TA, transit amplifying cell; VSMC, vascular smooth muscle cell.

expression profiles that change according to developmental stage and many IFs are upregulated in regenerating tissues. It is known that mechanical forces and intercellular interactions regulate cell fate decisions, and there IFs play a major role.[1] How this cell fate regulation is mediated remains mainly unresolved, despite recent enlightening findings. Lim et al[2] recently demonstrated that cytoskeletal organization directs cell fate already prior to formation of the morula. Keratins are asymmetrically distributed between blastomeres to the outermost cells, promoting apical polarization, and controlling developmental cell signaling, and thereby directing trophectoderm cell fate commitment.[2] These findings provide intriguing early evidence of IF-mediated cell fate specification during embryonic development. Further, the prevalence of disease-causing mutations in genes encoding for different IFs have revealed them as cellular structures impacting functions connected to cell signaling, organelle architecture, and transcriptional regulation.[3,4] Yet, the underlying molecular mechanisms linking IFs to the diseases are still mostly unknown. In this review, we want to highlight IFs and their role in steering developmental processes and cell fate decisions, by modulating cell signaling dynamics (Figure 1). We will emphasize the role of IFs in regulation of mesenchymal, neuronal, epithelial, and myogenic cell determination and discuss the role of nuclear IFs in relation to disease.

2 | MESENCHYMAL CELL FATE

2.1 | Vimentin is the major IF of mesenchymal cells

Vimentin is a ubiquitously expressed protein and the major IF of mesenchymal cells. One of the main roles of vimentin is to provide cells with mechanical stability. In addition to its mechanical properties vimentin is an important regulator of epithelial to mesenchymal transition (EMT) both during normal development and disease, and is therefore, often used as a marker for EMT. Vimentin is also known to be involved in processes that involve migratory behavior of cells during wound healing and tissue repair.

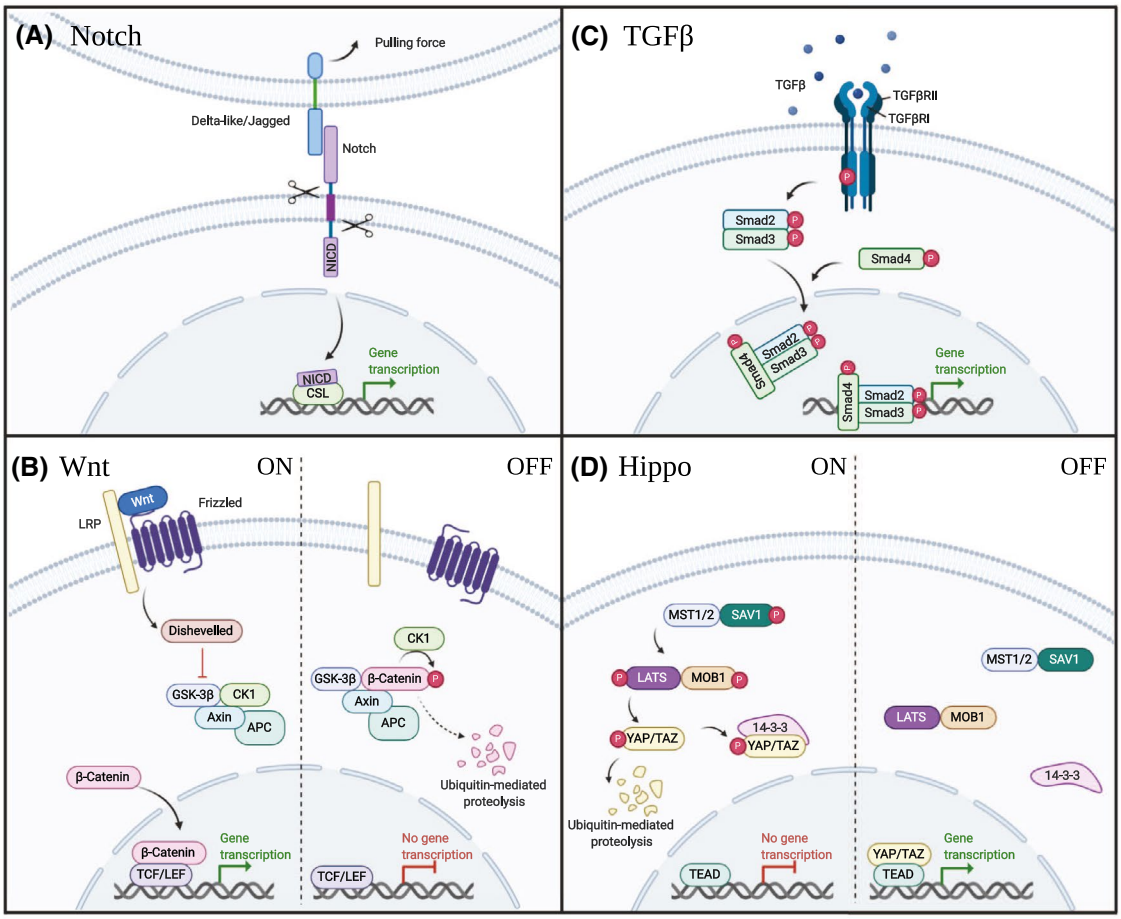
Originally vimentin knockout (KO) mice were considered to display a very mild, if any, phenotype.[5] Still, recent findings have linked vimentin deficiency with several types of developmental deficiencies, some of which may not become evident until the animal ages or is exposed to stress.[6-11] Already in 1989, Capetanaki et al[12] found that overexpression of vimentin in mice interferes with the development of the eye lens. During early development of the mouse embryo, vimentin expression is observed already during E8.5 in cells of the primitive mesoderm and its expression in neuronal cells also precedes the expression of tissue-specific IFs.[13] Recently, Cogné et al[14] discovered a vimentin mutation (L387P) that has been connected to a human disease phenotype. The mutation gives rise to a less stable vimentin variant, which is unable to form functional filaments. The patient carrying this mutation shows severe developmental defects manifesting as lipodystrophy, peripheral neuropathy, and frontonasal dysostosis among others.[14]

2.2 | Vimentin regulates cardiovascular tissue development and homeostasis

Vimentin has been associated with angiogenesis and vascular remodeling.[8,9,15,16] Halfway through embryonic development all blood vessels express vimentin.[13] An intact vimentin network is important for maintenance of endothelial barrier integrity[17] and ablation of vimentin in embryonic stem cells impairs their ability to differentiate toward an endothelial phenotype.[10] In ECs, vimentin has been shown to bind the Notch ligand Jagged1 and provide the force required for proper activation of the Notch signaling pathway.[9,16] Interestingly, the transmembrane domain of the Notch receptor has been linked to endothelial barrier stability through interaction with, for example, VE-cadherin, Lar, and the Rac1 GEF Trio[18] and it is intriguing to speculate whether this complex also interacts with vimentin at the endothelial cell junctions.[19] During formation of new blood vessels vimentin interacts with calpain and MT-MMP-1 facilitating degradation of the extracellular matrix (ECM), pawing way for new endothelial sprouts.[20] Endothelial sprouting is characterized by tip vs stalk cell selection, during which binding of vimentin to the Notch ligand Jagged1 balances and maintains the ratio between these cell identities. In absence of vimentin, Jagged1-mediated signaling through Notch is impaired, leading to reduced endothelial branching[9] in an antiangiogenic fashion characteristic for prevalent Delta-like (Dll) signaling (Figure 2). Schiffers et al[15] found that carotid artery ligation resulted in media hypertrophy in vimentin KO mice. Additionally, lack of vimentin leads to thickening of the endothelial basement membrane resulting in increased carotid stiffness.[8] Both endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) express vimentin, and absence of vimentin leads to a dedifferentiated VSMC phenotype.[16] Differentiation of the VSMCs layer starts at the endothelial cell layer and propagates outward through a mechanism called lateral induction, where Jagged1 activates Notch signaling through a positive feedback loop. In light of the effects of vimentin deficiency on endothelial functions[9] one must consider that lack of vimentin may disrupt Jagged activation of Notch and thereby lateral induction, resulting in reduced VSMC differentiation and enhanced proliferation of synthetic VSMCs.[16] The tuning of Jagged-mediated Notch signaling by vimentin in both endothelia and VSMCs provides direct evidence of intermediate filaments as potent cell fate mediators.

2.3 | Vimentin and EMT

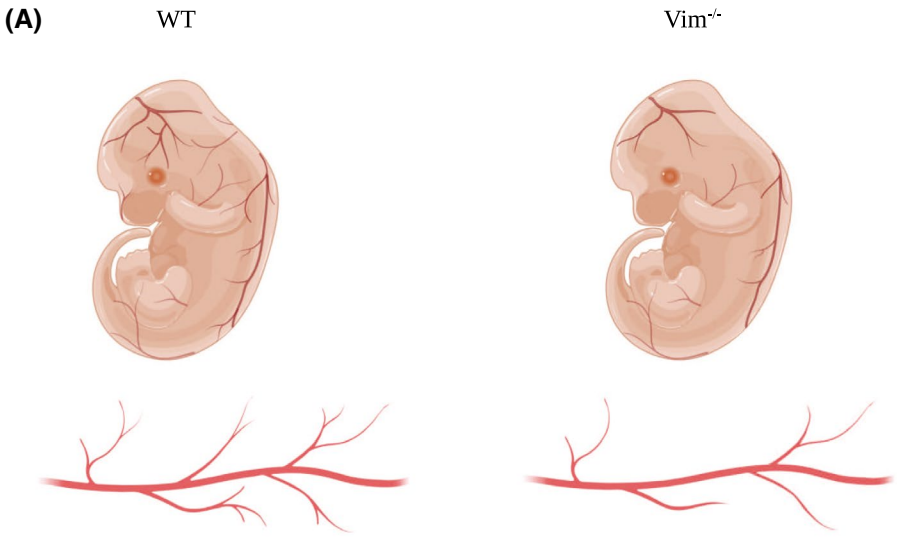
Vimentin has been well established as a regulator of EMT and is frequently used as a marker to identify cells that have undergone transition to a mesenchymal phenotype.[21-23] EMT is characterized by an altered cell shape with front-rear polarity, an increased expression of vimentin at the expense of keratins, and a loosening of cell-cell junctions with a concomitant increase in motility and invasion.[24,25] EMT is critical for tissue morphogenesis and development and is also implicated in cancer metastasis.[26,27] EMT is first observed during gastrulation when mesodermal cells are generated



(E)

Signaling pathway	IF	Developmental process
Notch	Vimentin	Angiogenesis[9]
		VSMC homeostasis[16]
	Keratin	Gastroenterological homeostasis[80, 136]
	GFAP/Vimentin	Adult neurogenesis[67,69]
	Nestin	Neural differentiation[55,65]
	Lamin	MSC differentiation[171,173]
TGF-β	Vimentin	Wound healing[11,111]
	Keratin	Alveolar epithelial differentation[113]
Hippo	Keratin	Epidermal homeostasis[82]
Wnt	Vimentin	Mammary gland development[142]

FIGURE 1 Intermediate filaments cross talk with different signaling pathways. A, The Notch signaling pathway is activated when a Notch ligand on a contacting cell binds to the Notch receptor. This initiates trans-endocytosis of the ligand-receptor complex and generates a pulling force, leading to proteolytic processing of the Notch receptor and release of the Notch intracellular domain (NICD). NICD translocates to the nucleus and interacts with the transcriptional regulator CSL (CBF-1, Suppressor of Hairless, Lag1) activating transcription of target genes. B, Wnt signaling is activated as soluble Wnt molecules bind to the Frizzled and LRP receptors. Frizzled recruits Dishevelled and inhibits the formation of degradation complex consisting of GSK-3β, CK1, APC, and Axin, allowing β-Catenin to translocate to the nucleus and bind TCF/LEF initiating transcription of target genes. In the absence of a Wnt signal, GSK-3β, CK1, APC, and Axin forms a degradation complex that phosphorylates β-Catenin. This phosphorylation targets β-Catenin for ubiquitination and proteasomal degradation. C, TGFβ initiates assembly of a tetrameric receptor complex (two copies of both TGFβRI and TGFβRII) at the cell membrane, followed by receptor phosphorylation and activation of the receptor kinase domain. Thereby the TGFβ receptor complex further phosphorylates Smad proteins, which subsequently form dimers and recruit Smad4. The formed Smad complex is transferred into the nucleus to control the transcription of target genes. D, The Hippo signaling pathway is made up of a kinase cascade where MST1/2 kinases (denoted Hippo in *Drosophila melanogaster*) and SAV1 form a complex to phosphorylate and activate LATS. LATS forms a complex with MOB1 to further phosphorylate and inhibit the function of the transcriptional activator YAP/TAZ (eg, through degradation or interaction with other proteins such as 14-3-3). Non-phosphorylated YAP/TAZ enters the nucleus and binds TEAD transcription factors initiating expression of target genes. E, Overview of the interaction between signaling pathways and intermediate filaments (IFs) during different developmental processes



(B)

Mechanism	Protein	Cellular process
Protein-protein interaction	Jagged1	Sprouting angiogenesis[9]
	Calpain	EC migration and ECM degradation[20]

FIGURE 2 Lack of vimentin delays vascular development. A, At E12.5 embryos lacking vimentin display a less refined vascular network due to disrupted angiogenesis. In absence of vimentin, the function of the proangiogenic Notch ligand Jagged1 is perturbed, leading to reduced vascular sprouting. Modified from Ref.9 B, Summary of the molecular processes connected to the $Vim^{-/-}$ phenotype

from the epiblast.[26] Vimentin is considered a central player in the EMT process and vimentin expression alone has been reported to induce the phenotypic changes associated with a mesenchymal cell fate.[22] Vimentin allows for cell flexibility through its filament network, which also forms interactions with actin filaments and microtubules to further aid in the motility and shape of the cell. These interactions are both direct and indirect through adaptor proteins such as plectins.[28-32] The cooperation of the cytoskeleton in this context has been shown to increase migration through elongation of invadopodia, and by influencing focal adhesions and actomyosin contractility.[33-37]

Vimentin further interacts with various EMT-linked signaling proteins, transcription factors, and adaptor proteins, which collectively affect multiple signaling pathways. These include regulation of the EMT-related transcription factor SLUG and oncogenic H-Ras through the tyrosine kinase Axl.[38] Vimentin also binds to phosphorylated ERK (pERK)

protecting it from dephosphorylation.[39] Further, vimentin has been shown to act as a scaffold recruiting SLUG to ERK in order to induce SLUG phosphorylation.[40] The direct interaction between Akt1 and vimentin induces phosphorylation of serine 39 in the head domain of vimentin, protecting vimentin from proteolysis and leading to enhanced migration and invasion in vivo.[41] Other direct interactions with vimentin that can influence the EMT phenotype include the tumor suppressor APC, integrin receptors, NLRP3 inflammasomes, and the scaffolding protein Scribble.[42-45] Vimentin can also bind 14-3-3 and this interaction has been demonstrated to prevent the MAPK pathway component Raf from binding to 14-3-3.[46] Similarly, vimentin interacts with the tumor suppressor Beclin through 14-3-3.[47] As 14-3-3 is a multifunctional adaptor, vimentin may influence multiple other 14-3-3 interacting proteins by regulating 14-3-3 availability.

Overexpression of vimentin is frequently reported in various epithelial cancers and is often correlated with invasive and migratory metastatic tumors and poor prognosis.[48-52] This topic is under intense investigation as the targeting of vimentin in cancer implies a promise of antimetastatic effects, but this complex area is outside the scope of this review and we refer the reader to multiple excellent reviews on vimentin in cancer and EMT.[23,24,53]

3 | NEURONAL CELL FATE

3.1 | Different IFs conjoin in the CNS

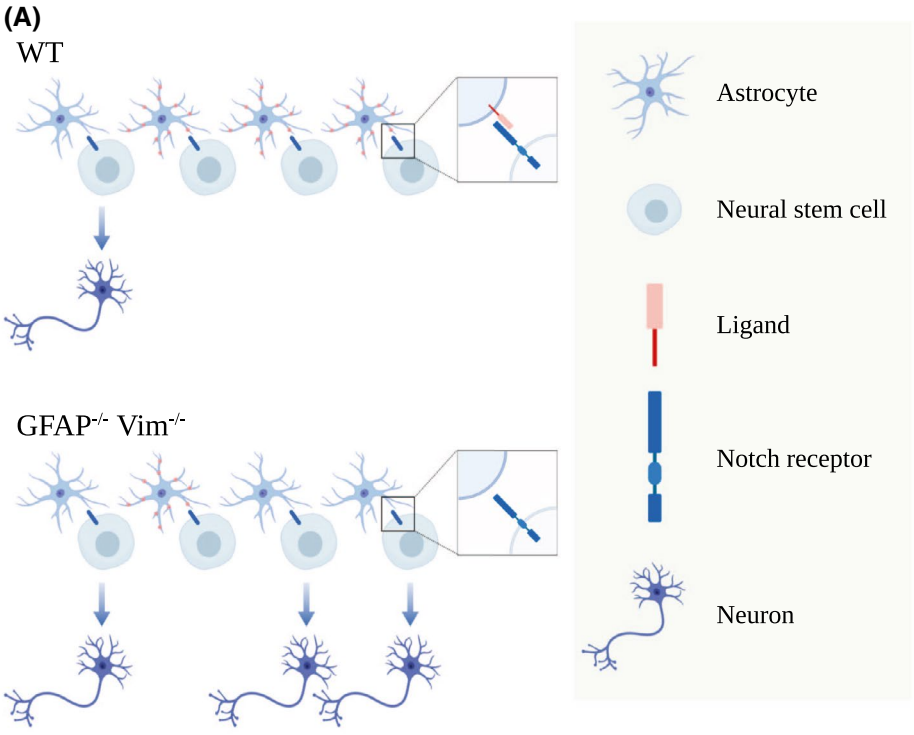
In a process called neurogenesis neural stem cells (NSCs) give rise to neurons and glial cells, the main constituents of the central nervous system (CNS). Development of the nervous system is characterized by alternating expression of different IFs. Undifferentiated cells express vimentin, neuroepithelial cells and neuroblasts express nestin, peripherin, and α-internexin.[54,55] As neuronal differentiation is initiated, the cells start expressing tissue-specific intermediate filaments called neurofilaments (NF). NF-light (NF-L) is the first NF to be expressed followed by NF-medium (NF-M) during neurite sprouting. NF-high (NF-H) is mainly expressed postnatally at the later stages of neuronal differentiation (reviewed in Ref. 54). Neurogenesis is initiated early during development when neural stem cells from the neural tube give rise to progenitor cells called radial glia. The radial glia will generate neurons during the later stages of neurogenesis as well as astrocytes and oligodendrocytes further during gliogenesis and oligodendrocytogenesis, respectively.[56] In the adult mammalian brain NSCs are found in the ventricular-subventricular zone and the subgranular zone. In addition to NFs, neurons may also express other intermediate filaments such as nestin and vimentin. The main intermediate filament in astrocytes is glial fibrillary acidic protein (GFAP),[57] but immature astrocytes express both nestin and vimentin.[58] Interestingly, mice devoid of nestin, vimentin, or GFAP develop normally and do not show signs of CNS aberrations.[5,57,59] The changes in IF expression during neuronal development coincides with cell differentiation and specification toward distinct cellular lineages. Degradation of nestin in NSCs marks the initial steps of neuronal differentiation and this degradation has been linked to simultaneous loss of Notch signaling, resulting in proteosomal degradation of nestin. Thus, loss of Notch leads to subsequent degradation of nestin, as ectopic expression of the Notch intracellular domain (NICD) maintains nestin levels and sustains the undifferentiated cellular state.[55] Vimentin expressed by astrocytes prior to differentiation, is to some extent replaced by GFAP as the astrocytes mature.[60]

3.2 | Astrocytic IFs regulate neuronal differentiation and regeneration

GFAP is described as the last IF to be expressed during development.[13] GFAP is predominantly expressed by the astrocytes of the CNS, which switch from expressing vimentin to expressing GFAP during the differentiation process. Mice lacking GFAP develop normally and are capable of producing offspring.[57,61,62] GFAP deficiency has been linked to aberrant long-term potentiation and long-term depression of hippocampal and cerebellar neurons, respectively,[61,63] together with a reduced eye blinking response.[63] Notch-induced nuclear factor 1A (NF1A) drives GFAP expression through demethylation of the *Gfap* promoter.[64] Mice lacking nestin are also viable.[59] Nestin does not appear to be required for the proliferation of NSCs. Still, nestin KO mice display increased neurogenesis in the hippocampal dentate gyrus. The nestin-mediated negative effects on neuronal differentiation are not NSC intrinsic, but rather mediated through astrocyte-initiated Notch signaling.[65] Nestin is involved in regulating vesicle dynamics in astrocytes and thereby also steers Notch signal activation from astrocytes,[65,66] as Notch ligands are endocytosed by the ligand-presenting cell upon interaction with Notch receptors. In absence of nestin, the number of Jagged containing vesicles in astrocytes is reduced and the distribution of Jagged into different vesicular compartments is perturbed, leading to reduced Notch signaling and enhanced neural differentiation.[65]

Reactive gliosis, a response by astrocytes to injury, is characterized by enhanced expression of intermediate filaments in astrocytes. Mice lacking vimentin and GFAP show an altered response to trauma, increased neuronal differentiation and better survival of neural grafts.[67] Astrocytes are the supporting cells of the CNS and they regulate the neurogenic niche through cell-contact and paracrine signaling.[68] Wilhelmsson et al[69] found that the increase in neuronal differentiation in mice lacking vimentin and GFAP was due to

reduced Notch signaling between astrocytes and neuronal precursors (Figure 3). Neuronal differentiation is regulated by Notch signaling in an inhibitory manner.[70] Thus, lack of vimentin and GFAP enhances neuronal differentiation as a direct consequence of reduced Notch signaling. The effects are, however, not as severe as in CSL (CBF-1, Suppressor of Hairless, Lag-1) KO mice. CSL is a part of the Notch transcriptional complex and mediates activation of Notch target gene expression (Figure 1A). In these mice the Notch signaling response is completely inhibited leading to exaggerated neuronal differentiation and stem cell depletion.[71] Such a difference in phenotype severity could be explained by compensatory Dll-mediated Notch signaling in the mice lacking vimentin and GFAP. This notion is supported by the fact that vimentin has been shown to specifically interact with Jagged1, but not Dll ligands.[9] Interestingly, the phosphorylation status of vimentin has been linked to neuronal differentiation. Neurospheres extracted from mice with mutated vimentin phosphorylation sites (mitotic phosphorylation sites mutated from serine to alanine: S6A, S24A, S38A, S46A, S55A, S64A, S65A, S71A, S72A, S82A, and S86A) show enhanced neuronal differentiation. The increase in differentiation is not caused by disturbed cell-cell communication between astrocytes and progenitors cells, suggesting perturbation of a cell intrinsic signaling mechanism within the neurosphere cell population.[72] Still, it is tempting to speculate that hampering with vimentin dynamics affects the interaction with Jagged1. Interaction of vimentin with other proteins, such as 14-3-3, has been shown to be phosphorylation dependent [46] and vimentin phosphorylation plays a role in proper localization of some cell surface proteins.[73] Further, Hagemann et al[74] showed disrupted adult neurogenesis in a mouse model for Alexander disease, a syndrome caused by mutations on the gene coding for GFAP.[75] In these mice, protein aggregation exhausts the proteasomal degradation machinery of the cell, disrupting degradation of NICD in GFAP expressing neural progenitors, and perturbing the balance between neurogenesis and gliogenesis.[74,76,77]



(B)

Mechanism	Protein	Cellular process
Protein trafficking/endocytosis	Jagged1	NSC differentiation[69]

FIGURE 3 Astrocytic intermediate filaments regulate Notch-mediated neurogenesis. A, Expression of GFAP and vimentin by astrocytes is required for Notch-mediated inhibition of neuronal differentiation. In absence of GFAP and vimentin the expression of the Notch ligand Jagged1 is reduced, leading to decreased Notch activation and subsequent neural differentiation. B, Summary of the molecular mechanisms deregulated in absence of GFAP and vimentin. Modified from Ref. 69

4 | EPITHELIAL CELL FATE

4.1 | Keratins govern epithelial tissues

Keratins are the major IFs of epithelial tissues. With 54 different genes encoding for keratins, these IFs constitute the largest family of IF proteins. Keratins are divided into acidic type I and neutral-basic type II proteins and they form heteropolymers consisting of type I and type II filaments. Keratins are found in the squamous epithelial cells of the epidermis (K1, K2, K5, K9, K10, & K14), simple type epithelial cells (K7, K8, K18, K19, and K20) and hair follicle epithelial cells (K31, K35, K81, K85, and K86).[78] The endothelium, a specialized type of epithelial tissue lining the walls of blood and lymphatic vessels, expresses minor amounts of keratins[79] with vimentin being the major IF expressed. Endothelial cells are, therefore, described previously in this review. Upon stress, epithelial cells induce expression of specific stress resilient keratins (K6, K16, & K17), which possess-specific characteristics beneficial, for example, wound healing and inflammation. Keratins are thought to provide cells with mechanical stability and tissues with appropriate architecture, but recently keratins are emerging as signaling platforms or modulators regulating several different cellular processes.[80-82] Mutations affecting keratins, cause an array of diseases called keratinopathies that mainly manifest trough disturbances in skin and nails, for example, epidermolysis bullosa simplex, ichthyosis hystrix, epidermolytic hyperkeratosis, and pachyonychia congenita[83] (full list of keratin-related diseases found on interfil.org). Meesmann epithelial corneal dystrophy[84] and some gastroenterological disorders have also been linked to keratins.[85-87]

4.2 | Keratins maintain the protective barrier of the skin

In the stratified epithelia of the skin different keratin pairs are expressed depending on the differentiation status. K5/K14 is expressed by the basal proliferating keratinocytes, and becomes replaced by K1/K10 in the differentiated cells of skin.[88] Loss of K14 is associated with severe skin blistering in mice around postnatal day 2.[89] Ablation of K14 in keratinocytes in vitro causes increased expression of keratinocyte differentiation markers K1 and involucrin,[88] indicating that K14 maintains keratinocytes in an undifferentiated state. Notch signaling is usually known to maintain stem cell fate and counteract cell differentiation. In skin, however, the current view is that Notch activation promotes differentiation of keratinocytes,[90] but some contradicting opinions have also been raised.[91] Blanpain et al[92] showed that Notch is involved in specifying spinous vs basal cell fate. Depletion of K14 decreased proliferation and increased NICD levels in keratinocytes.[88] Correspondingly, inhibition of Notch activity in keratinocytes led to suppressed expression of K1 and involucrin[93] in line with reduced differentiation of keratinocytes. In these cells Notch induces $p21^{Cip}$ expression and withdrawal from the cell cycle,[93] whereas ablation of K14 reduces Akt phosphorylation accompanied by reduced cell cycle progression.[88] $p21^{Cip}$ is an Akt target, thus, activation of Akt through phosphorylation may affect $p21^{Cip}$ and lead to enhanced proliferation, through inhibition of the antiproliferative effects of $p21^{Cip}$.[94] The signal inducing enhanced Notch expression and promoting keratinocyte differentiation is not yet known,[93] but Notch and K14 intertwine in a complex regulatory feedback system together with p63. p63 regulates K14 expression,[95] and thereby keratinocyte differentiation. Notch-induced differentiation is regulated by p63, but, on the contrary, Notch also suppresses p63 expression.[96]

Mice lacking K16 or K9 display footpad lesions mimicking palmoplantar keratoderma, a common feature of pachyonychia congenital (PC).[97,98] In humans PC is caused by mutations in K6a, K6b, K16, & K17, whereas K9 mutations are linked to epidermolytic palmoplantar keratoderma (EPPK). K9 is found in terminally differentiating keratinocytes of the palms and soles, and interestingly ablation of K16 in mice disrupts K9 expression and keratinocyte differentiation. The phenotype can be reversed by reactivation of K9 expression trough topical application of sulforaphane, a known activator of Nrf2 signaling,[99] but Nrf2 does not seem to directly regulate K9 expression.[100] Analysis of paw skin from K16 null mice revealed enhanced expression of several signaling pathway components, for example, Notch and Wnt, involved in epithelial differentiation,[100] but the molecular mechanism causing the aberrant differentiation remains elusive.

14-3-3σ, a keratinocyte-specific isoform of the 14-3-3 protein family, docks to different proteins and may also function as a signaling hub, bringing together various signaling molecules. 14-3-3σ is expressed by the differentiated cells of the skin and loss of 14-3-3σ allows the keratinocytes to escape terminal differentiation by maintaining telomerase activity and reducing $p16^{INK4a}$ expression.[101] 14-3-3 specifically binds keratins [82,102-104] and it is tempting to hypothesize that the interaction with keratin would be essential for bringing 14-3-3 into proximity of its other interaction partners. The downstream effector of the Hippo kinase cascade, YAP, interacts with 14-3-3 maintaining its cytoplasmic localization (Figure 1D). Recently, Guo et al[82] found that impaired K14 disulfide bond formation distorts the localization of 14-3-3σ in keratinocytes. The displacement of 14-3-3σ results in enhanced nuclear entry of YAP together with increased proliferation and defected terminal differentiation.[82] YAP signaling has also been linked to Notch suppression in the epidermis, which would further counteract keratinocyte terminal differentiation.[105]

When the epidermis is subjected to damage it requires efficient repair and regeneration to minimize blood loss and recreate the tissue barrier to the outside. This restoration process is called wound healing and it activates different cellular processes such as proliferation, migration, and differentiation of cells in the vicinity. This topic has recently been covered in an extensive review,[106] thus, we will only beriefly touch upon some of the key findings. IFs are instrumental for efficient wound closure and involved already in clot formation.[107] K6, K16, and K17 respond to stresses and their expression is enhanced at the injury site while the expression of differentiation-specific keratins, K1 and K10, is reduced (reviewed in Ref. 108). During embryonic wound closure, which is mediated by fibroblast driven forces, absence of vimentin is detrimental. When it comes to closure of adult wounds, lack of vimentin leads to delayed transdifferentiation of myofibroblasts and their inaccurate localization within the wounded tissue due to migratory defects.[109] In lens epithelial tissue, vimentin is secreted into the extracellular space upon injury. There the extracellular vimentin regulates the differentiation of mesenchymal repair cells into myofibroblasts.[110] Lack of vimentin also perturbs the proliferation of fibroblasts together with altered transformation of keratinocytes toward a migratory phenotype. These complications are linked to impaired TGFβ1 signaling (Figure 1C) and consequently delayed reepithelization.[11] In the alveolar epithelia of the lung, the vimentin promoter contains a SMAD-binding element, thus, TGFβ directly induces expression of vimentin.[111] In myoblasts, on the contrary, direct SMAD-binding elements are lacking and the TGFβ regulated vimentin expression is mediated by tandem AP-1 elements.[112] Similarly, TGFβ has been linked to K8 and K18 expression in differentiating alveolar epithelial cells and their reciprocal expression appears to regulate terminal differentiation.[113] However, the mechanisms behind this cross talk still remain unknown.

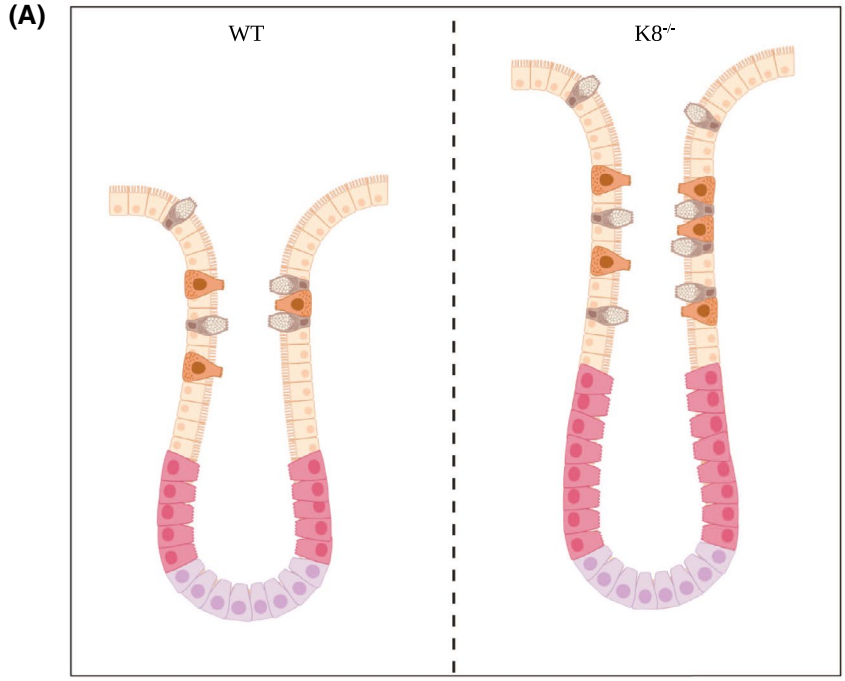
4.3 | IFs maintain gastroenterological homeostasis

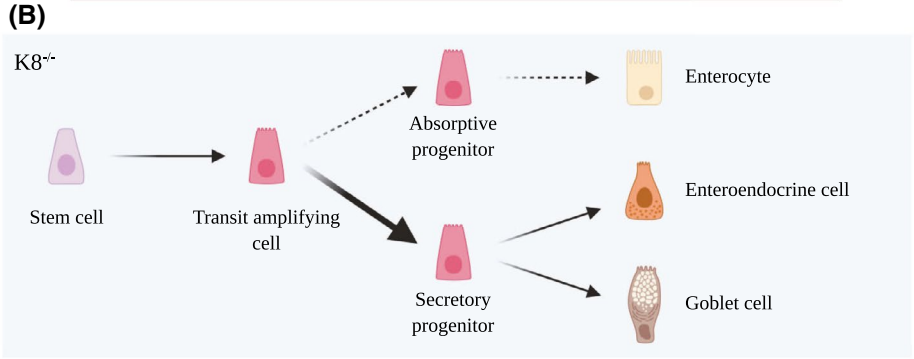
The intestinal simple type epithelial cell layer is constantly renewed, and thus, controlled cell proliferation and differentiation is a prerequisite for maintaining intestinal homeostasis. Both the small and large intestine contain an array of different cell types, and in these cells, keratins constitute the major IFs. Absorptive enterocytes, secretory goblet cells, enteroendocrine cells, and intestinal stem cells are found both in the small and large intestine. Paneth cells and tuft cells are specialized secretory cells of the small intestine with immunoprotective functions.[114,115] K8 and K19 is found uniformly throughout the intestine. K20 localizes to the differentiated cells of the villi and K18 is expressed uniformly by the epithelial cells of the colon, but restricted to enterocytes and goblet cells in the small intestine.[116]

Notch signaling regulates the proliferation and differentiation of intestinal epithelial cells and is essential for stem cell maintenance.[117] The general view is that Notch activity antagonizes goblet and enteroendocrine cell fates promoting differentiation of enterocytes.[118] It has also been proposed that the dose of Notch activity is essential for further specification between goblet or paneth cell fate vs enteroendocrine cell fate. Notch signaling may regulate cell fate specification in two distinct steps in the intestinal epithelium. First, in uncommitted progenitor cells Notch directs the decision between absorptive progenitors vs secretory progenitors, favoring differentiation along the absorptive lineage. Later, Notch is involved in further specification of secretory progenitors inducing goblet cell fate at the expense of paneth cells.[117,119] Wnt signaling is another central player regulating intestinal cell fate and this signaling pathway cross talks with Notch in maintaining gut homeostasis.[120] Wnts are secreted molecules that act in their local environment (Figure 1B). In the intestinal crypts, the paneth cells and stromal cells produce Wnt signals in order to induce proliferation and maintain the pool of the intestinal stem cells.[121,122] On the contrary, Wnt also controls the terminal differentiation of the paneth cells.[123]

The colon is responsible for water retention and vitamin absorption. Mice lacking K8 show hyper proliferation of colonic epithelial cells, increased crypt length and a phenotype resembling colitis.[124-126] Lack of K8 is linked to reduced Notch levels in colonic epithelial cells. This reduction is followed by decreased mRNA levels of Hey1 and Hey2 (Hairy/E(spl)-related with YRPW motif), accompanied by a shift in differentiation toward the secretory lineage[80] (Figure 4). This is in line with other studies showing a transition toward secretory cells upon Notch inhibition.[127,128] In the $K8^{-/-}$ colon, differentiation toward goblet and enteroendocrine cell fates is promoted at the expense of enterocytes. The number of transit amplifying (TA) cells is also increased in the absence of K8,[80] a finding that contradicts the complete block of proliferation observed upon Notch inhibition.[127] There are indications of a regulatory interaction between Notch and K8, but the possible interacting domains remain under investigation.[80] In addition, $K8^{-/-}$ mice show elevated levels of IL-22 in the colon.[129] IL-22 has recently been shown to promote TA cell proliferation and to inhibit expression of Notch and Wnt pathway components,[130] providing further diversity to the disturbed colonic homeostasis in the absence of K8.

In *Drosophila*, the Notch target gene Hey controls cellular identity through regulation of different signaling pathways and specific regulation of nuclear lamins. Brodsly et al[131] recently demonstrated that Hey maintains the cell fate of differentiated enterocytes and loss of Hey results in epithelial hyperplasia together with disturbed gut homeostasis. Loss of





(C)

Mechanism	Protein	Cellular process
Protein-protein interaction	Notch1	Intestinal homeostasis[80]

FIGURE 4 Keratins maintains cellular homeostasis in the colon. A, Lack of keratins 8 increases the proliferation of colonic epithelial cells and leads to elongated crypts. B, In absence of keratin 8 the differentiation of intestinal stem cells is shifted toward secretory cell fate due to reduced expression of Notch in colonic epithelial cells. C, Summary of the molecular processes related to the $K8^{-/-}$ phenotype. Modified from Ref. 80

Hey in enterocytes perturbs the balanced expression of stem cell-related B-type lamins (lamDm) and lamins characteristic of differentiated cells (lamin C). Further, lamin C negatively regulates expression of the Notch ligand Delta and enhances surface localization of the Wnt pathway component Armadillo (β-catenin in mammals), in polyploid cells of the *Drosophila* midgut.[131] Petrovsky and Großhans [132] interestingly showed that B-type lamins regulate cytokine-induced proliferation of intestinal stem cells in the *Drosophila* midgut. In this study B-type lamins were found to anatagonise Jak/Stat signaling,[132] providing further evidence of intermediate filaments as regulators of gut homeostasis. Additionally, lamin expression in T-cells has been shown to play a role in the outcome of inflammatory bowel disease (IBD). Lack of lamin A/C shifts the differentiation of T-cells toward regulatory T-cells at the expense of T helper (type 1) cells in a TGFβ and retinoic acid dependent manner, mitigating the IBD phenotype.[133]

K19 is not only found in the intestine, but also expressed by biliary epithelial cells (BEC) and liver progenitor cells.[134] Still, ablation of K19 does not cause an evident epithelial phenotype in the liver.[135] However, Chen et al[136] found that induction of cholestasis by introducing a 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) supplemented diet perturbed the proliferation of liver progenitor cells in K19 KO mice. The number of liver progenitor cells as well as

BECs was reduced in absence of K19.[136] Notch2 is known to drive BEC fate [137] and interestingly immunofluorescent analysis of liver samples revealed loss of Notch2 in BECs of K19 KO mice. Bile duct ligation resulted in a similar loss of Notch2 in BECs.[136] It is intriguing to speculate how K19 may regulate Notch2 expression in BECs, as one of the main symptoms of the pediatric disease Alagille syndrome is intrahepatic bile duct paucity.[138] The disease is caused by mutations on either *NOTCH2* or *JAGGED1*,[139,140] which implicates that the phenotype displayed by K19 KO mice could be caused by direct deregulation of Notch2 function or through the perturbed activation of Notch2 by the ligand Jagged1.

4.4 | Vimentin regulates mammary gland development

The mammary glands develop sequentially during female growth and development starting with quiescence after birth, continuing during puberty and reaching maturity upon pregnancy and lactation. Further, the mammary glands regress upon weaning through apoptosis and ECM remodeling.[141] Vimentin is expressed by basal mammary epithelial cells and stromal cells, whereas luminal cells are devoid of vimentin.[142] Mammary stem cells, on the contrary, express both vimentin and K15, an epithelial stem cell marker, thereby displaying a mixed epithelial-mesenchymal phenotype.[142,143]

Mice lacking vimentin are fertile and capable of nurturing their offspring. Nevertheless, vimentin appears to be important for mammary gland development. Peuhu et al[142] found that mammary ductal outgrowth is delayed in mice lacking vimentin (Figure 5). Vimentin regulates the ratio between basal and luminal mouse mammary epithelial cells (MMECs) and loss of vimentin led to loss of basal cell identity followed by increased mammary ductal lumen size. In addition, the epithelial regeneration capacity was impaired in absence of vimentin, as indicated by reduced mammosphere formation by MMECs isolated from $Vim^{-/-}$ mice. Gene expression analysis revealed perturbed expression of several developmentally important players in the basal MMECs, for example, proteins belonging to the Wnt and Hedgehog protein families.[142] However, the functions of the upregulated Wnt isoforms, Wnt11 and Wnt9a, in mammary gland development are still elusive.[144] Notch signaling is involved in the regulation of mammary gland development, especially during luminal lineage commitment.[145] Interestingly, Wnt and Notch signaling pathways come together during mammary stem cell differentiation. Pygo2, a Wnt coactivator, localizes with β-catenin at the Notch3 locus, inhibiting Notch3 promoted luminal cell fate.[146] Jagged is expressed in the developing mammary gland, mainly in the luminal cells.[145,147] Thus, it is

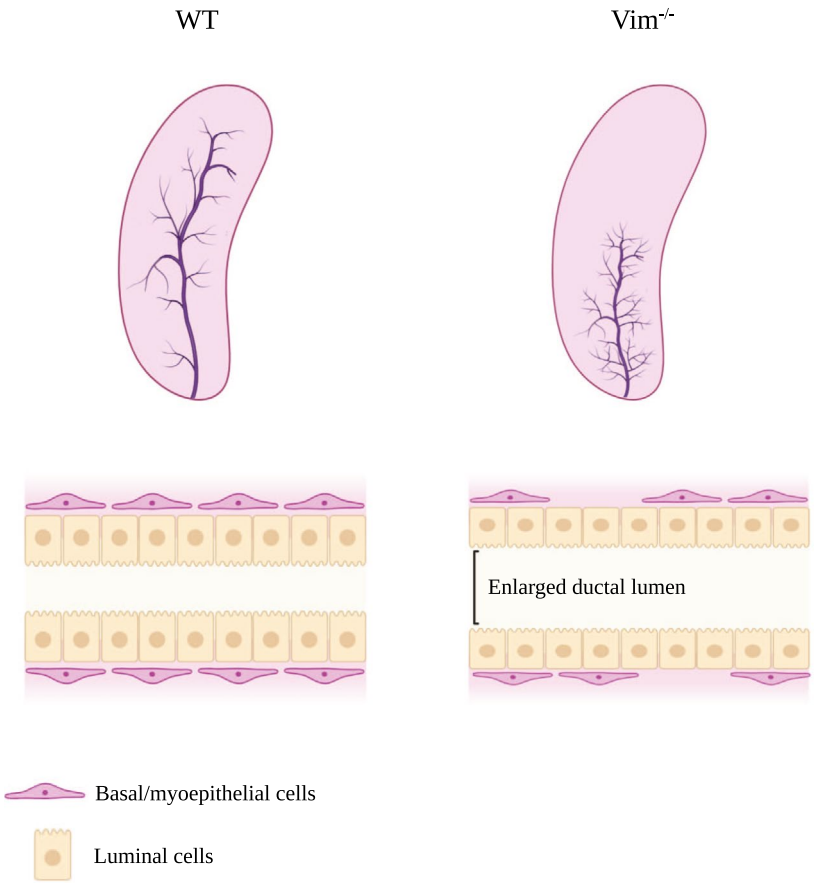


FIGURE 5 Vimentin is required for balanced development of the mammary gland. Lack of vimentin delays mammary ductal outgrowth in mice at 10 weeks of age. In absence of vimentin the ratio of basal vs luminal cells is perturbed resulting in loss of basal cells and enlargement of the ductal lumen. In absence of vimentin expression of Wnt signaling components is deregulated, possibly relating to the loss in basal cell fate. The molecular mechanisms leading to aberrant Wnt signaling are still unknown. Modified from Ref. 142

tempting to speculate whether vimentin may regulate Jagged function similarly in mammary gland differentiation as in angiogenesis.

5 | MYOGENIC CELL FATE IS CONTROLLED BY NESTIN

Myogenesis involves proliferation and differentiation of single nucleated myoblasts to form multinucleated contractile myotubes, characteristic of muscle tissue.[148] Nestin is a type VI intermediate filament containing a long tail domain that makes up the majority of the protein, combined with an unusually short head domain.[149] As previously stated, nestin is expressed during development with high expression in neural progenitor cells (NPCs), and it is commonly used as a marker for NPCs.[150] Several nestin KO models have been published. Park et al[151] first described an embryonically lethal phenotype with brain damage as a result of low numbers of NPCs. Another nestin KO model, as well as a nestin RNAi mouse model were both viable without a significant neuronal phenotype, but with defects in myogenesis and neuromuscular junctions.[59,152] Regulation of myoblast differentiation is governed by Cdk5 activity levels, and nestin has been detailed to regulate Cdk5-mediated myogenesis. The tail domain of nestin has been shown to function as a scaffold for active Cdk5 by binding to the Cdk5 activator p35.[152-156] The scaffolding of Cdk5/p35 protects the calpain-mediated cleavage of p35 to its hyperactive form p25, and knockdown of nestin results in hyperactivation of Cdk5/p25 and enhanced differentiation of myoblasts.[155] Indeed, down-regulation of either Cdk5 or p35 has been shown to hamper normal muscle development.[157] During muscular injury, nestin is reexpressed during regeneration.[158] Depletion of nestin leads to a similar phenotype in NSCs as in myoblasts, with abnormally increased differentiation. However, in NSCs the regulation is considered to be through Numb/Notch regulation, not Cdk5.[65] K8 and K19 are also expressed in striated muscle [159] and mice devoid of K19 display myopathy with a loss of contractile force in the muscle.[160] This muscle phenotype is related to the redistribution of mitochondria and is not a consequence of deregulated stem cell signaling.

6 | NUCLEAR INTERMEDIATE FILAMENTS AND CELL FATE

6.1 | Nuclear lamins and disease

Lamins are intermediate filament proteins forming the nuclear lamina. More than 100 different mutations in *LMNA* have been identified and linked to human disorders, such as Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy and familial partial lipodystrophy, Hutchinson-Gilford Progeria Syndrome (HGPS), Mandibuloacral dysplasia type A (MADA), Cardiomyopathy, dilated with hypergonadotropic hypogonadism (CMDHH), and Charcot-Marie-Tooth disease 2B1 (CMT2B1) (reviewed in Ref. 161).

Lamins are divided into two families. A-type lamins, consist of the major isoforms lamin A & C and two minor isoforms C2 & AΔ10. All of these are alternative splicing isoforms of the gene product encoded by *LMNA*.[162,163] B-type lamins contain the three isoforms B1, B2, & B3. B1 is encoded by *LMNB1*, whereas Lamin B2 and B3 are alternative splicing isoforms encoded by *LMNB2*.[164-166] Like other intermediate filaments, lamins consist of an N-terminal head and a coiled-coil central domain, which form dimers due to the interchain ionic interactions.[167] One unique feature of lamin A is a C-terminal tail containing a CaaX (C = Cystein, a = Aliphatic, X = any amino acid) motif important for association with the inner nuclear membrane.[168] This CaaX domain is missing in lamin C. The CaaX domain of the immature form of lamin A, called prelamin A, is farnesylated and this farnesylation eventually gives rise to the mature form of lamin A through proteolytic processing by the zinc metalloprotease ZMPSTE24.[169] B-type lamins are expressed in most cells throughout development. Lamin A/C, on the contrary, is found mainly in differentiated cells and adult stem cells of mesenchymal origin.[170] Zhang et al[171] summarized the effects of lamin A/C overexpression and silencing in different types of mesenchymal stem cells (MSCs) induced toward adipogenic or osteogenic fates. Knockdown of lamin A/C impaired osteogenic differentiation mainly through perturbation of Runx2-related mechanisms. The enhanced osteogenic differentiation caused by lamin A/C overexpression is linked to enhanced Wnt and Notch signaling.[171-173] Lamin A/C promotes translocation of β-catenin into the nucleus. This results in a positive feedback loop as β-catenin induces the expression of Wnt7b and Wnt10b which further stimulates osteogenic differentiation.[172] The same Wnts are involved in suppressing adipogenic differentiation as a result of lamin A/C overexpression. Wnt10b reduces PPARγ expression, thereby inhibiting adipogenesis.[174] Recently, lamins have been found to protect the nucleus from DNA damage and cell cycle arrest caused by mechanical overload.[175] Swift et al[176] connected lamin A expression and changes in Ig domain conformation to mechanical cues in MSCs. Furthermore, LMNA mutant myoblasts show disturbed responses to mechanical stress.[177] In different studies, lamin mechanosensitivity has been linked to cell fate determination trough cross talk with different signaling pathways, for example, YAP/TAZ,[176-178] serum response factor,[176,179] & retinoic acid.[176,180,181] Vimentin has also been connected to disturbed accumulation of body fat and lipid droplet stability,[14,182,183] but these findings have not implicated a role for vimentin in cell fate determination during adipogenesis, and therefore, falls outside the scope of this review.

Production of progerin, a pathological truncated variant of Lamin A, is the main cause of Hutchinson-Gilford Progeria Syndrome (HGPS) a disease in which the patients experience premature-aging symptoms. Individuals with HGPS have a point mutation in the LMNA gene which gives rise to a 50 amino acid deletion in the lamin A protein. The deleted region contains the site for processing mediated by ZMPSTE24. Lack of this processing site results in accumulation of farnesylated mutant prelamin A.[184,185] Progerin perturbs the structural integrity of the nucleus, resulting in deformation of the nuclear envelope.[186,187] The deformation has also been related to disrupted localization of nuclear pores, which may affect molecular trafficking to and from the nucleus and thereby perturb the communication between the nucleus and cytoplasm.[188] In addition, progerin also causes loss of peripheral heterochromatin and may therefore alter the gene expression profile.[187] Increased DNA damage, represented by γH2AX containing foci, is yet another consequence of cellular progerin accumulation.[189,190]

6.2 | Laminopathies and stem cell signaling

Stem cell depletion has been suggested to dislodge tissue homeostasis and cause the aging phenotype in HGPS patients. The compromised nuclear structure caused by progerin may prevent signaling molecules from entering the nucleus and thereby obstruct stem cell signaling. The Wnt signaling pathway is implicated in the maintenance of different stem cell populations. Nuclear localization of β-catenin is reduced in both patient derived fibroblasts and in cells of the inter follicular epidermis in a mouse model of HGPS (tetop-$^{LAG608G+}$; K5-tTA^{+}mice)[188] and in odontoblasts expressing progerin.[190] Similarly, Choi et al[191] demonstrated defective osteogenesis of patient derived progerin expressing induced pluripotent stem cells (iPSCs) and human bone marrow derived mesenchymal stem cells (hBM-MSCs), and that the faulty bone formation is due to suppressed β-catenin signaling.

Notch signaling relies on nuclear translocation of the proteolytically processed intracellular signaling fragment, NICD, and aberrant Notch function has been linked to HGPS.[189] In cells derived from HGPS patients the expression of the Notch signaling effectors HES1, HES5 (hairy and enhancer of split), and HEY1 is enhanced, which is unrelated to changes in the NICD levels. On the contrary, expression of progerin alters the cellular identity of immortalized MSCs through Notch-related mechanisms. Induction of differentiation along mesenchymal lineages in the presence of either progerin or NICD is similar, leading to enhanced osteogenic but reduced adipogenic differentiation.[173]

Emerin is a constituent of the nuclear envelope, which connects the cytoplasm to nucleus. Emerin interacts with both the actin and β-tubulin networks and binds the nuclear lamins.[192,193] In the nucleus emerin and prelamin A regulate each other's localization.[194] Mutations in the gene coding for emerin results in a disease called Emery-Dreifuss muscular dystrophy type-1 (X-linked EMDM), a type of striated muscle laminopathy.[195] Mutation of the LMNA gene causes the related autosomal dominant type of EMDM (AD-EMDM). Due to the close regulatory relationship between emerin and prelamin A, perturbed emerin function might be involved in several laminopathies. Emerin is known to interact with different signaling pathways, for example, Notch and Wnt signaling. Downregulation of emerin enhances signaling downstream of Notch and β-catenin. Nuclear entry of β-catenin is restricted by emerin, whereas NICD localizes together with emerin at the nuclear rim.[196,197] Thus, expression of mutant Lamin A/C variants may hamper with the functionality of these signaling pathways, because of disrupted emerin localization.

7 | MECHANISMS OF IF-MEDIATED CELL FATE DECISIONS

IFs utilize an array of different mechanisms to steer cell fate decisions. This can be achieved through direct interaction with signaling proteins or by regulating the localization of specific signaling molecules. Anchorage of keratins to the apical domain, followed by asymmetric division of keratins in daughter cells together with YAP dependent expression of CDX2, dictates cell fate already in a 16-cell embryo.[2] Vimentin, on the contrary, is, for example, known to regulate integrin trafficking and membrane localization.[73] In addition, vimentin may control cell fate specification by connecting extracellular mechanical cues with the intracellular transcriptional control machinery.[16] Similarly, nuclear lamins are essential in governing nuclear entry of certain signaling moieties[172,188] and presumably regulates nucleocytoplasmic shuttling of other transcription factors as well. Interestingly, keratins have also been found to shuttle in and out of the nucleus. Keratins K7, K8, K17, and K18 were found to enter and exit the nucleus in HeLa cells[198] and K17 was subsequently identified as a regulator of gene expression in tumor epithelial cells from skin and cervical tumors.[199,200] The IF-mediated regulation of signaling proteins is often dependent on the phosphorylation and assembly state of the IFs. The vimentin-mediated regulation of the Notch ligand Jagged1 is phosphorylation dependent and enhanced vimentin phosphorylation promotes Notch activation.[9] On the contrary,

inhibition of vimentin phosphorylation sequesters integrins in intracellular vesicles and thereby attenuates integrin signaling.[73] The importance of phosphorylation-mediated control of IFs is attested during mitosis. Mutation of serine residues on vimentin provokes failure of cytokinesis and upregulation of p21 and other senescence-related genes.[201] Inter-keratin disulfide bonding is essential for the assembly and organization of the keratin network[202,203] and disruption of these bonds not only affects the structure of the keratin network, but also displaces 14-3-3 and YAP in keratinocytes leading to perturbed epidermal homeostasis.[82] The dynamic regulation of IFs in this manner allows context dependent cell fate choices. For example, shear stress experienced by endothelial and epithelial cells induces phosphorylation of both keratins and vimentin. Shear stress reduces the levels of soluble keratin in alveolar cells subjected to shear stress.[204] Shear activates protein kinase C ζ, leading to enhanced K18 phosphorylation and intensified interaction between K18 and 14-3-3.[205] Similarly, shear stress enhanced the phosphorylation of vimentin and enhanced the Jagged1-mediated activation of Notch signaling.[16] IFs also sense and respond to other types of mechanical stimuli[206,207] and could thereby facilitate mechano-regulation of cell fate.[208] Cell stress in the form of hypoxia also alters IF expression. Hypoxia alters vimentin phosphorylation and assembly through activation of p21 activated kinase (PAK),[209] whereas keratin stability is compromised upon hypoxia.[210] Furthermore, IF phosphorylation, and thereby IF-associated signaling, is regulated by hormones. Vitamin D and thyroid hormones induces phosphorylation of vimentin in rat testes,[211,212] whereas the same hormones regulate phosphorylation of vimentin, GFAP, and NFs in rat cerebral cortex.[213,214] IFs may also be involved in generating oscillatory signaling cascades, characteristic for tissue patterning during development through interactions with different signaling molecules.[39,215,216] Cell behavior may be coordinated by IFs through regulation of cell-cell signaling in multicellular tissues. It is also worth noting that IFs and developmental signaling pathways may come together in a reciprocal regulatory network, where IFs regulate developmental transcriptional programs which in turn may control IF expression, a hypothesis supported by the highly developmental stage-specific expression profiles of different IFs.

8 | CONCLUDING REMARKS

Coordination of cell specification and organization is essential for tissue and organ development. The cellular microenvironment critically regulates cell fate, tissue development, and homeostasis. IFs provide a unique scaffolding framework that orchestrates cell-cell interactions and cell signaling dynamics, and thereby modulates the subsequent cell fate decisions. As the IFs respond to external stimuli and stressors,[217] IFs may integrate external and internal cues to support functional cell fate decisions in a fluctuating environment. The dynamic regulation of IFs allows context dependent cell fate decisions.[218,219] Interaction of IFs with specific signaling proteins allows IFs to specify signaling output, for example, through modulation of Jagged1, but not Dll4, mediated Notch signaling.[9] IF proteins are expressed in developmental stage and cell type-specific manner [13] and the differences in regulation, turnover rates, and mechanical properties between IF proteins are likely optimized for different cell and tissue-specific functions. IFs can also be considered to play a role in generating subcellular signaling compartments through the localization of filamentous and soluble forms of the IFs to different parts of the cell and thereby affect signaling at these local sites.[220] Proper localization of IFs is instrumental for maintaining cell polarity and organizing polarized cell signaling.[42,153,221,222] Complete understanding of how IF dynamics are regulated by changes in the cellular microenvironment and how this integrates with the cellular decision machinery is also lacking. Further, new innovative methods will have to be developed to tackle the details of how IFs are regulated in terms of turnover, dynamic exchange, and other remodeling events in vivo (current open questions summarized in Box 1). Recently, novel therapeutic tools modifying IFs have emerged and vimentin serves as a promising potential target in cancer therapy. Disruption of vimentin can reduce migration and invasion of highly motile metastatic cancer cells and several compounds targeting vimentin have shown anticancer properties (reviewed in Ref. 53). These include compounds such as fluvastatin leading to proteolysis of vimentin,[223] ajoene that disrupts the vimentin network,[224] simvastatin leading to reorganization and bundling of the vimentin network,[225] the specific vimentin targeting small molecule FiVe1 causing disorganization, phosphorylation, and mitotic catastrophe,[226] and an antibody targeting cell surface vimentin.[227] Although the specific mechanisms by which IFs regulate cell fate decisions and developmental signaling are emerging, there is still a fundamental knowledge gap in this area and more detailed knowledge on how IFs regulate signaling proteins is required. We need to identify the interaction sites of IFs and signaling proteins, study how the interactions are regulated by IF dynamics and posttranslational modifications. Enhanced understanding of the cross talk between IFs and developmental signaling pathways could clarify our perception of perturbances in these signaling pathways and how they relate to disease etiology. Several developmental diseases have puzzling phenotypes, where similar mutations have various disease outcomes. In such cases tissue-specific expression of IFs and their regulation of cell signaling dynamics may be a contributing factor for disease severity.

Box 1 Current questions on the mechanisms of IF mediated cell fate decisions

1. Is the expression of IFs regulated by developmental signaling pathways?
2. What is the role of IFs in coordinating cell behaviour in multicellular tissues?
3. How is the interaction between IFs and IF-interacting proteins regulated?
4. Are IFs regulated locally at the subcellular level and how does that affect cell signaling?
5. How do post-translational modifications (PTMs) regulate IFs in different cellular contexts?
6. Can we target IFs pharmacologically to steer cell fate?
7. Can stem cell signaling be controlled through mechanical regulation of IFs?
8. How is stem cell signaling affected when IFs respond to changes in the cellular microenvironment (e.g. metabolism, inflammation, fibrosis)?
9. Are there still unidentified IF mutations that cause developmental diseases?
10. How can the context dependent function of IFs be studied? Potential approaches include:

- Tools for controlling IF assembly and function (IF targeting drugs, peptide microinjections, optogenetics).
- Transgenic models for cell isolation and engineering (PTM mutants, spatio-temporal control of gene expression, lineage tracing).
- Techniques for visualization of IF functions (Single molecule resolution imaging, AFM for filament nano-dissection).
- Biomimetic approaches (3D cultures, organoids, organ-on-chip technology).
- Mathematical modeling and generation of computational tools.

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AUTHOR CONTRIBUTIONS

M. Sjöqvist, D. Antfolk, F. Suarez Rodriquez, and C. M. Sahlgren wrote the review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Discher D, Dong C, Fredberg JJ, et al. Biomechanics: cell research and applications for the next decade. *Ann Biomed Eng*. 2009;37(5):847-859.
2. Lim HYG, Alvarez YD, Gasnier M, et al. Keratins are asymmetrically inherited fate determinants in the mammalian embryo. *Nature*. 2020;585(7825):404-409.
3. Steen K, Chen D, Wang F, et al. A role for keratins in supporting mitochondrial organization and function in skin keratinocytes. *Mol Biol Cell*. 2020;31(11):1103-1111.
4. Bera M, Sengupta K. Nuclear filaments: role in chromosomal positioning and gene expression. *Nucleus*. 2020;11(1):99-110.
5. Colucci-Guyon E, Portier MM, Dunia I, Paulin D, Pournin S, Babinet C. Mice lacking vimentin develop and reproduce without an obvious phenotype. *Cell*. 1994;79(4):679-694.
6. Terzi F, Henrion D, Colucci-Guyon E, et al. Reduction of renal mass is lethal in mice lacking vimentin. Role of endothelin-nitric oxide imbalance. *J Clin Invest*. 1997;100(6):1520-1528.
7. Mendez MG, Restle D, Janmey PA. Vimentin enhances cell elastic behavior and protects against compressive stress. *Biophys J*. 2014;107(2):314-323.
8. Langlois B, Belozertseva E, Parlakian A, et al. Vimentin knockout results in increased expression of sub-endothelial basement membrane components and carotid stiffness in mice. *Sci Rep*. 2017;7(1):11628.
9. Antfolk D, Sjoqvist M, Cheng F, et al. Selective regulation of Notch ligands during angiogenesis is mediated by vimentin. *Proc Natl Acad Sci U S A*. 2017;114(23):E4574-E4581.
10. Boraas LC, Ahsan T. Lack of vimentin impairs endothelial differentiation of embryonic stem cells. *Sci Rep*. 2016;6:30814.
11. Cheng F, Shen Y, Mohanasundaram P, et al. Vimentin coordinates fibroblast proliferation and keratinocyte differentiation in wound healing via TGF-β–Slug signaling. *Proc Natl Acad Sci U S A*. 2016;113(30):E4320-E4327.
12. Capetanaki Y, Smith S, Heath JP. Overexpression of the vimentin gene in transgenic mice inhibits normal lens cell differentiation. *J Cell Biol*. 1989;109(4 Pt 1):1653-1664.
13. Duprey P, Paulin D. What can be learned from intermediate filament gene regulation in the mouse embryo. *Int J Dev Biol*. 1995;39(3):443-457.
14. Cogné B, Bouameur JE, Hayot G, et al. A dominant vimentin variant causes a rare syndrome with premature aging. *Eur J Hum Genet*. 2020;28(9):1218-1230.
15. Schiffers PM, Henrion D, Boulanger CM, et al. Altered flow-induced arterial remodeling in vimentin-deficient mice. *Arterioscler Thromb Vasc Biol*. 2000;20(3):611-616.

16. van Engeland NCA, Suarez Rodriguez F, Rivero-Müller A, et al. Vimentin regulates Notch signaling strength and arterial remodeling in response to hemodynamic stress. *Sci Rep*. 2019;9(1):12415.
17. Liu T, Ghamloush MM, Aldawood A, et al. Modulating endothelial barrier function by targeting vimentin phosphorylation. *J Cell Physiol*. 2014;229(10):1484-1493.
18. Polacheck WJ, Kutys ML, Yang J, et al. A non-canonical Notch complex regulates adherens junctions and vascular barrier function. *Nature*. 2017;552(7684):258-262.
19. Wallez Y, Huber P. Endothelial adherens and tight junctions in vascular homeostasis, inflammation and angiogenesis. *Biochim Biophys Acta*. 2008;1778(3):794-809.
20. Kwak HI, Kang H, Dave JM, et al. Calpain-mediated vimentin cleavage occurs upstream of MT1-MMP membrane translocation to facilitate endothelial sprout initiation. *Angiogenesis*. 2012;15(2):287-303.
21. Chung BM, Rotty JD, Coulombe PA. Networking galore: intermediate filaments and cell migration. *Curr Opin Cell Biol*. 2013;25:600-612.
22. Mendez MG, Kojima S, Goldman RD. Vimentin induces changes in cell shape, motility, and adhesion during the epithelial to mesenchymal transition. *FASEB J*. 2010;24(6):1838-1851.
23. Satelli A, Li S. Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cell Mol Life Sci*. 2011;68: 3033-3046.
24. Kokkinos MI, Wafai R, Wong MK, Newgreen DF, Thompson EW, Waltham M. Vimentin and epithelial-mesenchymal transition in human breast cancer - observations in vitro and in vivo. *Cells Tissues Organs*. 2007;185:191-203.
25. Messica Y, Laser-Azogui A, Volberg T, et al. The role of vimentin in regulating cell invasive migration in dense cultures of breast carcinoma cells. *Nano Lett*. 2017;17(11):6941-6948.
26. Nakaya Y, Sheng G. EMT in developmental morphogenesis. *Cancer Lett*. 2013;341:9-15.
27. Thiery JP, Acloque H, Huang RYJ, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139:871-890.
28. Esue O, Carson AA, Tseng Y, Wirtz D. A direct interaction between actin and vimentin filaments mediated by the tail domain of vimentin. *J Biol Chem*. 2006;281(41):30393-30399.
29. Duarte S, Viedma-Poyatos Á, Navarro-Carrasco E, Martínez AE, Pajares MA, Pérez-Sala D. Vimentin filaments interact with the actin cortex in mitosis allowing normal cell division. *Nat Commun*. 2019;10(1):4200.
30. Wiche G, Osmanagic-Myers S, Castañón MJ. Networking and anchoring through plectin: a key to IF functionality and mechanotransduction. *Curr Opin Cell Biol*. 2015;32:21-29.
31. Burgstaller G, Gregor M, Winter L, Wiche G. Keeping the vimentin network under control: cell-matrix adhesion-associated plectin 1f affects cell shape and polarity of fibroblasts. *Mol Biol Cell*. 2010;21(19):3362-3375.
32. Svitkina TM, Verkhovsky AB, Borisy GG. Plectin sidearms mediate interaction of intermediate filaments with microtubules and other components of the cytoskeleton. *J Cell Biol*. 1996;135(4):991-1007.
33. Schoumacher M, Goldman RD, Louvard D, Vignjevic DM. Actin, microtubules, and vimentin intermediate filaments cooperate for elongation of invadopodia. *J Cell Biol*. 2010;189(3):541-556.
34. Sutoh Yoneyama M, Hatakeyama S, Habuchi T, et al. Vimentin intermediate filament and plectin provide a scaffold for invadopodia, facilitating cancer cell invasion and extravasation for metastasis. *Eur J Cell Biol*. 2014;93(4):157-169.
35. Lynch CD, Lazar AM, Iskratsch T, Zhang X, Sheetz MP. Endoplasmic spreading requires coalescence of vimentin intermediate filaments at force-bearing adhesions. *Mol Biol Cell*. 2013;24(1):21-30.
36. Gregor M, Osmanagic-Myers S, Burgstaller G, et al. Mechanosensing through focal adhesion-anchored intermediate filaments. *FASEB J*. 2014;28(2):715-729.
37. Battaglia RA, Delic S, Herrmann H, Snider NT. Vimentin on the move: new developments in cell migration. *F1000Res*. 2018;7:F1000 Faculty Rev-1796.
38. Vuoriluoto K, Haugen H, Kiviluoto S, et al. Vimentin regulates EMT induction by Slug and oncogenic H-Ras and migration by governing Axl expression in breast cancer. *Oncogene*. 2011;30(12):1436-1448.
39. Perlson E, Michaelevski I, Kowalsman N, et al. Vimentin Binding to phosphorylated Erk sterically hinders enzymatic dephosphorylation of the kinase. *J Mol Biol*. 2006;364(5):938-944.
40. Virtakoivu R, Mai A, Mattila E, et al. Vimentin-ERK signaling uncouples Slug gene regulatory function. *Cancer Res*. 2015;75(11):2349-2362.
41. Zhu QS, Rosenblatt K, Huang KL, et al. Vimentin is a novel AKT1 target mediating motility and invasion. *Oncogene*. 2011;30(4):457-470.
42. Phua DC, Humbert PO, Hunziker W. Vimentin regulates scribble activity by protecting it from proteasomal degradation. *Mol Biol Cell*. 2009;20(12):2841-2855.
43. Kim J, Yang C, Kim EJ, et al. Vimentin filaments regulate integrin-ligand interactions by binding to the cytoplasmic tail of integrin β3. *J Cell Sci*. 2016;129(10):2030-2042.
44. Sakamoto Y, Boëda B, Etienne-Manneville S. APC binds intermediate filaments and is required for their reorganization during cell migration. *J Cell Biol*. 2013;200(3):249-258.
45. Dos Santos G, Rogel MR, Baker MA, et al. Vimentin regulates activation of the NLRP3 inflammasome. *Nat Commun*. 2015;6:6574.
46. Tzivion G, Luo ZJ, Avruch J. Calyculin A-induced vimentin phosphorylation sequesters 14-3-3 and displaces other 14-3-3 partners in vivo. *J Biol Chem*. 2000;275(38):29772-29778.
47. Wang RC, Wei Y, An Z, et al. Akt-mediated regulation of autophagy and tumorigenesis through Beclin 1 phosphorylation. *Science*. 2012;338(6109):956-959.
48. Wei J, Xu G, Wu M, et al. Overexpression of vimentin contributes to prostate cancer invasion and metastasis via Src regulation. *Anticancer Res*. 2008;28(1A):327-334.
49. Sethi S, Macoska J, Chen W, Sarkar FH. Molecular signature of epithelial-mesenchymal transition (EMT) in human prostate cancer bone metastasis. *Am J Transl Res*. 2011;3(1):90-99.
50. Hu L, Lau SH, Tzang CH, et al. Association of Vimentin overexpression and hepatocellular carcinoma metastasis. *Oncogene*. 2004;23(1):298-302.
51. Korsching E, Packeisen J, Liedtke C, et al. The origin of vimentin expression in invasive breast cancer: epithelial- mesenchymal transition, myoepithelial histogenesis or histogenesis from progenitor cells with bilinear differentiation potential? *J Pathol*. 2005;206(4):451-457.
52. Kidd ME, Shumaker DK, Ridge KM. The role of vimentin intermediate filaments in the progression of lung cancer. *Am J Respir Cell Mol Biol*. 2014;50(1):1-6.

53. Strouhalova K, Přechová M, Gandalovičová A, Brábek J, Gregor M, Rosel D. Vimentin intermediate filaments as potential target for cancer treatment. *Cancers*. 2020;12(1):184.
54. Lariviere RC, Julien JP. Functions of intermediate filaments in neuronal development and disease. *J Neurobiol*. 2004;58(1):131-148.
55. Mellodew K, Suhr R, Uwanogho DA, et al. Nestin expression is lost in a neural stem cell line through a mechanism involving the proteasome and Notch signalling. *Dev Brain Res*. 2004;151(1–2):13-23.
56. Zahr SK, Kaplan DR, Miller FD. Translating neural stem cells to neurons in the mammalian brain. *Cell Death Differ*. 2019;26(12):2495-2512.
57. Pekny M, Levéen P, Pekna M, et al. Mice lacking glial fibrillary acidic protein display astrocytes devoid of intermediate filaments but develop and reproduce normally. *EMBO J*. 1995;14(8):1590-1598.
58. Zerlin M, Levison SW, Goldman JE. Early patterns of migration, morphogenesis, and intermediate filament expression of subventricular zone cells in the postnatal rat forebrain. *J Neurosci*. 1995;15(11):7238-7249.
59. Mohseni P, Sung HK, Murphy AJ, et al. Nestin is not essential for development of the CNS but required for dispersion of acetylcholine receptor clusters at the area of neuromuscular junctions. *J Neurosci*. 2011;31(32):11547-11552.
60. Dahl D. The vimentin-GFA protein transition in rat neuroglia cytoskeleton occurs at the time of myelination. *J Neurosci Res*. 1981;6(6):741-748.
61. McCall MA, Gregg RG, Behringer RR, et al. Targeted deletion in astrocyte intermediate filament (Gfap) alters neuronal physiology. *Proc Natl Acad Sci U S A*. 1996;93(13):6361-6366.
62. Gomi H, Yokoyama T, Fujimoto K, et al. Mice devoid of the glial fibrillary acidic protein develop normally and are susceptible to scrapie prions. *Neuron*. 1995;14(1):29-41.
63. Shibuki K, Gomi H, Chen L, et al. Deficient cerebellar long-term depression, impaired eyeblink conditioning, and normal motor coordination in GFAP mutant mice. *Neuron*. 1996;16(3):587-599.
64. Namihira M, Kohyama J, Semi K, et al. Committed neuronal precursors confer astrocytic potential on residual neural precursor cells. *Dev Cell*. 2009;16(2):245-255.
65. Wilhelmsson U, Lebkuechner I, Leke R, et al. Nestin regulates neurogenesis in mice through notch signaling from astrocytes to neural stem cells. *Cereb Cortex*. 2019;29(10):4050-4066.
66. Lasič E, Trkov Bobnar S, Wilhelmsson U, et al. Nestin affects fusion pore dynamics in mouse astrocytes. *Acta Physiol*. 2020;228(3):e13399.
67. Widestrand Å, Faijerson J, Wilhelmsson U, et al. Increased neurogenesis and astrogenesis from neural progenitor cells grafted in the hippocampus of GFAP−/− Vim−/− mice. *Stem Cells*. 2007;25(10):2619-2627.
68. Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. *Nature*. 2002;417(6884):39-44.
69. Wilhelmsson U, Faiz M, de Pablo Y, et al. Astrocytes negatively regulate neurogenesis through the Jagged1-mediated Notch pathway. *Stem Cells*. 2012;30(10):2320-2329.
70. Louvi A, Artavanis-Tsakonas S. Notch signalling in vertebrate neural development. *Nat Rev*. 2006;7(2):93-102.
71. Imayoshi I, Sakamoto M, Yamaguchi M, Mori K, Kageyama R. Essential roles of Notch signaling in maintenance of neural stem cells in developing and adult brains. *J Neurosci*. 2010;30(9):3489-3498.
72. Chen M, Puschmann TB, Marasek P, et al. Increased neuronal differentiation of neural progenitor cells derived from phosphovimentin-deficient mice. *Mol Neurobiol*. 2018;55(7):5478-5489.
73. Ivaska J, Vuoriluoto K, Huovinen T, Izawa I, Inagaki M, Parker PJ. PKCepsilon-mediated phosphorylation of vimentin controls integrin recycling and motility. *EMBO J*. 2005;24(22):3834-3845.
74. Hagemann TL, Paylor R, Messing A. Deficits in adult neurogenesis, contextual fear conditioning, and spatial learning in a Gfap mutant mouse model of Alexander disease. *J Neurosci*. 2013;33(47):18698-18706.
75. Hsiao VC, Tian R, Long H, et al. Alexander-disease mutation of GFAP causes filament disorganization and decreased solubility of GFAP. *J Cell Sci*. 2005;118(9):2057-2065.
76. Liu Y, Namba T, Liu J, Suzuki R, Shioda S, Seki T. Glial fibrillary acidic protein-expressing neural progenitors give rise to immature neurons via early intermediate progenitors expressing both glial fibrillary acidic protein and neuronal markers in the adult hippocampus. *Neuroscience*. 2010;166(1):241-251.
77. Tang G, Perng MD, Wilk S, Quinlan R, Goldman JE. Oligomers of mutant glial fibrillary acidic protein (GFAP) Inhibit the proteasome system in alexander disease astrocytes, and the small heat shock protein alphaB-crystallin reverses the inhibition. *J Biol Chem*. 2010;285(14):10527-10537.
78. Strnad P, Usachov V, Debes C, Gräter F, Parry DAD, Omary MB. Unique amino acid signatures that are evolutionarily conserved distinguish simple-type, epidermal and hair keratins. *J Cell Sci*. 2011;124(Pt 24):4221-4232.
79. Miettinen M, Fetsch JF. Distribution of keratins in normal endothelial cells and a spectrum of vascular tumors: implications in tumor diagnosis. *Hum Pathol*. 2000;31(9):1062-1067.
80. Lahdeniemi IAK, Misiorek JO, Antila CJM, et al. Keratins regulate colonic epithelial cell differentiation through the Notch1 signalling pathway. *Cell Death Differ*. 2017;24(6):984-996.
81. Vijayaraj P, Kroeger C, Reuter U, Hartmann D, Magin TM. Keratins regulate yolk sac hematopoiesis and vasculogenesis through reduced BMP-4 signaling. *Eur J Cell Biol*. 2010;89(4):299-306.
82. Guo Y, Redmond CJ, Leacock KA, et al. Keratin 14-dependent disulfides regulate epidermal homeostasis and barrier function via 14-3-3σ and YAP1. *Elife*. 2020;9:e53165.
83. Vijayaraj P, Söhl G, Magin TM. Keratin transgenic and knockout mice: functional analysis and validation of disease-causing mutations. *Methods Mol Biol*. 2007;360:203-251.
84. Allen EHA, Courtney DG, Atkinson SD, et al. Keratin 12 missense mutation induces the unfolded protein response and apoptosis in Meesmann epithelial corneal dystrophy. *Hum Mol Genet*. 2016;25(6):1176-1191.
85. Owens DW, Wilson NJ, Hill AJM, et al. Human keratin 8 mutations that disturb filament assembly observed in inflammatory bowel disease patients. *J Cell Sci*. 2004;117(10):1989-1999.
86. Tao GZ, Strnad P, Zhou Q, et al. Analysis of keratin polypeptides 8 and 19 variants in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007;5(7):857-864.
87. Ku N-O, Lim JK, Krams SM, et al. Keratins as susceptibility genes for end-stage liver disease. *Gastroenterology*. 2005;129(3):885-893.
88. Alam H, Sehgal L, Kundu ST, Dalal SN, Vaidya MM. Novel function of keratins 5 and 14 in proliferation and differentiation of stratified epithelial cells. *Mol Biol Cell*. 2011;22(21):4068-4078.

89. Lloyd C, Yu QC, Cheng J, et al. The basal keratin network of stratified squamous epithelia: defining K15 function in the absence of K14. *J Cell Biol*. 1995;129(5):1329-1344.
90. Nickoloff BJ, Qin JZ, Chaturvedi V, Denning MF, Bonish B, Miele L. Jagged-1 mediated activation of notch signaling induces complete maturation of human keratinocytes through NF-kappaB and PPARgamma. *Cell Death Differ*. 2002;9(8):842-855.
91. Palazzo E, Morandi P, Lotti R, et al. Notch cooperates with survivin to maintain stemness and to stimulate proliferation in human keratinocytes during ageing. *Int J Mol Sci*. 2015;16(11):26291-26302.
92. Blanpain C, Lowry WE, Pasolli HA, Fuchs E. Canonical notch signaling functions as a commitment switch in the epidermal lineage. *Genes Dev*. 2006;20(21):3022-3035.
93. Rangarajan A, Talora C, Okuyama R, et al. Notch signaling is a direct determinant of keratinocyte growth arrest and entry into differentiation. *EMBO J*. 2001;20(13):3427-3436.
94. Chang F, Lee JT, Navolanic PM, et al. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: a target for cancer chemotherapy. *Leukemia*. 2003;17(3):590-603.
95. Romano R-A, Ortt K, Birkaya B, Smalley K, Sinha S. An active role of the ΔN isoform of p63 in regulating basal keratin genes K5 and K14 and directing epidermal cell fate. *PLoS One*. 2009;4(5):e5623.
96. Nguyen B-C, Lefort K, Mandinova A, et al. Cross-regulation between Notch and p63 in keratinocyte commitment to differentiation. *Genes Dev*. 2006;20(8):1028-1042.
97. Lessard JC, Coulombe PA. Keratin 16–null mice develop palmoplantar keratoderma, a hallmark feature of pachyonychia congenita and related disorders. *J Invest Dermatol*. 2012;132(5):1384-1391.
98. Fu DJ, Thomson C, Lunny DP, et al. Keratin 9 is required for the structural integrity and terminal differentiation of the palmoplantar epidermis. *J Invest Dermatol*. 2014;134(3):754-763.
99. Dinkova-Kostova AT, Holtzclaw WD, Cole RN, et al. Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. *Proc Natl Acad Sci U S A*. 2002;99(18):11908-11913.
100. Zieman AG, Poll BG, Ma J, Coulombe PA. Altered keratinocyte differentiation is an early driver of keratin mutation-based palmoplantar keratoderma. *Hum Mol Genet*. 2019;28(13):2255-2270.
101. Dellambra E, Golisano O, Bondanza S, et al. Downregulation of 14-3-3sigma prevents clonal evolution and leads to immortalization of primary human keratinocytes. *J Cell Biol*. 2000;149(5):1117-1130.
102. Benzinger A, Muster N, Koch HB, Yates JR, Hermeking H. Targeted proteomic analysis of 14-3-3 sigma, a p53 effector commonly silenced in cancer. *Mol Cell Proteomics*. 2005;4(6):785-795.
103. Margolis SS, Perry JA, Forester CM, et al. Role for the PP2A/B56delta phosphatase in regulating 14-3-3 release from Cdc25 to control mitosis. *Cell*. 2006;127(4):759-773.
104. Kim S, Wong P, Coulombe PA. A keratin cytoskeletal protein regulates protein synthesis and epithelial cell growth. *Nature*. 2006;441(7091):362-365.
105. Totaro A, Castellan M, Battilana G, et al. YAP/TAZ link cell mechanics to Notch signalling to control epidermal stem cell fate. *Nat Commun*. 2017;8:15206.
106. Cheng F, Eriksson JE. Intermediate filaments and the regulation of cell motility during regeneration and wound healing. *Cold Spring Harb Perspect Biol*. 2017;9(9):a022046.
107. Cerecedo D, Martínez-Vieyra I, Mondragõn R, Mondragõn M, González S, Galván IJ. Haemostatic role of intermediate filaments in adhered platelets: importance of the membranous system stability. *J Cell Biochem*. 2013;114(9):2050-2060.
108. Depianto D, Coulombe PA. Intermediate filaments and tissue repair. *Exp Cell Res*. 2004;301(1):68-76.
109. Eckes B, Colucci-Guyon E, Smola H, et al. Impaired wound healing in embryonic and adult mice lacking vimentin. *J Cell Sci*. 2000;113(13):2455-2462.
110. Walker JL, Bleaken BM, Romisher AR, Alnwibit AA, Menko AS. In wound repair vimentin mediates the transition of mesenchymal leader cells to a myofibroblast phenotype. *Mol Biol Cell*. 2018;29(13):1555-1570.
111. Rogel MR, Soni PN, Troken JR, Sitikov A, Trejo HE, Ridge KM. Vimentin is sufficient and required for wound repair and remodeling in alveolar epithelial cells. *FASEB J*. 2011;25(11):3873-3883.
112. Wu Y, Zhang X, Salmon M, Lin X, Zehner ZE. TGFβ1 regulation of vimentin gene expression during differentiation of the C2C12 skeletal myogenic cell line requires Smads, AP-1 and Sp1 family members. *Biochim Biophys Acta - Mol Cell Res*. 2007;1773(3):427-439.
113. Jiang P, Gil de Rubio R, Hrycaj SM, et al. Ineffectual AEC2-to-AEC1 differentiation in IPF: persistence of KRT8 hi transitional state. *Am J Respir Crit Care Med*. 2020.
114. Clevers HC, Bevins CL. Paneth cells: maestros of the small intestinal crypts. *Annu Rev Physiol*. 2013;75(1):289-311.
115. Ting H-A, von Moltke J. The immune function of tuft cells at gut mucosal surfaces and beyond. *J Immunol*. 2019;202(5):1321-1329.
116. Zhou Q, Toivola DM, Feng N, Greenberg HB, Franke WW, Bishr OM. Keratin 20 helps maintain intermediate filament organization in intestinal epithelia. *Mol Biol Cell*. 2003;14(7):2959-2971.
117. Noah TK, Shroyer NF. Notch in the intestine: regulation of homeostasis and pathogenesis. *Annu Rev Physiol*. 2013;75:263-288.
118. Jensen J, Pedersen EE, Galante P, et al. Control of endodermal endocrine development by Hes-1. *Nat Genet*. 2000;24(1):36-44.
119. Li HJ, Kapoor A, Giel-Moloney M, Rindi G, Leiter AB. Notch signaling differentially regulates the cell fate of early endocrine precursor cells and their maturing descendants in the mouse pancreas and intestine. *Dev Biol*. 2012;371(2):156-169.
120. Nakamura T, Tsuchiya K, Watanabe M. Crosstalk between Wnt and Notch signaling in intestinal epithelial cell fate decision. *J Gastroenterol*. 2007;42(9):705-710.
121. Sato T, Van Es JH, Snippert HJ, et al. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. *Nature*. 2011;469(7330):415-418.
122. Kabiri Z, Greicius G, Madan B, et al. Stroma provides an intestinal stem cell niche in the absence of epithelial Wnts. *Dev*. 2014;141(11):2206-2215.
123. van Es JH, Jay P, Gregorieff A, et al. Wnt signalling induces maturation of Paneth cells in intestinal crypts. *Nat Cell Biol*. 2005;7(4):381-386.
124. Baribault H, Penner J, Iozzo RV, Wilson-Heiner M. Colorectal hyperplasia and inflammation in keratin 8-deficient FVB/N mice. *Genes Dev*. 1994;8(24):2964-2973.
125. Toivola DM, Krishnan S, Binder HJ, Singh SK, Omary MB. Keratins modulate colonocyte electrolyte transport via protein mistargeting. *J Cell Biol*. 2004;164(6):911-921.

126. Asghar MN, Silvander JSG, Helenius TO, et al. The amount of keratins matters for stress protection of the colonic epithelium. *PLoS One*. 2015;10(5):e0127436.
127. van Es JH, de Geest N, van de Born M, Clevers H, Hassan BA. Intestinal stem cells lacking the Math1 tumour suppressor are refractory to Notch inhibitors. *Nat Commun*. 2010;1(2):18.
128. Milano J, McKay J, Dagenais C, et al. Modulation of notch processing by gamma-secretase inhibitors causes intestinal goblet cell metaplasia and induction of genes known to specify gut secretory lineage differentiation. *Toxicol Sci*. 2004;82(1):341-358.
129. Misiorek JO, Lähdeniemi IAK, Nyström JH, et al. Keratin 8-deletion induced colitis predisposes to murine colorectal cancer enforced by the inflammasome and IL-22 pathway. *Carcinogenesis*. 2016;37(8):777-786.
130. Zha JM, Li HS, Lin Q, et al. Interleukin 22 expands transit-amplifying cells while depleting Lgr5 + stem cells via inhibition of Wnt and Notch signaling. *CMGH*. 2019;7(2):255-274.
131. Brodsly NF, Bitman-Lotan E, Boico O, et al. The transcription factor Hey and nuclear lamins specify and maintain cell identity. *Elife*. 2019;8:e44745.
132. Petrovsky R, Großhans J. Expression of lamina proteins lamin and kugelkern suppresses stem cell proliferation. *Nucleus*. 2018;9(1):104-118.
133. Toribio-Fernández R, Herrero-Fernandez B, Zorita V, et al. Lamin A/C deficiency in CD4 $^{+}$ T-cells enhances regulatory T-cells and prevents inflammatory bowel disease. *J Pathol*. 2019;249(4):509-522.
134. Strnad P, Stumptner C, Zatloukal K, Denk H. Intermediate filament cytoskeleton of the liver in health and disease. *Histochem Cell Biol*. 2008;129(6):735–749.
135. Tao GZ, Toivola DM, Zhong B, et al. Keratin-8 null mice have different gallbladder and liver susceptibility to lithogenic diet-induced injury. *J Cell Sci*. 2003;116(Pt 22):4629-4638.
136. Chen Y, Guldiken N, Spurny M, et al. Loss of keratin 19 favours the development of cholestatic liver disease through decreased ductular reaction. *J Pathol*. 2015;237(3):343-354.
137. Tchorz JS, Kinter J, Müuller M, Tornillo L, Heim MH, Bettler B. Notch2 signaling promotes biliary epithelial cell fate specification and tubulogenesis during bile duct development in mice. *Hepatology*. 2009;50(3):871-879.
138. Vajro P, Ferrante L, Paolella G. Alagille syndrome: an overview. *Clin Res Hepatol Gastroenterol*. 2012;36(3):275-277.
139. Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. *Nat Genet*. 1997;16(3):235-242.
140. Kamath BM, Bauer RC, Loomes KM, et al. NOTCH2 mutations in Alagille syndrome. *J Med Genet*. 2012;49(2):138-144.
141. Inman JL, Robertson C, Mott JD, Bissell MJ. Mammary gland development: cell fate specification, stem cells and the microenvironment. *Development*. 2015;142(6):1028-1042.
142. Peuhu E, Virtakoivu R, Mai A, Warri A, Ivaska J. Epithelial vimentin plays a functional role in mammary gland development. *Development*. 2017;144(22):4103-4113.
143. Soady KJ, Kendrick H, Gao Q, et al. Mouse mammary stem cells express prognostic markers for triple-negative breast cancer. *Breast Cancer Res*. 2015;17(1).
144. Alexander CM, Goel S, Fakhraldeen SA, Kim S. Wnt signaling in mammary glands: plastic cell fates and combinatorial signaling. *Cold Spring Harb Perspect Biol*. 2012;4(10):a008037. https://doi.org/10.1101/cshperspect.a008037.
145. Raouf A, Zhao Y, To K, et al. Transcriptome analysis of the normal human mammary cell commitment and differentiation process. *Cell Stem Cell*. 2008;3(1):109-118.
146. Gu B, Watanabe K, Sun P, Fallahi M, Dai X. Chromatin effector Pygo2 mediates Wnt-notch crosstalk to suppress luminal/alveolar potential of mammary stem and basal cells. *Cell Stem Cell*. 2013;13(1):48-61.
147. Bouras T, Pal B, Vaillant F, et al. Notch signaling regulates mammary stem cell function and luminal cell-fate commitment. *Cell Stem Cell*. 2008;3(4):429-441.
148. Bentzinger CF, Wang YX, Rudnicki MA. Building muscle: molecular regulation of myogenesis. *EMBO Rep*. 2013;14(12):1062-1072.
149. Steinert PM, Chou YH, Prahlad V, et al. A high molecular weight intermediate filament-associated protein in BHK- 21 cells is nestin, a type VI intermediate filament protein: limited co- assembly in vitro to form heteropolymers with type III vimentin and type IV α-internexin. *J Biol Chem*. 1999;274(14):9881-9890.
150. Dahlstrand J, Lardelli M, Lendahl U. Nestin mRNA expression correlates with the central nervous system progenitor cell state in many, but not all, regions of developing central nervous system. *Dev Brain Res*. 1995;84(1):109-129.
151. Park D, Xiang AP, Mao FF, et al. Nestin is required for the proper self-renewal of neural stem cells. *Stem Cells*. 2010;28(12):2162-2171.
152. Yang J, Dominguez B, De Winter F, Gould TW, Eriksson JE, Lee KF. Nestin negatively regulates postsynaptic differentiation of the neuromuscular synapse. *Nat Neurosci*. 2011;14(3):324-330.
153. Sahlgren CM, Mikhailov A, Vaittinen S, et al. Cdk5 Regulates the Organization of Nestin and Its Association with p35. *Mol Cell Biol*. 2003;23(14):5090-5106.
154. Sahlgren CM, Pallari HM, He T, Chou YH, Goldman RD, Eriksson JE. A nestin scaffold links Cdk5/p35 signaling to oxidant-induced cell death. *EMBO J*. 2006;25(20):4808-4819.
155. Pallari HM, Lindqvist J, Torvaldson E, et al. Nestin as a regulator of Cdk5 in differentiating myoblasts. *Mol Biol Cell*. 2011;22(9):1539-1549.
156. Lindqvist J, Torvaldson E, Gullmets J, et al. Nestin contributes to skeletal muscle homeostasis and regeneration. *J Cell Sci*. 2017;130(17):2833-2842.
157. Philpott A, Porro EB, Kirschner MW, Tsai LH. The role of cyclin-dependent kinase 5 and a novel regulatory subunit in regulating muscle differentiation and patterning. *Genes Dev*. 1997;11(11):1409-1421.
158. Íková D, Soukup T, Mokrý J. Nestin expression reflects formation, revascularization and reinnervation of new myofibers in regenerating rat hind limb skeletal muscles. *Cells Tissues Organs*. 2009;189(5):338-347.
159. Ursitti JA, Lee PC, Resneck WG, et al. Cloning and characterization of cytokeratins 8 and 19 in adult rat striated muscle: interaction with the dystrophin glycoprotein complex. *J Biol Chem*. 2004;279(40):41830-41838.
160. Stone MR, O'Neill A, Lovering RM, et al. Absence of keratin 19 in mice causes skeletal myopathy with mitochondrial and sarcolemmal reorganization. *J Cell Sci*. 2007;120(22):3999-4008.
161. Butin-Israeli V, Adam SA, Goldman AE, Goldman RD. Nuclear lamin functions and disease. *Trends Genet*. 2012;28(9):464-471.
162. Dittmer TA, Misteli T. The lamin protein family. *Genome Biol*. 2011;12(5):222.
163. Lin F, Worman HJ. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem*. 1993;268(22):16321-16326.

164. Lin F, Worman HJ. Structural organization of the human gene (LMNB1) encoding nuclear lamin B1. *Genomics*. 1995;27(2):230-236.
165. Biamonti G, Giacca M, Perini G, et al. The gene for a novel human lamin maps at a highly transcribed locus of chromosome 19 which replicates at the onset of S-phase. *Mol Cell Biol*. 1992;12(8):3499-3506.
166. Furukawa K, Hotta Y. cDNA cloning of a germ cell specific lamin B3 from mouse spermatocytes and analysis of its function by ectopic expression in somatic cells. *EMBO J*. 1993;12(1):97-106.
167. Parry DA, Conway JF, Steinert PM. Structural studies on lamin. Similarities and differences between lamin and intermediate-filament proteins. *Biochem J*. 1986;238(1):305-308.
168. Kitten GT, Nigg EA. The CaaX motif is required for isoprenylation, carboxyl methylation, and nuclear membrane association of lamin B2. *J Cell Biol*. 1991;113(1):13-23.
169. Davies BSJ, Fong LG, Yang SH, Coffinier C, Young SG. The posttranslational processing of prelamin A and disease. *Annu Rev Genomics Hum Genet*. 2009;10(1):153-174.
170. Meshorer E, Gruenbaum Y. Gone with the Wnt/Notch: stem cells in laminopathies, progeria, and aging. *J Cell Biol*. 2008;181(1):9-13.
171. Zhang B, Yang Y, Keyimu R, Hao J, Zhao Z, Ye R. The role of lamin A/C in mesenchymal stem cell differentiation. *J Physiol Biochem*. 2019;75(1):11-18.
172. Bermeo S, Vidal C, Zhou H, Duque G. Lamin A/C acts as an essential factor in mesenchymal stem cell differentiation through the regulation of the dynamics of the Wnt/β-catenin pathway. *J Cell Biochem*. 2015;116(10):2344-2353.
173. Scaffidi P, Misteli T. Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. *Nat Cell Biol*. 2008;10(4):452-459.
174. Bennett CN, Longo KA, Wright WS, et al. Regulation of osteoblastogenesis and bone mass by Wnt10b. *Proc Natl Acad Sci U S A*. 2005;102(9):3324-3329.
175. Cho S, Vashisth M, Abbas A, et al. Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell-cycle arrest. *Dev Cell*. 2019;49(6):920-935.e5.
176. Swift J, Ivanovska IL, Buxboim A, et al. Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation. *Science*. 2013;341(6149):1240104.
177. Bertrand AT, Ziaei S, Ehret C, et al. Cellular microenvironments reveal defective mechanosensing responses and elevated YAP signaling in LMNA-mutated muscle precursors. *J Cell Sci*. 2014;127(13):2873-2884.
178. Zhang J, Yang H, Abali BE, Li M, Xia Y, Haag R. Dynamic mechanics-modulated hydrogels to regulate the differentiation of stem-cell spheroids in soft microniches and modeling of the nonlinear behavior. *Small*. 2019;15(30):e1901920.
179. Ho CY, Jaalouk DE, Vartiainen MK, Lammerding J. Lamin A/C and emerin regulate MKL1-SRF activity by modulating actin dynamics. *Nature*. 2013;497(7450):507-513.
180. Pellegrini C, Columbaro M, Capanni C, et al. All-trans retinoic acid and rapamycin normalize Hutchinson Gilford progeria fibroblast phenotype. *Oncotarget*. 2015;6(30):29914-29928.
181. Ivanovska IL, Swift J, Spinler K, Dingal D, Cho S, Discher DE. Cross-linked matrix rigidity and soluble retinoids synergize in nuclear lamina regulation of stem cell differentiation. *Mol Biol Cell*. 2017;28(14):2010-2022.
182. Wilhelmsson U, Stillemark-Billton P, Borén J, Pekny M. Vimentin is required for normal accumulation of body fat. *Biol Chem*. 2019;400(9):1157-1162.
183. Lieber JG, Evans RM. Disruption of the vimentin intermediate filament system during adipose conversion of 3T3-L1 cells inhibits lipid droplet accumulation. *J Cell Sci*. 1996;109(13):3047-3058.
184. Pendás AM, Zhou Z, Cadiñanos J, et al. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase–deficient mice. *Nat Genet*. 2002;31(1):94-99.
185. Bergo MO, Gavino B, Ross J, et al. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. *Proc Natl Acad Sci U S A*. 2002;99(20):13049-13054.
186. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. 2003;423(6937):293-298.
187. Goldman RD, Shumaker DK, Erdos MR, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2004;101(24):8963-8968.
188. Sola-Carvajal A, Revêchon G, Helgadottir HT, et al. Accumulation of progerin affects the symmetry of cell division and is associated with impaired Wnt signaling and the mislocalization of nuclear envelope proteins. *J Invest Dermatol*. 2019;139(11):2272-2280.e12.
189. Scaffidi P, Misteli T. Lamin A-dependent nuclear defects in human aging. *Science*. 2006;312(5776):1059-1063.
190. Choi H, Kim T-H, Jeong J-K, Strandgren C, Eriksson M, Cho E-S. Expression of the hutchinson-gilford progeria mutation leads to aberrant dentin formation. *Sci Rep*. 2018;8(1):15368.
191. Choi JY, Lai JK, Xiong Z-M, et al. Diminished canonical β-catenin signaling during osteoblast differentiation contributes to osteopenia in progeria. *J Bone Miner Res*. 2018;33(11):2059-2070.
192. Holaska JM, Kowalski AK, Wilson KL. Emerin caps the pointed end of actin filaments: evidence for an actin cortical network at the nuclear inner membrane. *PLoS Biol*. 2004;2(9):e231.
193. Salpingidou G, Smertenko A, Hausmanowa-Petrucewicz I, Hussey PJ, Hutchison CJ. A novel role for the nuclear membrane protein emerin in association of the centrosome to the outer nuclear membrane. *J Cell Biol*. 2007;178(6):897-904.
194. Capanni C, Coco R, Mattioli E, et al. Emerin-prelamin A interplay in human fibroblasts. *Biol Cell*. 2009;101(9):541-554.
195. Bione S, Maestrini E, Rivella S, et al. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet*. 1994;8(4):323-327.
196. Lee B, Lee TH, Shim J. Emerin suppresses Notch signaling by restricting the Notch intracellular domain to the nuclear membrane. *Biochim Biophys Acta - Mol Cell Res*. 2017;1864(2):303-313.
197. Markiewicz E, Tilgner K, Barker N, et al. The inner nuclear membrane protein Emerin regulates β-catenin activity by restricting its accumulation in the nucleus. *EMBO J*. 2006;25(14):3275-3285.
198. Kumeta M, Hirai Y, Yoshimura SH, Horigome T, Takeyasu K. Antibody-based analysis reveals "filamentous vs. non-filamentous" and "cytoplasmic vs. nuclear" crosstalk of cytoskeletal proteins. *Exp Cell Res*. 2013;319(20):3226-3237.
199. Hobbs RP, Depianto DJ, Jacob JT, et al. Keratin-dependent regulation of Aire and gene expression in skin tumor keratinocytes. *Nat Genet*. 2015;47(8):933-938.

200. Escobar-Hoyos LF, Shah R, Roa-Peña L, et al. Keratin-17 promotes p27KIP1 nuclear export and degradation and offers potential prognostic utility. *Cancer Res*. 2015;75(17):3650-3662.
201. Matsuyama M, Tanaka H, Inoko A, et al. Defect of mitotic vimentin phosphorylation causes microophthalmia and cataract via aneuploidy and senescence in lens epithelial cells. *J Biol Chem*. 2013;288(50):35626-35635.
202. Feng X, Coulombe PA. A role for disulfide bonding in keratin intermediate filament organization and dynamics in skin keratinocytes. *J Cell Biol*. 2015;209(1):59-72.
203. Feng X, Coulombe PA. Complementary roles of specific cysteines in keratin 14 toward the assembly, organization, and dynamics of intermediate filaments in skin keratinocytes. *J Biol Chem*. 2015;290(37):22507-22519.
204. Flitney EW, Kuczmarski ER, Adam SA, Goldman RD. Insights into the mechanical properties of epithelial cells: the effects of shear stress on the assembly and remodeling of keratin intermediate filaments. *FASEB J*. 2009;23(7):2110-2119.
205. Sivaramakrishnan S, Schneider JL, Sitikov A, Goldman RD, Ridge KM. Shear stress induced reorganization of the keratin intermediate filament network requires phosphorylation by protein kinase C ζ. *Mol Biol Cell*. 2009;20(11):2755-2765.
206. Patteson AE, Vahabikashi A, Pogoda K, et al. Vimentin protects cells against nuclear rupture and DNA damage during migration. *J Cell Biol*. 2019;218(12):4079-4092.
207. De Pascalis C, Pérez-González C, Seetharaman S, et al. Intermediate filaments control collective migration by restricting traction forces and sustaining cell-cell contacts. *J Cell Biol*. 2018;217(9):3031-3044.
208. Wickström SA, Niessen CM. Cell adhesion and mechanics as drivers of tissue organization and differentiation: local cues for large scale organization. *Curr Opin Cell Biol*. 2018;54:89-97.
209. Liu T, Guevara OE, Warburton RR, Hill NS, Gaestel M, Kayyali US. Regulation of vimentin intermediate filaments in endothelial cells by hypoxia. *Am J Physiol Physiol*. 2010;299(2):C363-C373.
210. Na N, Chandel NS, Litvan J, Ridge KM. Mitochondrial reactive oxygen species are required for hypoxia-induced degradation of keratin intermediate filaments. *FASEB J*. 2010;24(3):799-809.
211. Zamoner A, Pierozan P, Vidal LF, et al. Vimentin phosphorylation as a target of cell signaling mechanisms induced by 1α,25-dihydroxyvitamin D3 in immature rat testes. *Steroids*. 2008;73(14):1400-1408.
212. Zamoner A, Corbelini PF, Funchal C, Menegaz D, Barreto Silva FRM, Pessoa-Pureur R. Involvement of calcium-dependent mechanisms in T3-induced phosphorylation of vimentin of immature rat testis. *Life Sci*. 2005;77(26):3321-3335.
213. Zamoner A, Funchal C, Heimfarth L, Silva FRMB, Pessoa-Pureur R. Short-term effects of thyroid hormones on cytoskeletal proteins are mediated by GABAergic mechanisms in slices of cerebral cortex from young rats. *Cell Mol Neurobiol*. 2006;26(2):209-224.
214. Zanatta L, Goulart PB, Gonçalves R, et al. 1α,25-Dihydroxyvitamin D3 mechanism of action: modulation of L-type calcium channels leading to calcium uptake and intermediate filament phosphorylation in cerebral cortex of young rats. *Biochim Biophys Acta - Mol Cell Res*. 2012;1823(10):1708-1719.
215. Hiratsuka T, Bordeu I, Pruessner G, Watt FM. Regulation of ERK basal and pulsatile activity control proliferation and exit from the stem cell compartment in mammalian epidermis. *Proc Natl Acad Sci U S A*. 2020;117(30):17796-17807.
216. Seymour PA, Collin CA, Egeskov-Madsen ALR, et al. Jag1 modulates an oscillatory Dll1-Notch-Hes1 signaling module to coordinate growth and fate of pancreatic progenitors. *Dev Cell*. 2020;52(6):731-747.e8.
217. Toivola DM, Strnad P, Habtezion A, Omary MB. Intermediate filaments take the heat as stress proteins. *Trends Cell Biol*. 2010;20(2):79-91.
218. Hyder CL, Pallari HM, Kochin V, Eriksson JE. Providing cellular signposts–post-translational modifications of intermediate filaments. *FEBS Lett*. 2008;582(14):2140-2148.
219. Pallari HM, Eriksson JE. Intermediate filaments as signaling platforms. *Sci STKE*. 2006;2006(366):pe53.
220. Perlson E, Hanz S, Ben-Yaakov K, Segal-Ruder Y, Seger R, Fainzilber M. Vimentin-dependent spatial translocation of an activated MAP kinase in injured nerve. *Neuron*. 2005;45(5):715-726.
221. Liu CY, Lin HH, Tang MJ, Wang YK. Vimentin contributes to epithelial-mesenchymal transition ancer cell mechanics by mediating cytoskeletal organization and focal adhesion maturation. *Oncotarget*. 2015;6(18):15966-15983.
222. Runembert I, Queffeulou G, Federici P, et al. Vimentin affects localization and activity of sodium-glucose cotransporter SGLT1 in membrane rafts. *J Cell Sci*. 2002;115(4):713-724.
223. Kanugula AK, Dhople VM, Völker U, Ummanni R, Kotamraju S. Fluvastatin mediated breast cancer cell death: a proteomic approach to identify differentially regulated proteins in MDA-MB-231 cells. *PLoS One*. 2014;9(9):e108890.
224. Kaschula CH, Tuveri R, Ngarande E, et al. The garlic compound ajoene covalently binds vimentin, disrupts the vimentin network and exerts anti-metastatic activity in cancer cells. *BMC Cancer*. 2019;19(1):248.
225. Trogden KP, Battaglia RA, Kabiraj P, Madden VJ, Herrmann H, Snider NT. An image-based small-molecule screen identifies vimentin as a pharmacologically relevant target of simvastatin in cancer cells. *FASEB J*. 2018;32(5):2841-2854.
226. Bollong MJ, Pietilä M, Pearson AD, et al. A vimentin binding small molecule leads to mitotic disruption in mesenchymal cancers. *Proc Natl Acad Sci U S A*. 2017;114(46):E9903-E9912.
227. Noh H, Yan J, Hong S, et al. Discovery of cell surface vimentin targeting mAb for direct disruption of GBM tumor initiating cells. *Oncotarget*. 2016;7(44):72021-72032.

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