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REVIEW

Roles of vimentin in health and disease

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More than 27 yr ago, the vimentin knockout (*Vim*$^{-/-}$) mouse was reported to develop and reproduce without an obvious phenotype, implying that this major cytoskeletal protein was nonessential. Subsequently, comprehensive and careful analyses have revealed numerous phenotypes in *Vim*$^{-/-}$ mice and their organs, tissues, and cells, frequently reflecting altered responses in the recovery of tissues following various insults or injuries. These findings have been supported by cell-based experiments demonstrating that vimentin intermediate filaments (IFs) play a critical role in regulating cell mechanics and are required to coordinate mechanosensing, transduction, signaling pathways, motility, and inflammatory responses. This review highlights the essential functions of vimentin IFs revealed from studies of *Vim*$^{-/-}$ mice and cells derived from them.

Of the three cytoskeletal systems, intermediate filament (IF) proteins are encoded by the largest gene family. Comprised of >70 members, IFs show remarkable diversity in their sequences, expression patterns, and distribution in various tissues (Herrmann and Aebi 2016). Vimentin, a type III IF protein, is one of the most well-known and extensively studied members of the IF protein family, reflecting their assembly into major cytoskeletal systems in cells of mesenchymal and ectodermal origin. Vimentin IFs were originally described as 10-nm-diameter filaments in several types of cultured cells, including embryonic chicken cells, HeLa cells, and hamster and mouse embryonic fibroblasts (Taylor 1966; Goldman and Follett 1969; Ishikawa et al. 1969; Goldman 1971). Some early studies in various cell types proposed that IFs were a smaller form of microtubules or "minimicrotubules," slowing progress in the field for some time (Taylor 1966; Wisniewski et al. 1968). However, by the mid-1970s, fully polymerized vimentin IFs were isolated from cell-free preparations devoid of microtubules and actin filaments (Starger and Goldman 1977). These preparations could be depolymerized and repolymerized in vitro, demonstrating that their biochemical properties and structure were distinctly different from the other cytoskeletal systems (Zackroff and Goldman 1979). In 1983, the hamster vimentin gene was cloned and sequenced, further defining its unique structural properties (Quax et al. 1983). Subsequently, it was shown that vimentin is highly conserved, as it displays extensive sequence homology among species ranging from fish to humans (Herrmann and Aebi 2004; Hyder et al. 2008), suggesting essential evolutionarily conserved functions. However, vimentin's functional significance was seriously challenged when it was reported that genetically modified mice lacking vimentin (*Vim*$^{-/-}$ mice) develop and reproduce normally without an obvious phenotype (Colucci-Guyon et al. 1994). This outcome has been frequently taken as evidence that vimentin is of little physiological importance. However, soon after this initial report, investigators discovered a remarkable array of disease-related phenotypes linked to the *Vim*$^{-/-}$ mice (Tables 1, 2). This review intentionally focuses on the results obtained with this mouse model to provide an overview of the impressive diversity of phenotypes attributable to vimentin at the cell, tissue, and organ levels. In addition, it relates these phenotypes to alterations in cellular and molecular mechanisms using cells derived from *Vim*$^{-/-}$ mice (Fig. 1). Collectively, the information derived from studies involving *Vim*$^{-/-}$ mice has had a significant impact on the entire IF research field, has opened up new opportunities to study the structure and function of vimentin IFs, and has influenced the understanding of the pathogenesis of several diseases.

Vimentin is required for normal wound healing

One of the most profound and major defects analyzed in *Vim*$^{-/-}$ mice is the inability to heal wounds properly

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[*Keywords*: intermediate filaments; vimentin; vimentin-null mouse]

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Table 1. *A summary of the phenotypes and functions revealed by vimentin-null ($Vim^{-/-}$) mice*

	References
Cell proliferation, differentiation, migration, and tissue remodeling • Impaired wound healing in embryonic and adult mice • Impaired endothelial differentiation of endothelial stem cells • Impaired mechanical stability, migration, and contractile capacity in fibroblasts • Impaired hepatic stellate cell transdifferentiation • Impaired fibroblast proliferation and collagen organization • Impaired keratinocyte transdifferentiation and re-epithelialization • Protection from corneal fibrosis • Protection from pulmonary fibrosis	Eckes et al. 1998, 2000; Geerts et al. 2001; Lund et al. 2010; Bargagna-Mohan et al. 2012, 2015; dos Santos et al. 2015; Cheng et al. 2016; Li et al. 2017; Surolia et al. 2019
Vascular Functions • Marked leakiness of the vascular endothelium • Poorly developed vasculature with reduced branching • Impaired multilayer communication and structural homeostasis of the arterial wall • Partial resistance to atherosclerosis • Increased arterial stiffness • Altered flow-induced arterial remodeling • Impaired flow-induced dilation in mesenteric resistance arteries • Decreased velocity of leukocytes and transmigration through endothelial cells and translocation of VASP • Loss of cell rigidity in circulating lymphocytes • Defective lymphocyte adhesion and transcellular diapedesis at extravasation • Vascular endothelial cells from $Vim^{-/-}$ mice failed to form von Willebrand factor strings after histamine stimulation • Inability to completely close the ductus arteriosus	Henrion et al. 1997; Schiffers et al. 2000; Brown et al. 2001; Nieminen et al. 2006; Ishola et al. 2015; Boraas and Ahsan 2016; Antfolk et al. 2017; Langlois et al. 2017; Håversen et al. 2018; van Engeland et al. 2019; Salvador et al. 2021
Renal functions • Decreased Na–glucose cotransport activity in renal cells • Impaired recovery of Na–glucose cotransport following renal ischemia • Unable to survive 75% reduction of kidney mass; no lethality observed in WT littermates	Terzi et al. 1997; Runembert et al. 2002, 2004
Metabolism and fat accumulation • Decreased subendothelial lipid accumulation in atherosclerosis • Lower body mass index • Lower accumulation of body fat (both with normal and high-fat diet) • Defective ovarian steroidogenesis • Impaired lipolysis and hormone-sensitive lipase (HSL) translocation	Shen et al. 2010, 2012; Håversen et al. 2018; McDonald-Hyman et al. 2018; Kim et al. 2021

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Table 1. *Continued*

	References
• Low blood glucose and high blood triglycerides. • Reveal vimentin as a key metabolic and functional controller of Treg activity	
Viral and bacterial infections	Mor-Vaknin et al. 2013; dos Santos et al. 2015; Huang et al. 2016; Koch et al. 2020; Roy et al. 2020
• Protected against bacterial colitis • Neonatal mice from *E. coli* K1-induced bacterial meningitis • Resistance to influenza infection • Suppression of cytomegalovirus replication	
Tumorigenesis	Peuhu et al. 2017; Richardson et al. 2018; Berr et al. 2020
• No metastases in lung adenocarcinoma model • Mammary ductal outgrowth delayed with reduced tumor formation and attenuation of breast cancer stem cell-associated surface markers	
Nervous system (for other phenotypes in the nervous system, see Table 2)	Perlson et al. 2005; Triolo et al. 2012
• Thickened myelin sheaths • Inhibited retrograde transport of activated MAP kinase • Slow recovery from sciatic nerve crush	

(Fig. 2). In this regard, *Vim*$^{-/-}$ embryos fail to heal an excision wound within the time frame it takes for wild-type embryos to heal fully. Similar excision wound studies using adult *Vim*$^{-/-}$ mice also showed delays in the migration of fibroblasts into the wound site and subsequent wound contraction (Eckes et al. 2000). The latter is attributable to the delayed appearance of myofibroblasts. A more recent study showed that the *Vim*$^{-/-}$ mice display a general wound healing deficiency, occurring irrespectively of whether the wound is caused by excision, incision, or burning (Cheng et al. 2016). These deficiencies include slow scab formation, defective fibroblast functions, impaired inflammatory and immune responses, and faulty angiogenesis (Fig. 2).

Further insights into the migration defects in wound healing detected in the *Vim*$^{-/-}$ mice come from comparative studies of mouse embryonic fibroblasts (MEFs) derived from WT and *Vim*$^{-/-}$ mice. Compared with WT MEFs, the *Vim*$^{-/-}$ MEFs display reduced mechanical stability, motility, and directional migration toward chemoattractive stimuli (Eckes et al. 1998). From a mechanistic viewpoint, studies of *Vim*$^{-/-}$ MEFs revealed that the bidirectional interactions between vimentin IFs and the actomyosin network mediate cell motility (Jiu et al. 2015). Specifically, these interactions restrict the retrograde flow of actin and consequently control nuclear positioning during cell migration. This vimentin IF–actomyosin interaction also affects RhoA kinase signaling (Jiu et al. 2017). Vimentin IFs have also been shown to integrate mechanical stimuli from the environment and modulate the dynamics of both the microtubule and actomyosin networks (Gan et al. 2016; Costigliola et al. 2017). During single-cell migration, polymerized elongated vimentin IFs slow the actin retrograde flow rates, which buffer traction stresses. In contrast, actin flows are more than an order of magnitude faster in *Vim*$^{-/-}$ cells (Costigliola et al. 2017). These findings indicate that vimentin IFs are a load-bearing superstructure that restrains F-actin's retrograde flow and governs the alignment of traction stresses regulating cell migration. Using traction force microscopy and sharp tip atomic force microscopy, it has been shown that *Vim*$^{-/-}$ MEFs exhibit significant decreases in the stiffness of their cortical regions (Vahabikashi et al. 2019). These findings also help to explain why the migratory activity of *Vim*$^{-/-}$ MEFs is impaired and the wound fails to generate sufficient force for wound contraction. Apart from defects in fibroblast functions, the wound healing deficiencies in *Vim*$^{-/-}$ mice have also been related to defects in TGF-β signaling, epithelial-to-mesenchymal transition (EMT) (Cheng et al. 2016; Cheng and Eriksson 2017), and vascularization (Nieminen et al. 2006; Antfolk et al. 2017) as described below.

Vimentin is a key regulator of fibrosis

Given the role of vimentin IFs in wound healing, several laboratories have used *Vim*$^{-/-}$ mice in studies exploring the process of fibrosis, which is a consequence of dysregulated tissue repair involving the excessive deposition of

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Table 2. *The two-edged sword of vimentin in the nervous system*

Negative	• **Lower resistance of CNS to mechanical stress and ischemia** with altered gap junctional communication among astrocytes and decreased astrocyte glutamine levels and glutamate transport (Ding et al. 1998; Pekny et al. 1999a; Lundkvist et al. 2004; Li et al. 2008; Verardo et al. 2008; de Pablo et al. 2013; Wunderlich et al. 2015) • **Faster progression of some neurodegenerative diseases** (Macauley et al. 2011; Kraft et al. 2013) • **Increased loss and gain of sensorimotor neuronal connections, altered global functional connectivity, and impaired functional recovery after ischemic stroke,** despite increased glial and axonal plasticity responses (Aswendt et al. 2022)
Ambiguous	• **Attenuated reactive gliosis**, including reduced astrocyte process hypertrophy, up-regulation of 14-3-3 proteins, and Erk and c-fos activation (Pekny et al. 1999b; Wilhelmsson et al. 2004; Nakazawa et al. 2007; Sihlbom et al. 2007) • **Increased hippocampal neurogenesis (baseline, postischemic, and posttraumatic)**, reduced vesicle trafficking in astrocytes and Notch signaling to neural progenitor cells, and facilitated forgetting and altered long-term memory (Larsson et al. 2004; Potokar et al. 2007, 2010; Järlestedt et al. 2010; Wilhelmsson et al. 2012, 2019b; Lebkuechner et al. 2015) • **Slower astrocyte migration** (Lepekhin et al. 2001)
Positive	• **Reduced pathological neovascularization** in oxygen-induced retinopathy (Lundkvist et al. 2004) • **Reduced photoreceptor cell death and monocyte infiltration** in retinal degeneration (Nakazawa et al. 2007) • **Improved posttraumatic axonal and synaptic regeneration** (Menet et al. 2003; Wilhelmsson et al. 2004; Cho et al. 2005) • **Better integration of neural grafts and increased differentiation of transplanted neural stem cells into neurons and astrocytes** (Kinouchi et al. 2003; Widestrand et al. 2007; Wilhelmsson et al. 2012)

Examples of ambiguous, negative, and positive effects of vimentin absence in the CNS, illustrating possible adaptive and maladaptive roles of vimentin expression/up-regulation in given disease situations. Interestingly, attenuated astrocyte responses might result in a slower healing/restorative process and, in some situations, lead to better regeneration and functional outcome. In astrocytes, GFAP partially compensates for vimentin absence (Eliasson et al. 1999; Pekny et al. 1999b), and thus many of the phenotypes were observed only in $Vim^{-/-}$ mice lacking GFAP.

extracellular matrix (ECM) components by activated fibroblasts. Specifically, WT mice, but not $Vim^{-/-}$ mice, show increased collagen deposition following various pathophysiological insults known to cause fibrosis in WT animals. In general terms, fibrosis is associated with the loss of parenchymal cells and the disruption of tissue architecture, organ dysfunction, and, ultimately, organ failure. For example, in the lungs, fibrosis can be induced by exposure to bleomycin or asbestos. Interestingly, $Vim^{-/-}$ mice are protected from lung fibrosis in part due to a reduced inflammatory response, specifically a decrease in transforming growth factor β (TGF-β) (dos Santos et al. 2015). TGF-β1 is a major profibrogenic cytokine secreted by human and mouse alveolar epithelial cells in response to severe bleomycin- or asbestos-induced injury (Kim et al. 2006; Rogel et al. 2011). The TGF-β1–Smad pathway up-regulates vimentin expression as mouse alveolar epithelial cells undergo the EMT (Rogel et al. 2011). These results indicate that vimentin is required for the mesenchymal cell expansion associated with fibrosis. In complementary studies, human alveolar epithelial cells isolated from patients with idiopathic pulmonary fibrosis (IPF) show increased expression of vimentin, N-cadherin, and α-smooth muscle actin (SMA), all markers of the conversion to mesenchymal cells accompanying the EMT. Inhibition of TGF-β receptor kinase inhibits vimentin expression, causing the alveolar cells to revert to an epithelial phenotype (Kim et al. 2006; Marmai et al. 2011; Reyfman and Gottardi 2019).

The accumulation of fibroblasts leads to excessive collagen deposition and matrix remodeling, which distort the tissue architecture and contribute to the progressive decline in organ function. Notably, $Vim^{-/-}$ mice suppress collagen deposition and thereby maintain lung compliance (e.g., the mice show little change in lung stiffness) and function (dos Santos et al. 2015), protecting the host from lung fibrosis. Mechanistically, $Vim^{-/-}$ mice are protected in part because vimentin IFs stabilize collagen mRNAs, which are needed to promote collagen synthesis and collagen deposition (Challa and Stefanovic 2011). $Vim^{-/-}$ mice also fail to develop the renal fibrosis exhibited by WT mice following unilateral ureteral obstruction (UUO) (Wang et al. 2018). Similar to lungs, interstitial collagen deposition also decreases in $Vim^{-/-}$ mice following UUO.

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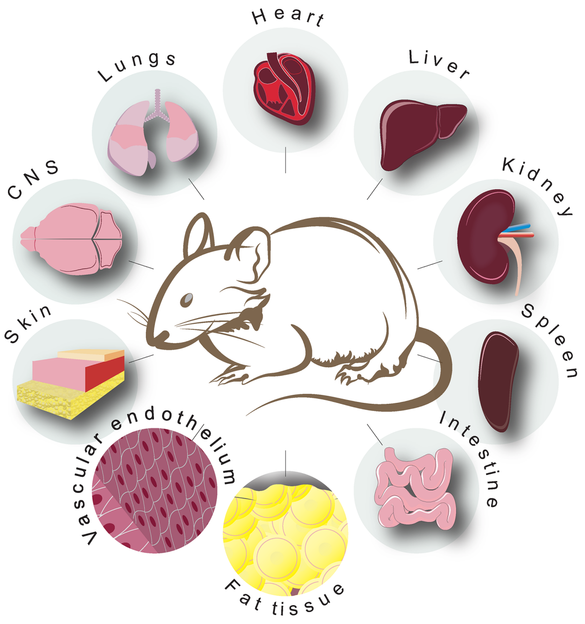

Figure 1. Overview of affected organs in mice lacking vimentin. The figure shows the various organs affected by vimentin gene ablation. Some phenotypes are apparent at steady state, but many phenotypes have been discovered when *Vim*$^{-/-}$ mice are subjected to stress, injury, or the modeling of different diseases.

Traditionally, aging and changes in inflammatory responses were considered key factors influencing whether wound healing leads to progressive fibrosis or ends with healthy wound repair (see "Vimentin Is Required for Normal Wound Healing" above). Studies using the *Vim*$^{-/-}$ mice reveal that vimentin can trigger maladaptive fibrotic responses that lead to dysregulated tissue repair and tissue destruction. The development of pharmacologic agents that selectively target vimentin to disrupt EMT, cell migration, and the organization and deposition of extracellular matrix proteins may help tip the balance between healthy wound repair and fibrosis.

Role of vimentin in the metastatic cascade

Vimentin is highly expressed in primary and metastatic tumors derived from epithelial tissues, which normally express keratin intermediate filaments. Vimentin expression in tumor tissue correlates with increased metastatic potential (Kidd et al. 2014; Liu et al. 2016) and poor overall survival in lung, prostate, and breast cancers (Domagala et al. 1990; Burch et al. 2013; Dauphin et al. 2013). Despite the abundance of clinical evidence supporting a link between vimentin expression and the metastatic process, a causal, in vivo link between vimentin and disease progression was not established until genetically engineered mouse cancer models using *Vim*$^{-/-}$ mice were established. For example, the *LSL-Kras*^{G12D}/*TP53*$^{fl/fl}$/*Vim*$^{-/-}$ mouse model has been used to demonstrate that vimentin is required for tumor growth and metastasis. Mechanistically, *Vim*$^{-/-}$ mice display increased survival rates and reduced tumor burden by inducing ferroptosis, an iron-dependent form of programmed cell death (Berr et al. 2020). In addition, the cell-autonomous ability of Luciferase-tagged vimentin-expressing Luc-KPV$^{+/+}$cells to metastasize can be assessed using an allograft tumor model. Luc-KPV$^{+/+}$cells metastasize to the lung, while vimentin-null (Luc-KPV$^{-/-}$) cells or tumor cells expressing a mutant form of vimentin that cannot assemble full-length vimentin IFs (Luc-KPV^{Y117L}) (Berr et al. 2020) fail to metastasize. In a complementary lung adenocarcinoma mouse model, *Kras*^{G12D}/*Lkb1*$^{fl/fl}$/*Vim*$^{-/-}$, vimentin-expressing, but not *Vim*$^{-/-}$ cancer-associated fibroblasts surround epithelial-like collective invasion packs to facilitate metastasis (Richardson et al. 2018; Sharma et al. 2019). Using the *Vim*$^{-/-}$ mice, these lung cancer models provide causal data that vimentin IFs are required for cancer metastasis and validate the robust clinical data linking vimentin to advanced-stage tumors and poor patient outcomes.

Studies using the *Vim*$^{-/-}$ mouse cancer models validate vimentin IFs' role in regulating the metastatic cascade: EMT, invasion, and migration (Fig. 3; Kidd et al. 2014). This is also supported by cell biological studies, which demonstrate that the up-regulation of vimentin expression in epithelial-derived tumor cells is a prerequisite for EMT induction (Kidd et al. 2014; Virtakoivu et al. 2015; Cheng et al. 2016; Peuhu et al. 2017; Wang et al. 2018). Vimentin expression and the accompanying EMT are induced by transforming growth factor β1 (TGF-β1) stimulation (Rogel et al. 2011), Snail overexpression (Cano et al. 2000), ZEB2 overexpression (Bindels et al. 2006), and Slug phosphorylation by ERK (Virtakoivu et al. 2015) in mouse and human epithelial-derived carcinoma cell lines. Lung epithelial cells treated with TGF-β1 rapidly induce vimentin expression via a Smad-binding element located in the 5′ promotor region of the *VIM* gene (Rogel et al. 2011). Upon the assembly of vimentin IFs, these lung epithelial cells adopt a mesenchymal phenotype. Microinjection of vimentin is sufficient to rapidly induce mesenchymal features in epithelial cells, such as a change in cell shape, loss of desmosomes, and increased cell motility (Mendez et al. 2010). Due to their role in the EMT, it is not surprising that vimentin IFs also play pivotal roles in the ability of cells to invade their surrounding matrix. This is supported by the finding that vimentin IFs facilitate the formation of invadopodia required for cancer cell extravasation and invasion for the initiation of metastasis (Sutoh Yoneyama et al. 2014). Mechanistically, intact vimentin IFs are required to elongate invadopodia, since depleting vimentin with siRNA or disrupting filaments with a dominant-negative probe prevents the elongation (Schoumacher et al. 2010). The unique biophysical properties of vimentin IFs likely enable the cancer cell to breach the basement membrane. These properties include strain stiffening and enhanced resistance to bending and stretching mechanical stresses (Janmey et al. 1991; Guzmán et al. 2006; Köster et al. 2015). Vimentin IFs contribute to tumor tissue stiffening (Rathje et al. 2014; Northey et al. 2017). This is supported by the observation that highly invasive breast carcinoma cells devoid of vimentin

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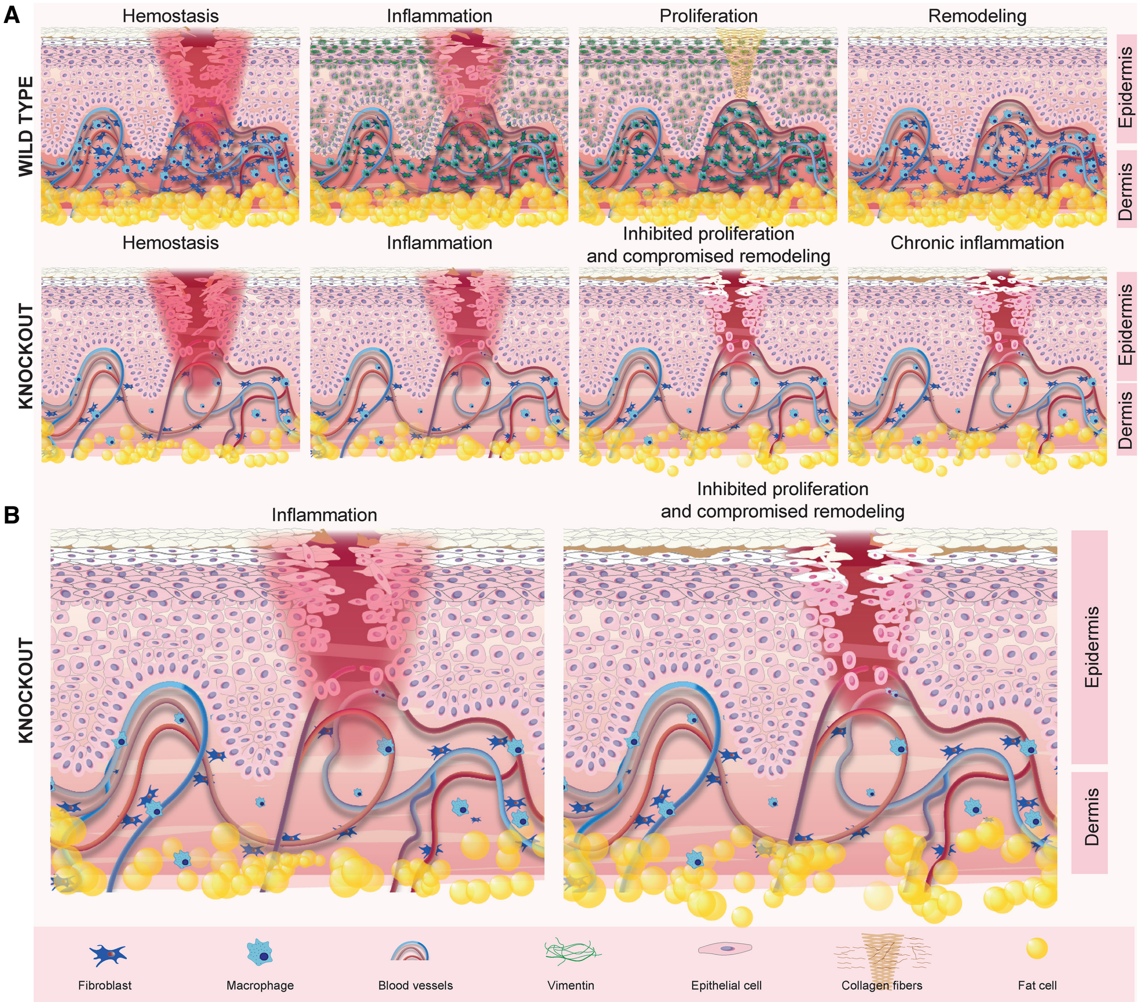

Figure 2. Severely compromised wound healing in mice lacking vimentin. (*A*) Perturbed wound healing has been one of the more significant phenotypes ascribed to *Vim*$^{-/-}$ mice. The figure describes normal wound healing (*top* panel) and the wound healing defects in *Vim*$^{-/-}$ mice (*bottom* panel). It has been demonstrated that the inhibited wound healing in *Vim*$^{-/-}$ mice is due to lost coordination and processing of cellular activities that are key for normal wound healing: fibroblast proliferation, collagen deposition, modeling keratinocyte transdifferentiation, re-epithelialization, angiogenesis, and vascularization. The figure demonstrates that loss of vimentin disrupts all of these functions, leading to slow, poor, and incomplete wound healing. The phenotype is similar for incision, excision, and burn wounds. As these wound models are very different in their character, the observations demonstrate that vimentin has a general role in determining the progression of epidermal regeneration regardless of the type of epidermal injury. The figure also illustrates a loss of fat accumulation in the *Vim*$^{-/-}$ mice, a constitutive defect in these mice that may have several ramifications for the affected tissues. Active research on *Vim*$^{-/-}$ mice has recapitulated many of the cellular signaling and other mechanisms underlying the observed defects. These are described in detail in different parts of this review. (*B*) A close-up of the proliferation stage depicts all the different cells and processes that vimentin is facilitating.

are more pliant and less contractile, and lose directional persistence of migration (Mendez et al. 2010; Zhu et al. 2011; Liu et al. 2015).

The experimental data obtained from the *Vim*$^{-/-}$ mouse and various cell culture studies demonstrate that vimentin IFs are unequivocally major initiators of the EMT and, as such, play a crucial role in tumor progression and metastasis. Furthermore, these data support the hypothesis that modifying the dynamics and mechanotransduction of cancer cells by altering the expression and assembly of vimentin IFs impairs their proliferation, migration, and invasion in 2D and 3D environments. To develop targeted cancer therapy, additional research is required to understand the complexity of vimentin IFs' roles in the metastatic cascade.

Vimentin regulates inflammatory responses

There is evidence that vimentin IFs play essential roles in coordinating signaling pathways that regulate inflammatory response mediator levels in resident tissue recruit inflammatory cells from the blood, including lymphocytes and phagocytes (Cheng and Eriksson 2017). Following

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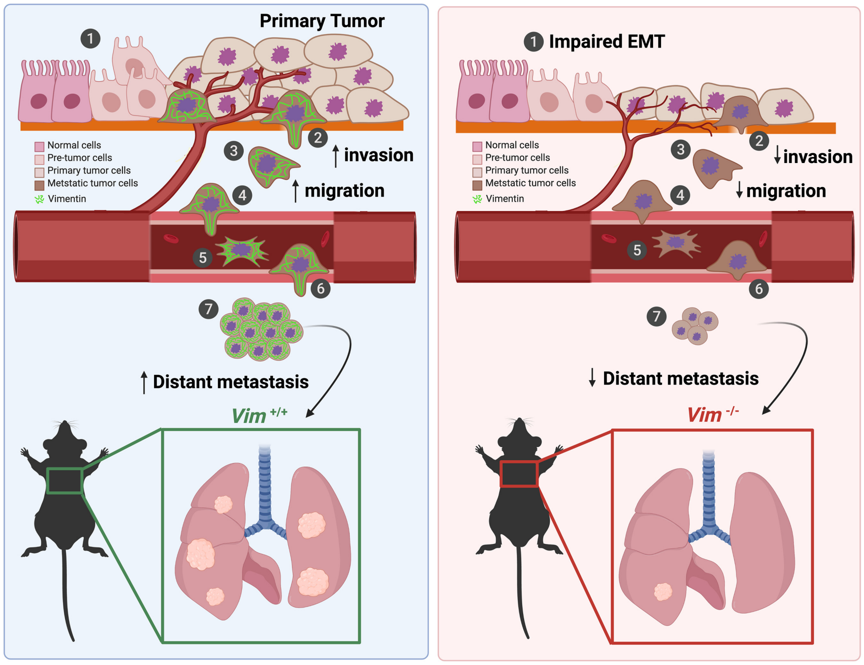

Figure 3. Vimentin plays a role in the metastatic cascade. (1) Vimentin is expressed in epithelial-derived tumor cells as they undergo the epithelial-to-mesenchymal transition (EMT). EMT is characterized by the down-regulation of epithelial markers (such as E-cadherin and keratins) and the up-regulation of mesenchymal markers (such as vimentin). (2) The migration of metastatic tumor cells away from the primary tumor is mediated by the formation of lamellipodia. Vimentin IFs play an integral role in lamellipodia formation and maintenance of cell polarity in migrating cells. (3) Dynamic reorganization of vimentin IFs in the lamellipodia is necessary for the formation of cellular polarity, leading to an increase in migration. (2, 4, and 6). Vimentin is required for invadopodia maturation. In *Vim*$^{-/-}$ mice, there was a significant decrease in the formation of mature invadopodia, cell migration, tumor growth, and distant metastasis.

leukocyte adhesion to blood vessels, both the leukocytes and the endothelial cells form microvilli that elongate and embrace the cells; these microvilli are enriched in vimentin but not in actin or tubulin. This process is followed by the penetration of leukocytes through the endothelial cell cytoplasm (Nieminen et al. 2006). Given this involvement of vimentin, it has been of interest to study the inflammatory response in *Vim*$^{-/-}$ mice. The results show that lymphocyte homing at peripheral lymph nodes and spleen is reduced in *Vim*$^{-/-}$ mice. Furthermore, ICAM-1 and VCAM-1 expression and clustering are strongly reduced in *Vim*$^{-/-}$ endothelial cells, and *Vim*$^{-/-}$ lymphocytes cannot correctly polarize and maintain directional movement (Nieminen et al. 2006). Leukocytes derived from *Vim*$^{-/-}$ mice (Nieminen et al. 2006) also fail to form the docking/transmigration cup as was originally described in normal leukocytes (Carman and Springer 2004).

These defects are likely related to the finding that in normal WT mice, vimentin IFs typically provide lymphocytes with structural support by regulating their mechanical deformations during chemokine-induced polarization and migration through pores in the endothelium. In support of this, there is a pronounced reorganization of vimentin IFs in circulating lymphocytes in WT mice, and this reorganization plays an essential role in extravasation (Brown et al. 2001). In agreement with this finding, the restructuring of vimentin IFs induced by the phosphoinositide 3-kinase γ (PI3Kγ)–Akt signaling pathway is required for the chemokine-induced transmigration of leukocytes to sites of inflammation (Barberis et al. 2009). Additional support for the critical role of vimentin IFs in lymphocyte migration comes from the finding that vimentin IFs are located in macrophage filopodia and podosomes. Podosomes are dynamic cell adhesion structures involved in the directional motility and transmigration of myeloid cells in WT mice (Calle et al. 2006). Moreover, vimentin binds to fimbrin, a major focal adhesion protein in mouse macrophages (Correia et al. 1999). The comparative studies of *Vim*$^{-/-}$ and WT mice demonstrate the essential roles of vimentin IFs in immune cell functions related to migration, extravasation, homing, and target recognition.

Vim$^{-/-}$ mice have also provided important insights into the role of vimentin IFs in regulating the activation of the NLRP3 inflammasome. This large multiprotein complex regulates proinflammatory cytokines, specifically IL-1β and IL-18. Lipopolysaccharide (LPS) is a potent inducer of inflammation and a known activator of the NLRP3 inflammasome (dos Santos et al. 2012). Interestingly, *Vim*$^{-/-}$ mice are protected from LPS-induced injury, and this may be related to the fact that they exhibit decreased caspase-1 activity and reduced IL-1β levels (dos Santos et al. 2015). Moreover, experimental reconstitution of bone marrow from *Vim*$^{-/-}$ donor mice into irradiated WT recipient mice prevents the secretion of IL-1β following the induction of injury. In vitro experiments further demonstrate that vimentin directly interacts with NLRP3 and caspase-1 and serves as a protein scaffold on which the NLRP3 inflammasome is assembled (dos Santos et al. 2015). In addition, disrupting vimentin IF organization in macrophages with withaferin A (a compound known to disrupt vimentin IF organization in fibroblasts) (Grin et al. 2012) abolishes the formation of NLRP3 inflammasomes (dos Santos et al. 2015; Lang et al. 2018). In agreement with these findings, vimentin IFs interact with macrophage inhibitory factor (MIF), which is also required for NLRP3 inflammasome activation (Lang et al. 2018). These studies demonstrate that vimentin IFs are needed for the assembly of the NLRP3 inflammasome protein complex in the innate immune response system (dos Santos et al. 2015; Lang et al. 2018).

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Another way vimentin IFs regulate inflammation involves regulatory T cells (Tregs). Tregs are a specialized subpopulation of T cells that function to suppress the immune response, preventing autoimmune and inflammatory disorders (Prigge et al. 2020). When Tregs interact with an antigen-presenting cell (APC), vimentin IFs reorganize to form a superstructure known as the distal pole complex (DPC) that modulates the suppressive activity of Tregs. Although Tregs have not yet been analyzed in *Vim*$^{-/-}$ mice, it is interesting to note that WT Tregs silenced for vimentin expression were significantly better at suppressing alloreactive T cell priming in a murine model "graft versus host" disease (GVHD) (McDonald-Hyman et al. 2018). These studies provide a proof of principle that disrupting vimentin IFs is a feasible and translationally relevant method to enhance Treg therapy of GVHD (McDonald-Hyman et al. 2018). This link has been reinforced by a study showing clear up-regulation of vimentin in polarized Treg cells (Mohammad et al. 2018).

In addition to releasing cytokines and growth factors, inflammatory macrophages or phagocytes also generate nitric oxide (NO) and reactive oxygen species (ROS), which strongly influence the physiological states of neighboring cells and tissues. Therefore, it has been interesting to study macrophages derived from *Vim*$^{-/-}$ mice. The results have shown that the *Vim*$^{-/-}$ macrophages produce elevated amounts of ROS and NO (Mor-Vaknin et al. 2013) when compared with WT macrophages derived from WT mice in which ROS production is suppressed by interaction with the p47phox active subunit of the NADPH oxidase (Sumimoto 2008; Mor-Vaknin et al. 2013). Thus, the loss of vimentin IFs causes enhanced ROS production in macrophages, resulting in oxidative damage in surrounding tissues. ROS promotes proinflammatory signaling in macrophages (Håversen et al. 2018) and is linked to endothelial dysfunction (Langlois et al. 2017). Further evidence that vimentin IFs regulate ROS-mediated inflammatory responses comes from a study of dextran sodium sulfate-induced colitis in *Vim*$^{-/-}$ mice. The results demonstrate that *Vim*$^{-/-}$ mouse phagocytes increase the production of ROS and NO, causing more inflammatory damage to the intestines of the *Vim*$^{-/-}$ mice than WT controls. This same study shows an essential role for vimentin IFs in regulating bacterially induced inflammatory responses (Mor-Vaknin et al. 2013).

Numerous comparative studies of *Vim*$^{-/-}$ and WT mice reveal roles for vimentin IFs in many important functions of immune cells related to cellular localization and sequestration of signaling and other key molecules. Given that vimentin IFs are regulated by numerous post-translational modifications triggered by immune cell signaling involving factors such as RhoA kinase, PKA, and PKC; and that they interact with key signaling and sensory systems such as the integrins, NLRP3, caspase1, and 14-3-3 (for review, see Hyder et al. 2011), it is not surprising that these type III intermediate filament cytoskeletal components play essential roles in regulating immune cell functions. Therefore, *Vim*$^{-/-}$ mice have been invaluable in identifying the critical and diverse roles that vimentin IFs play in immune responses. Importantly, these studies provide a rationale for developing novel therapeutic approaches targeting the regulation of vimentin expression to modulate immune cell responses.

Vimentin regulates the vascular endothelium

Early studies of *Vim*$^{-/-}$ mice show that vimentin IFs are essential for modulating vascular constriction or tone. Evidence supporting this function derives from partial nephrectomy studies in WT and *Vim*$^{-/-}$ mice. In WT mice, this surgery triggers rapid and sustained vasodilation of the renal vascular system, permitting the animals to survive, while the same surgical procedure results in renal failure and death in 100% of *Vim*$^{-/-}$ mice (Terzi et al. 1997). This study also describes a concurrent elevation of endothelin-1 (ET-1) synthesis, which causes a reduction in NO levels. Notably, the death of the *Vim*$^{-/-}$ mice is entirely prevented by administering an endothelin receptor antagonist (Terzi et al. 1997). These data demonstrate that vimentin IFs modulate vascular tone through the endothelin–NO axis.

Related primarily to tissue homeostasis and tissue repair, the vasculature of *Vim*$^{-/-}$ mouse embryos is poorly developed compared with WT mouse embryos, as evidenced by markedly fewer vessels with less branching. In addition, aortic ring assays prepared from adult *Vim*$^{-/-}$ mice treated with VEGF show significant decreases in blood vessel sprout number and length compared with WT controls (Antfolk et al. 2017). In response to hemodynamic stress, *Vim*$^{-/-}$ mice also have defects in arterial remodeling and vascular smooth muscle cell differentiation (van Engeland et al. 2019).

Another phenotype detected in *Vim*$^{-/-}$ mice is impaired endothelial barrier function, manifested as a leaky and poorly developed vasculature (Nieminen et al. 2006; Antfolk et al. 2017). Not surprisingly, this appears to be related to poor healing of the endothelium of *Vim*$^{-/-}$ mice (Boraas and Ahsan 2016), which in turn is associated with the dysregulated generation of granulation tissue as well as abnormal angiogenic sprouting (for review, see Dave and Bayless 2014). Similarly, the absence of vimentin in Müller cells of the *Vim*$^{-/-}$ mouse retina resulted in reduced pathological vascularization after retinal ischemia—specifically, decreased ability of newly formed vessels to traverse the inner limiting membrane of the retina and invade the vitreous body (Lundkvist et al. 2004).

The impairment of angiogenesis and endothelial cell functions in *Vim*$^{-/-}$ mice has been linked to the role of vimentin in the Notch signaling pathway. Specifically, vimentin IFs bind to and regulate the signal strength of the proangiogenic Notch ligand, Jagged (Antfolk et al. 2017). Mechanistically, this modulation of signal strength has been related to the shear stress-induced phosphorylation of serine-38 in the N-terminal domain of vimentin. This phosphorylated vimentin interacts with Jagged1 and increases Notch activation potential (van Engeland et al. 2019). Therefore, the abnormal remodeling of the arterial walls of *Vim*$^{-/-}$ mice likely stems from reduced Jagged1–Notch transactivation strength, which in turn

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disrupts lateral signal induction through the arterial wall (van Engeland et al. 2019).

Apart from Notch signaling, other activities mediated by vimentin IFs may influence the properties of the vasculature in *Vim*$^{-/-}$ mice. It is known, for example, that vimentin IFs are generally involved in mechanosensing and plasticity through their interactions with focal adhesions (FAs) and the actomyosin network (Gregor et al. 2014; Shen et al. 2021). In addition, live-cell observations of endothelial cells expressing fluorescently tagged vimentin show that shear stress causes rapid deformation of vimentin IF networks, suggesting a role in mechanosensing and mechanotransduction (Helmke et al. 2000, 2001). Indeed, *Vim*$^{-/-}$ mice have elevated levels of phosphorylated FA kinase and its targets, Src and ERK1/2 (Langlois et al. 2017). This signaling defect, along with reduced Jagged1–Notch transactivation (van Engeland et al. 2019), has been postulated to associate with increased carotid stiffness, contractility, and endothelial dysfunction independent of blood pressure and the collagen/elastin ratio. This increase in arterial stiffness in *Vim*$^{-/-}$ mice involves changes in vasomotor tone and organization of the endothelial basement membrane (Langlois et al. 2017; van Engeland et al. 2019).

Vimentin plays a role in fat metabolism, lipid droplet homeostasis, and body weight

Vimentin IFs form a complex cage surrounding the lipid droplets in adipocytes. The vimentin IFs associated with this cage are linked to the lipid droplets (LDs) by perilipin to form the "LD–PLIN–vimentin connection," and vimentin IFs are thought to be involved in the formation of LDs (Franke et al. 1987; Heid et al. 2014). Based on these findings, it was interesting to determine the impact of the complete absence of vimentin expression on the overall physiology of adipocytes and LDs. In this regard, comparative morphological studies of WT and *Vim*$^{-/-}$ mice show a reduction in the size of adipocytes and their constituent LDs in the absence of vimentin IFs (Shen et al. 2010). *Vim*$^{-/-}$ mice fed a standard diet gained less body weight compared with WT controls, and the lower body weight and lower body mass index of *Vim*$^{-/-}$ mice is due primarily to the lower accumulation of body fat (Wilhelmsson et al. 2019c).

The absence of vimentin also is connected to partial resistance to atherosclerosis induced by the transfer of *Vim*$^{-/-}$ mouse-derived bone marrow to bone marrow-depleted *Vim*$^{+/+}$ mice deficient in the low-density lipoprotein receptor (Håversen et al. 2018). After these mice are fed an atherogenic diet, lipid accumulation below the endothelium of the aortic wall decreases despite increased expression of oxidative stress markers and proinflammatory cytokines by the *Vim*$^{-/-}$ macrophages. Similar results are obtained by feeding an atherogenic diet to *Vim*$^{-/-}$ mice made hypercholesterolemic by infection with an adeno-associated virus containing a gain-of-function proprotein convertase (PCSK9) (Håversen et al. 2018). These studies suggest that vimentin has a proatherogenic role by regulating inflammatory responses in macrophages during atherogenesis (Håversen et al. 2018).

The loss of the vimentin IF cage surrounding LDs in *Vim*$^{-/-}$ mice also affects lipolysis. In WT cells, energy stored in fat is released as fatty acids and cholesterol through lipolysis, controlled mainly by the sympathetic nervous system and insulin. Thus, catecholamines, acting through β-adrenergic receptors, activate adenylyl cyclase, raise intracellular concentrations of cyclic AMP, and stimulate cyclic AMP-dependent protein kinase (PKA) (Duncan et al. 2007). In turn, PKA phosphorylates hormone-sensitive lipase (HSL), the main fatty acid-mobilizing enzyme that facilitates the transfer of cholesterol to mitochondria (Kraemer and Shen 2002). Importantly, there is evidence that vimentin IFs participate in lipolysis through direct, hormonally regulated interactions with HSL (Shen et al. 2003, 2010). Studies of *Vim*$^{-/-}$ mice also lend significant support for the function of vimentin IFs in lipolysis, as they have a reduced influx of cholesterol into the mitochondria located in both the adrenal glands and ovaries, causing decreases in corticosterone and progesterone (Shen et al. 2012). Vimentin IFs influence lipolysis by interacting with the β3-adrenergic receptor, influencing the stimulation and subsequent activation of ERK. In this regard, a proteomics study showed vimentin IFs associated with the β3-adrenergic receptor following its activation. In addition, depletion of vimentin with shRNA completely inhibited β3-adrenergic receptor-mediated ERK activation and significantly reduced lipolysis in WT mice (Kumar et al. 2007). Thus, vimentin IFs appear to be necessary for the mobilization of cholesterol from lipid droplets to mitochondria for steroidogenesis and overall lipid droplet homeostasis. It is possible that the smaller body size of *Vim*$^{-/-}$ mice (Wilhelmsson et al. 2019c) is connected to the defect in cell size regulation and mTORC1 signaling recently reported in cells from *Vim*$^{-/-}$ mice (Mohanasundaram et al. 2021). The functional connections between lipid storage and vimentin IFs revealed by comparative studies of WT and *Vim*$^{-/-}$ mice may be related to the first vimentin mutation reported in humans, one manifestation of which is lipodystrophy (Cogné et al. 2020; Eriksson 2020).

Interestingly, male *Vim*$^{-/-}$ mice, but not female *Vim*$^{-/-}$ mice, show increased mortality, but the cause of death is unknown (Wilhelmsson et al. 2019c). However, since *Vim*$^{-/-}$ mice have a decreased production of corticosterone (Shen et al. 2012), the main glucocorticoid regulating energy, immune reactions, and stress responses, it is interesting to speculate that the increased mortality of *Vim*$^{-/-}$ males reflects their higher susceptibility to environmental stress (Wilhelmsson et al. 2019c).

The two-edged sword of vimentin in the central nervous system

Vimentin is expressed in multiple cell types of the nervous system, including neurons, astrocytes, other glial cell types, endothelial cells, neural progenitor cells, and immature neurons. *Vim*$^{-/-}$ mice show hypermyelination

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of peripheral nerves and, despite the fact that myelin-forming Schwann cells normally express vimentin, this phenotype seems to be caused by Schwann cell-extrinsic mechanisms that remain to be identified (Triolo et al. 2012). *Vim*$^{-/-}$ mice also show slower neurite outgrowth and a slower recovery of sensation following sciatic nerve crush (Perlson et al. 2005).

Vimentin is an important component of the cytoplasmic IFs of astrocytes. These cells play key roles in the organization of the CNS and control many functions of the brain, spinal cord, and retina in health and disease (Pekny and Pekna 2014; Pekny et al. 2016, 2019). The up-regulation of vimentin and glial fibrillary acidic protein (GFAP; another type III IF protein), as well as nestin and synemin, the IF proteins of astrocytes, is the hallmark of astrocyte reactivity and reactive gliosis in response to injury, ischemia, or neurodegeneration (Hol and Pekny 2015). The reactivity of astrocytes in *Vim*$^{-/-}$ mice is attenuated after neurotrauma (Wilhelmsson et al. 2004), and the migratory speed of *Vim*$^{-/-}$ astrocytes is decreased (Lepekhin et al. 2001).

In *Vim*$^{-/-}$ mice, GFAP can partially compensate for the absence of vimentin (Eliasson et al. 1999; Pekny et al. 1999b), and thus many revealing phenotypes of vimentin deficiency become apparent only in *Vim*$^{-/-}$ mice on a *GFAP*$^{-/-}$ background; i.e., in mice with astrocytes that completely lack cytoplasmic IFs (nestin or synemin cannot form IFs in *GFAP*$^{-/-}$*Vim*$^{-/-}$ astrocytes).

In *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice, astrocytes are present in normal numbers and form normally tiled cellular domains. Upon injury, however, *GFAP*$^{-/-}$*Vim*$^{-/-}$ astrocytes fail to develop their typical hypertrophy of main astrocyte processes (Wilhelmsson et al. 2004) and exhibit other signs of attenuated reactive gliosis, including decreased ERK and c-FOS activation (Nakazawa et al. 2007) or less prominent up-regulation of the 14-3-3 adapter proteins (Sihlbom et al. 2007). While retinal ischemia induces increased stiffness of endfeet and inner processes of retinal Müller cells in WT mice, it fails to do so in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice (Lu et al. 2011).

The finding that astrocyte reactivity is attenuated in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice with slower wound healing after brain and spinal cord trauma (Pekny et al. 1999b; Wilhelmsson et al. 2004) has raised the question of whether the slower healing/restorative process might support better regeneration and lead to a better functional outcome (Pekny and Pekna 2014). Indeed, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice are both worse and better off depending on the specific situation (Table 2).

On the one hand, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show lower resistance of the CNS to mechanical stress (Lundkvist et al. 2004; Verardo et al. 2008) and ischemia (Ding et al. 1998; Li et al. 2008; de Pablo et al. 2013; Wunderlich et al. 2015). Ischemic stroke, when induced in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice, results in a larger tissue loss, with less efficient endothelin-3-induced blockage of gap junction communication among astrocytes (Li et al. 2008), decreased astrocyte glutamine levels (Pekny et al. 1999a), decreased glutamate transport capacity (Li et al. 2008) and lower resistance to oxidative stress (de Pablo et al. 2013), showing that both vimentin and GFAP are important for the neuroprotective functions of astrocytes in acute ischemic stroke. Similarly, fewer cells of the inner retina of *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice survive after retinal ischemia reperfusion (Wunderlich et al. 2015). Interestingly, the absence of vimentin and GFAP does not affect the tissue loss in photothrombotic brain injury (Liu et al. 2014) or neonatal hypoxic–ischemic brain injury (Järlestedt et al. 2010), indicating that the effect of reactive gliosis at the acute stage after injury depends on the lesion type and might differ between immature and adult brains. *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show an altered response of astrocytes to neuronal degeneration and exhibit a faster progression of Alzheimer's and Batten disease in mouse models (Macauley et al. 2011; Kraft et al. 2013; Kamphuis et al. 2015). The regeneration after sciatic nerve crush in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice takes longer, but the resulting outcome is not worse (Berg et al. 2013). Remodeling of the corticospinal tract and axonal regeneration after a photothrombotic stroke takes longer, and it was unclear whether it reaches the same level as in WT mice (Liu et al. 2014). The most recent study demonstrated that after brain injury, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice showed maladaptive neuronal connectivity associated with impaired functional recovery; i.e., increased synaptic plasticity in the perilesional region and increased loss and gain of neuronal connections in sensorimotor networks (Aswendt et al. 2022).

On the other hand, pathological neovascularization that accompanies oxygen-induced retinopathy is reduced in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice (Lundkvist et al. 2004), and so is photoreceptor cell death and monocyte infiltration in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice subjected to sodium hyaluronate-induced retinal degeneration (Nakazawa et al. 2007). Moreover, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show increased hippocampal neurogenesis in an unchallenged situation (Larsson et al. 2004; Wilhelmsson et al. 2012) with an effect on memory extinction, potentially attributable to the increased rate of reorganization of the hippocampal circuitry (Wilhelmsson et al. 2019b), increased neurogenesis after ischemia (Järlestedt et al. 2010) and neurotrauma (Wilhelmsson et al. 2012), and improved posttraumatic regeneration of neuronal axons and synapses (Menet et al. 2003; Wilhelmsson et al. 2004; Cho et al. 2005). *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show reduced Notch signaling from astrocytes to neural stem cells (Wilhelmsson et al. 2012; Lebkuechner et al. 2015), a major inhibitory axis controlling adult neurogenesis, and it has been shown that intracellular vesicle trafficking in astrocytes depends on vimentin, GFAP, and also nestin (Potokar et al. 2007, 2010; Vardjan et al. 2012; Wilhelmsson et al. 2019a; Lasič et al. 2020). Interestingly, the CNS environment of *GFAP*$^{-/-}$ mice is also more supportive of integration and survival of neural grafts (Kinouchi et al. 2003) and supports increased neuronal and astrocyte differentiation of transplanted neural stem cells (Widestrand et al. 2007), indicating that a reduction in the graft-induced reactive gliosis might be the way to improve the success of transplantation of neural grafts or neural progenitor cells in the CNS. However, it remains to be established to what extent the improved graft integration results from attenuated reactive gliosis and to what extent it is the direct consequence of the altered Notch

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signaling (and possibly other signaling) between host astrocytes and grafted progenitor cells.

Conclusion

It is quite obvious that the *Vim*$^{-/-}$ mouse model has dramatically advanced our understanding of the molecular and cellular functions of not only vimentin IFs but of cytoplasmic IFs in general. As vimentin is expressed in multiple cell types of mesodermal and ectodermal origin, it is perhaps not surprising that the *Vim*$^{-/-}$ mice show a remarkable repertoire of phenotypes. *Vim*$^{-/-}$ mice have been instrumental in linking vimentin IFs to physiologic and pathophysiologic functions related to tissue repair and wound healing; fibrosis; angiogenesis; tumorigenesis; digestive diseases, including Crohn's disease and colitis; inflammatory functions; and host response to infections. Changes in cell morphology, adhesion, stiffness, and migration are commonly reported phenotypes associated with *Vim*$^{-/-}$ mice. These phenotypes have been linked to reduced wound healing capacity and an inability to properly remodel capillaries and arteries, leading to impaired vascular functions. Some of these phenotypes reflect altered cell activation and cell dynamics, as well as a compromised ability to respond to environmental and physiologic stresses that disrupt tissue integrity. Other phenotypes have positive outcomes, such as improved regenerative responses in the CNS. Thus, by observing stress resilience and tissue repair in the *Vim*$^{-/-}$ mouse model, important information has been gained on the functions of vimentin and the mechanisms underlying stress and regenerative responses. While the impairment in vimentin-mediated signaling and other functions often results in detrimental phenotypes, depending on the context, elimination of vimentin has also had favorable impacts on certain conditions. For example, certain diseases involve vimentin-mediated maladaptive responses and have consequences that are inhibited or blunted by the absence of vimentin. This review is focused on the impact of the absence of vimentin. In the future, it will be of great interest to compare the effects of loss- or gain-of-function mutations in mouse models. Examples include engineering mice carrying mutations in the vimentin gene at one or more of its numerous phosphorylation sites involved in regulating its assembly states; e.g., phosphovimentin-deficient mice. This approach has already provided insights into the regulatory function of vimentin during development (Matsuyama et al. 2013; Tanaka et al. 2015; Chen et al. 2018; de Pablo et al. 2019). In addition, studies of mice carrying the vimentin mutations known to cause human diseases could also prove to be very useful in defining specific pathways involved in the vimentin-associated pathologies (Muller et al. 2009; Cogné et al. 2020). Notably, there is renewed interest in extracellular vimentin, first reported over two decades ago (Evans et al. 1993), and its ability to act as a danger-associated molecular pattern (DAMP) receptor (Yu et al. 2018). Extracellular vimentin represents an understudied but important area of investigation.

By cataloging the characteristics of *Vim*$^{-/-}$ mice, researchers have provided a biological context in which drugs and other therapies targeting intermediate filaments can be developed and tested. However, a limitation of the constitutive ablation of vimentin in mice has been the inability to assess the effects of tissue-specific gene ablation. Therefore, an important next step for the field will be the generation of tissue-specific and inducible ablation of vimentin in mice. Another area of research yet to be explored is that vimentin is frequently expressed in early development and later replaced with cell-specific IF proteins such as desmin in muscle (Vaittinen et al. 1999) or neurofilament triplet proteins in neurons (Kirkcaldie and Dwyer 2017). This transition is a gradual process. Moreover, while purified vimentin can self-assemble in vitro, it should be pointed out that it is frequently found as part of IF heteropolymers in the native state of cells and tissues (Herrmann and Aebi 2000). Therefore, it would be interesting to determine whether there is compensatory up-regulation or early onset of expression of other IF types during differentiation in the *Vim*$^{-/-}$ mouse model. The physiological consequences of the changes in IF gene expression at the wrong times in development may ultimately reflect alterations in the specific mechanical and signaling properties of different IF cytoskeletal networks (Chang and Goldman 2004; Etienne-Manneville 2018; Patteson et al. 2020).

It is interesting to note that reports of human diseases associated with vimentin mutants are strikingly rare. This may partly reflect dire consequences resulting in early termination. There has been little information reflecting on the possible phenotypes one should expect when screening for vimentin mutations. The data from vimentin-deficient mice should be invaluable in determining the types of phenotypes that might be expected in any future screening approaches.

Although the primary goal of this review has been to demonstrate the consequences of knocking out vimentin expression at a more organismic level, it is worthwhile to speculate on the basic cellular and biochemical mechanisms that might help explain the broad range of phenotypes reported in *Vim*$^{-/-}$ mice. One of the most obvious functions attributed to vimentin IFs at the cellular level is their role in regulating cells' mechanical and motile properties. For example, it has been shown that vimentin-null MEFs exhibit defective directional cell motility in 2D culture assays (Mendez et al. 2010). In contrast, in 3D transwell migration assays, the *Vim*$^{-/-}$ MEFs move faster through small pores but experience a dramatic increase in nuclear rupture and DNA damage repair (Patteson et al. 2019). It has also been demonstrated that the force exerted on soft substrates is greatly diminished in *Vim*$^{-/-}$ MEFs and that both their cytoplasmic stiffness and cortical stiffness are significantly reduced (Guo et al. 2014; Hu et al. 2019; Vahabikashi et al. 2019). These alterations are likely related to the recent discovery that vimentin IFs and F-actin form interpenetrating networks in the cell cortex, and that vimentin IFs regulate the dynamics of actin subunit exchange (Wu et al. 2022). These findings could have significant impacts during early development, when individual cells participate in various forms of active

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migration through various types of 3D networks. The biochemical and physical properties of vimentin IFs assembled in vitro from purified vimentin have also revealed remarkable strain-stiffening properties (Janmey et al. 1991; Qin et al. 2009) when subjected to forces that would typically rupture F-actin and microtubules. Therefore, it is likely that a combination of these basic properties of vimentin IF contributes significantly to the wide range of phenotypes seen in *Vim*$^{-/-}$ mice.

In almost three decades since the *Vim*$^{-/-}$ mouse model was introduced, many investigators have defined functional roles for vimentin in numerous organ, tissue, and cell systems using *Vim*$^{-/-}$ mice. The large amount of data that has accumulated should put to rest any remaining notions that vimentin IFs are dispensable members of the cytoskeletal repertoire of mammalian systems.

Competing interest statement

The authors declare no competing interests.

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