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**Abstract**

Vimentin, an abundant cytoplasmic intermediate filament protein, is recognized for its important role in stabilizing intracellular structure. Vimentin has been recognized for its mechanical role in cell plasticity and stress absorbers. Additionally, the functions of vimentin, similar to all other cytoplasmic intermediate filaments, are correlated to its ability to interact with cellular components responsible for signaling as well as kinases, therefore exerting control on gene regulatory networks. Moreover, several studies reveal a novel form of vimentin present at the surface of the plasma membrane or released in the extracellular environment in different physiological and pathological conditions. Based on data pertaining to vimentin's location outside of the cell, novel functions have emerged. The vimentin promoter is complex and appears to be controlled by a combination of positive and negative regulatory elements. In this review, we first present the involvement of these regulatory elements as well as epigenetic regulation of vimentin in different physiological and pathological contexts, including cell growth, cell differentiation, cancer, epithelial to mesenchymal transition and viral infection. Furthermore, this review also analyzes the secretion of vimentin, its presence at the cell surface, the role of extracellular vimentin as a specific marker, its function as a receptor for the von Willebrand factor as well as the entry of viruses, requirements for pathogen invasion, transcellular migration, and the immune response. Finally, a discussion is featured regarding the delocalization of vimentin that may contribute to diseases and disorders.

**Key words**

Cytoskeleton, Intermediate filaments, Post-translational modifications, Epithelial to mesenchymal transition, Viral infection.

**Abbreviations**

**Akt1**, RAC-alpha serine/threonine-protein kinase
**AP-1,** activating protein-1
**ASE,** anti-silencer element
**CaMKII,** Calcium/calmodulin-dependent protein kinase II
**Cdk1,** cyclin-dependent kinase 1
**Cdk5,** cyclin-dependent kinase 5
**DS,** distal silencing element
**EMT,** epithelial-mesenchymal transition
**EPHB3,** ephrin type-B receptor 3
**EZH2,** enhancer of zeste homolog 2
**GC,** GC–rich box
**GlcNAc,** N-acetylglucosamine
**H4TF1,** histone 4 transcription factor 1
**H3K4me1,** mono-methylated histone H3 lysine 4.
**H3K4me2,** di-methylated histone H3 lysine 4.
**H3K27me3,** lysine 27 residues of histone H3 trimethylation
**HTLV-1,** human T-cell leukemia virus type I
**IF,** intermediate filament
**lncRNA,** long non-coding RNA
**LSD1,** lysine-specific demethylase 1
**miR,** MicroRNA
**MAPKAP-KII,** mitogen-activated protein kinase-activated protein kinase-2
**MoAb,** monoclonal antibody
**NE2,** negative element 2
**NF-κB,** nuclear factor kappa-light-chain-enhancer of activated B cells
**PAK,** p21-activated kinase
**PEA3,** polyoma enhancer activator 3
**PKA**, cAMP-dependent protein kinase A
**PKC**, protein kinase C
**Plk-1**, polo like kinase 1
**PS,** proximal silencing element
**PSGL-1,** P-selectin glycoprotein ligand-1
**RNF208,** RING finger protein 208
**ROCK**, Rho-associated protein kinase.
**SOCS1,** suppressor of cytokine signaling protein 1
**TNIP1,** TNF-α induced protein 3 interacting protein 1
**ULFs,** unit-length filaments
**vWF,** von Willebrand factor

## 1. Introduction

Intermediate filaments (IFs) constitute a multigenic family whose members are expressed in a cell-specific manner. Intracellular IFs, having a size between that of actin filaments and microtubules, are comprised of several distinct tissue-specific proteins. The coiled-coil alpha-helical structure responsible for polymerization into individual 10 nm filaments, is composed of a sequence conservation that defines an extensive gene family, which includes nuclear lamins, found universally in metazoans, and cytoplasmic IFs, which are known to be quite diverse and capable of forming cell type-specific networks within animal cells [1–4].

Among IF genes, sequence homologies are concentrated in the coding region whereas regulatory sequences are considerably more divergent. From an evolutionary point of view, vimentin emerged before other type III IF genes that could be derived from a vimentin-like ancestor [5]. Under normal physiological conditions, vimentin IFs are required for mesenchymal cell plasticity. Furthermore, they are instrumental in ensuring the migration of cancer cells following epithelial-mesenchymal transition (EMT) [6].

The importance of EMT is initially revealed during gastrulation due to its role in the transformation of polarized epithelial cells into migratory mesenchymal cells, which subsequently form the embryonic and extra-embryonic mesoderm. The EMT is a highly conserved cellular program that occurs during several critical stages of embryonic development and, as such, heavily contributes to the formation and in the differentiation of multiple tissues and organs. In addition, it has been implicated in promoting carcinoma invasion and metastasis [7]. Therefore, the mesenchymal state relies on the ability of cells to migrate to distant organs and maintain stemness, enabling subsequent differentiation into multiple cell types during development.

Embryonic development is characterized by a transient expression of vimentin in mesodermal and neural precursor cells from the early embryo. Subsequently, vimentin disappears from these cells, which in turn begin to accumulate other IFs. The first IFs are detectable in oocytes and are composed of cytokeratins 5, 6, 8 and 16. Low expression of cytokeratins 8 and 18 can be detected in early cleavage and morula stage of mouse embryos [8–10]. In the central and peripheral nervous system, neurofilament expression is preceded by that of vimentin, and both types of IFs coexist within the same cell for a short period of time [11,12]. Without vimentin, the activation of glial fibrillary acidic protein in satellite glial cells could not occur [13,14].

Vimentin is expressed during the early stages of development of the embryo within highly plastic precursor cells whereas in postnatal life its expression is limited to endothelial cells, fibroblasts, and smooth muscle cells. While vimentin expression is restricted to some cell types in adult animals, it can be re-induced *in vivo* during regeneration such as during epithelial wound healing [15], mammary gland regeneration [16], muscle regeneration [17,18], liver regeneration [19], nervous system regeneration

[20] and in many cell types upon in cell culture such as muscle satellite cells and epithelial cells culture [21–23]. This reinduction of vimentin is related to the EMT, cell migration, cell contraction and cell-extracellular matrix interaction. It appears that vimentin would be necessary during the repair to control the synthesis and organization of cell-specific IF [24–26].

In contrast to the idea that the IF network in the cytoplasm is stable based on the *in vitro* IF assembly studies, *in vivo* pulse chase experiments indicate that the IF network is dynamics. IFs assemble from a soluble pool of tetrameric IF precursors/subunits [27–30]. Vimentin IF assembly/disassembly is an important structural requirement to execute cellular functions such as cell migration and cell division. It consists of the constant exchange between polymerized vimentin and soluble vimentin precursors, referred to as unit-length filaments (ULFs) in cells, that permit efficient remodeling of the IF network according to physiological stimuli or diverse stresses [27]. Post-translational modifications (PTMs) such as phosphorylation of vimentin is involved in vimentin assembly/disassembly and function [28,31,32]. In addition, the vimentin network can be disassembled by proteolysis, and the cleavage of vimentin can occur through the actions of enzymes such as caspase, calpain and viral proteases, demonstrating their influence on vimentin IF function [33–36].

Vimentin also serves as a scaffold for many other proteins and participates in the regulation of cell migration, adhesion, and division through the direct interaction with two other major filamentous components, *i.e.* actin filaments and microtubules [37–39]. Vimentin is enriched in F-actin interactome during metaphase and is actively involved in actin cortex organization, mechanics and mitosis in a plectin-dependent manner [37,38]. Vimentin interacts intracellularly with plectin, acting as a cytoskeletal cross-linker for the three major components of the cytoskeleton which are in turn important for the localization and dynamics of these cytoskeletal systems and cell morphogenesis [40,41]. It has been shown that vimentin IFs can bind to microtubules [39]. Underneath the plasma membrane, vimentin interacts with integrin subunits such as β1 and β3 integrin, and is involved in cell adhesion in a phosphorylation-dependent manner [42–44]. It has been further demonstrated that phosphorylated vimentin interacts with signaling molecules such as 14-3-3, beclin 1, Akt1, involving cellular functions such as autophagy and cell migration [45–47]. In addition, vimentin interacts with many other partners such as desmin, synemin, GFAP, and nestin; additional IF types [26,48,49].

The invalidation of the vimentin gene in mice has yielded surprising results. Firstly, vimentin knock-out mice have been reported to develop and reproduce without an obvious phenotype [50]. Further detailed analysis of vimentin knock-out mice revealed the abnormalities in their cells and tissues, including defects in migration and scarring [15], wound healing [51], lipid metabolism [52], inflammation and immune responses [53,54], glia and neuronal functions [13,20,55] and arterial stiffness [56,57], highlighting the subtle role of vimentin in several biological processes [26,58,59]. In humans, a number of IFs mutation-associated phenotypes have been identified, often linked to mechanical or metabolic stresses [60–62]. As described in a recent report, a 39-year-old patient possessing a de novo

heterozygous missense variant (c.1160 T>C-p.Leu387Pro) exhibited a multisystem disorder associated with frontonasal dysostosis and premature aging [63]. Moreover, two other missense variants (c.451G>A-p.Glu151Lys; c.623A>G-Gln208Arg) [64,65] and one frameshift mutation (c.15del-p.Val6fs) [66] in the human vimentin gene have also been identified in individuals diagnosed with cataracts. Similarly, in 2008, Bornheim et al [67] demonstrated that transgenic mice possessing a dominant vimentin R113C point mutation develop cataracts.

The functionalities of IFs are directly associated to their interactions with signaling molecules and cell kinases, which subsequently allows for their control of gene regulatory networks [68]. As a member of the "immediate early genes" family, vimentin expression rapidly increases in response to viral infection and inflammatory stimuli, which may further promote viral entry. Moreover, vimentin is overexpressed in various epithelial cancers, including prostate cancer, breast cancer, malignant melanoma, gastrointestinal tumors, tumors of the central nervous system, and lung cancer, which clearly demonstrates the underlying role of vimentin in cancer (see reviews) [7,26,49,69]. Recent data have revealed novel roles of vimentin at the cell surface as well as in the extracellular environment. This review will focus on the regulation of vimentin and its involvement in different cellular processes as well as pathologies, focusing particularly on cell surface and extracellular vimentin.

## 2. The molecular mechanism of vimentin expression

### 2.1. The vimentin promoter is composed of multiple regulatory elements

The vimentin gene has been mapped to chromosome 10p12 in humans and to chromosome 2A in mice [70–72]. It has been cloned and extensively characterized in several vertebrate organisms such as humans, mice, hamsters and chickens [73–81].

The vimentin gene belongs to the family of immediate-early genes that are rapidly activated when cells are stimulated from quiescence to mitosis [75,79,82,83]. Enhancer binding sites as well as negative elements have been characterized in human, hamster and chicken genes [84–89]. While vimentin expression is restricted to some cell types in animals, it can be re-induced in most cell types upon *in vitro* cell culture as well as in pathogenic situations. Two enhancers, the distal one containing a tandem of the AP-1/Jun binding site whereas the proximal one consists of NF-κB binding sites, are involved in the control of vimentin gene expression. These enhancers hold the potential to explain one of the molecular mechanisms through which the vimentin gene is a mitogen-inducible gene [86,90,91]. Cellular factors related to the NF-κB family are required for the induction of the vimentin gene by the tumor promoter phorbol 12-myristate 13-acetate and by the human T-cell leukemia virus type I (HTLV-1) tax gene product. The regulation of vimentin expression requires additional regulatory elements, including upstream silencer and desilencer elements, in order to induce the appropriate expression of the gene in accordance with the cellular circumstances [92–94]. **Figure 1** presents the human vimentin promoter that is composed of the multiple regulatory elements. The following paragraphs summarize

the involvement of these binding sites and their corresponding activating or repressing factors in the regulation of vimentin during cell growth, cell and tissue differentiation, cancer, EMT as well as viral infection.

### 2.2. Regulation of vimentin in cell growth

Within the IF family, vimentin has been observed to exhibit a complex pattern with tissue- and development-specific expression. Vimentin is initially largely expressed in the embryo and becomes progressively limited to cells belonging to the mesenchymal lineage. Vimentin is expressed in the vast majority of cultured cells. In these cells, vimentin expression is regulated by the cell cycle [75], growth factors such as TGFβ1, FGF and PDGF [95], and the INF-γ cytokine [96]. This regulation involves the tandem site AP-1, which binds heterodimers of basic, leucine-zipper (bZIP) proteins of either Jun (c-Jun, JunB, JunD), Fos (cFos , FosB, Fra1 and Fra2), ATF (ATF-1, ATF-2)/CREB, or homodimers of Jun/Jun [97,98]. In addition to this inducible site, the vimentin promoter requires the binding of transcription factors Sp1/Sp3 on the first GC-box [99,100]. The deletion of this box considerably reduces the level of transcription of the promoter [100]. Lastly, c-Jun, or its assumed dominant negative mutant TAM67, is capable of regulating vimentin gene expression through a direct interaction with Sp1 when the latter is bound to GC-box 1 [101].

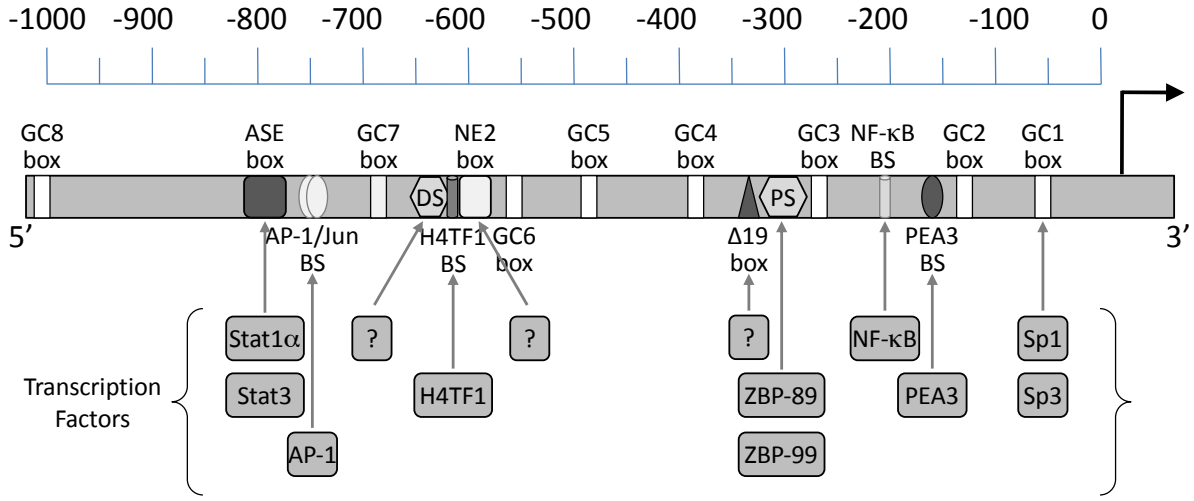


***Figure 1. A diagram representation of binding sites (BS) of transcription factors in the 5'-end of the human vimentin gene.*** *The position of regulatory elements, GC boxes, PEA3 binding site, NF-κB binding site, PS, Δ19 box, NE2 box, H4TF1 binding site, DS, AP-1/jun binding site, and ASE box are indicated in the figure. 8* ***GC–rich boxes*** *are described [99] but only the most proximal box 1 (GC1) is indispensable for promoter activation. GC boxes can bind Sp1 or Sp3 transcriptional activators [100]. The* ***PEA3*** *binding site (-173/-159) subgroup belongs to the Ets transcription factor family and has been identified as being overexpressed in multiple cancers [102]. The members of Ets family are responsible for inducing cell growth, invasion, and migration in various tumor cells, which subsequently causes tumor development, metastasis, and drug resistance. The* ***NF-κB*** *binding site (-230/-224) comprises a group of transcription factors involved in immune and stress responses, while its abnormal regulation leads to cancer, inflammatory and autoimmune diseases. In the case of the human vimentin promoter, this binding site of NF-κB has been identified as mediating the transactivation effect of the Tax protein from the HTLV-I virus [90]. The* ***PS*** *(-329/-289) and the* ***DS*** *(-645/-631) are proximal and distal silencing elements, respectively, responsible for down-regulating the human vimentin promoter [99].*

*The **H4TF1** binding site (-642/-617), the histone 4 transcription factor 1 and **NE2** box (-616/-589) are involved in the downregulation of vimentin gene expression during skeletal muscle differentiation, close to the DS [103]. The **Δ19** has been reported to contain a region exerting a negative effect in the context of a heterologous promoter [87], but has a positive effect in the context of its normal vimentin promoter [104]. The **AP-1/Jun** binding site (-765/-751) is assembled from jun-jun, jun-fos, or jun-ATF family protein homo- or heterodimers. AP-1 is among the class of basic leucine zipper (bZIP) transcription factors. The **ASE** (-815/-775) has no enhancer property by itself, but can override the effect of the proximal (PS) and distal (DS) silencer elements [105]. The ASE anti-silencer element specifically binds Stat1α or Stat3 [105]. Activated Stat3 can interact with ZBP-89, resulting in the binding to the proximal silencing element in order to overcome its repressor effect [106]. **GC**, GC rich box; **PEA3**, Polyoma enhancer activator 3; **NF-κB**, nuclear factor kappa-light-chain-enhancer of activated B cells; **PS**, proximal silencing element; **NE2**, negative element 2; **H4TF1**, Histone 4 transcription factor 1; **DS**, Distal silencing element; **AP-1**, Activating protein-1; **ASE**, anti-silencer element; **BS**, binding site.*

### 2.3. Regulation of vimentin in cell and tissue differentiation

Vimentin is expressed in migrating mesenchymal cells and this expression is often decreased to facilitate the actions of tissue-specific IF proteins such as that of desmin in muscle. The down-regulation of positive transcription factors such as Sp1/Sp3, c-jun and Stat3 cannot solely explain the total extinction of vimentin expression in differentiated cells. Several studies [104,107–109] have revealed that PS, one of the two silencer elements (PS and DS) present in the vimentin promoter (**Figure 1**), is able to bind ZBP-89, a zinc finger transcription factor from the Kruppel-like family, and repress known target genes. Both ZBP-89 and its homolog ZBP-99 can inhibit the role of Sp1 in activating the vimentin promoter. This is made possible through an interaction with Sp1 that blocks its ability to form the necessary interaction with the transcriptional machinery responsible for vimentin promoter activation. This repressing factor can compete with Sp1 for the binding of the transcription factor hTAFII130, which belongs to the basal transcriptional complex [109]. Overexpression of hTAFII130 is capable of reversing the repression caused by ZBP-89 on the vimentin promoter, suggesting that ZBP-89 represses Sp1 through an interference of the required Sp1 and hTAFII130 interaction. In addition, ZBP-89 functions as an adaptor by recruiting histone deacetylase 1 to the vimentin promoter. By modifying the acetylation status of core histones and altering the local chromatin structure, histone deacetylases have an influential role in repressing target gene expression [108]. Treatment of Trichostatin A, a histone deacetylase inhibitor, can relieve the repression effects of both ZBP-89 and histone deacetylase 1. It has been reported that ZBP-89 contributes to the down-regulation of the vimentin gene during myogenesis [110]. Additionally, it has been observed that H4TF1 (-642/-617), the histone 4 transcription factor 1 and a 105-kDa unknown factor binding to NE2 (-616/-589) are involved in the down-regulation of vimentin gene expression during skeletal muscle differentiation, close to the distal silencing element (DS) [84,103,105,110].

### 2.4. Regulation of vimentin in cancer and epithelial to mesenchymal transition (EMT)

Vimentin IF proteins have been involved in several aspects of cancer initiation and progression, including tumorigenesis, EMT and the metastasis. EMT is characterized by the loss of cell polarity and

cell-to-cell interactions, modulation of cell-matrix adhesion as well as enhanced proteolytic activity such as extracellular matrix degradation, cytoskeletal reorganization and enhancement of cell motility [111]. During EMT, epithelial cells progressively lose their epithelial characteristics, including E-cadherin down-regulation, while concurrently acquiring mesenchymal markers, such as vimentin, fibronectin and alpha smooth muscle actin. Vimentin is activated during the EMT process whilst cytokeratin is down-regulated and/or replaced by a different isoform. Additionally, increased vimentin expression has been observed within several tumor cell lines and tissues including prostate cancer, breast cancer, endometrial cancer, tumors of the central nervous system, malignant melanoma, and gastrointestinal tract tumors that include pancreatic, colorectal, and hepatic cancers (for review see [7,26]).

The expression of vimentin in cancer cells and during EMT depends on the interaction of the vimentin promoter with transcription factors. These include positive-acting factors such as AP-1 [112], NF-κB [113,114], PEA3 [102], as well as negative or anti-negative factors such as ZBP-89 [115], ASE and Stat3 [106]. In addition, the expression of vimentin could most likely be indirectly regulated by the beta-catenin/Smad/ZEB2/SIP1 pathway during EMT in association with breast tumor cell migration [116].

### 2.5. Regulation of vimentin in viral infection

Vimentin expression is quickly induced in response to viral infection [90,91,117–119]. It has been reported that infection of the retrovirus HTLV-I directly causes the development of adult T-cell leukemia. Mechanistically, the Tax oncoprotein of HTLV-1 promotes T-cell transformation through the constitutive activation of the NF-κB transcription factor. In particular, Tax activates the expression of the vimentin gene through an NF-κB sequence situated in the upstream region of the gene [90,91]. A pronounced disruption of both vimentin and cytokeratin networks was observed in HeLa epithelial cellular clones stably transfected with the Tax sequence. The disruption resulted in remarkable morphological alterations with vimentin filaments concentrated in discrete spots throughout the cytoplasm, and cytokeratin filaments forming a dense ring around the nucleus [120]. Human T cell lines chronically infected with HTLV-I are known to secrete high levels of cytokines TNFα, IL1α and IL6. TNFα activates NF-κB, which subsequently produces cytoskeletal changes and increases vimentin expression. This increased vimentin expression could work in an autocrine (positive feedback loop) as well as in a paracrine fashion. Whether NF-κB is also involved in the upregulation of vimentin induced by viral infections remains an unanswered question to investigate.

### 2.6. Epigenetic regulation of vimentin expression

The regulation of vimentin expression could be complex. It has been previously reported that the suppression of vimentin expression by ras transformation in mammary epithelial cell lines and the relief of this suppression by TGFβ is probably not controlled by the well-characterized proximal promoter and rather through sequences in the first or second intron [121]. In addition, vimentin expression is also regulated epigenetically. DNA methylation is an immensely significant epigenetic mechanism largely

involved in the gene regulation and silencing of cancer cells. The correlation between vimentin DNA methylation and subsequent vimentin levels in solid tumors, including colorectal, cervical, pancreatic and gastric cancer has been documented [122–125]. Cong et al. have demonstrated that the methylation levels of the vimentin promoter are inversely correlated with vimentin levels in gastric cancer. Furthermore, the treatment of cells comprising the high methylation level of the vimentin gene with an inhibitor of DNA methylation, 5-aza-2′-deoxycytidine, restores vimentin expression significantly [123]. Similarly, hypermethylation of the vimentin promoter in cervical cancer cells has been reported to repress vimentin expression [124] whereas, in neuronal progenitor cells, upregulation of vimentin is related to the hypomethylation of its promoter [126].

Histone methylation and chromatin modifications play critical roles in many epigenetic phenomena. Liu et al. have described the recruitment of lysine-specific demethylase 1 (LSD1), a nuclear histone demethylase and a member of the amine oxidase family, to the vimentin promoter and its role in catalyzing the demethylation of mono- and di-methylated histone H3 lysine 4 (H3K4me1, H3K4me2, respectively) in human papillomavirus 16 E7-induced EMT [127]. The authors demonstrate that human papillomavirus 16 E7 increased the expression of LSD1, formed a complex with LSD1 and induced the expression of vimentin which is correlated in various epithelial cancers with tumor growth, invasion, and poor prognosis. Pharmacological inhibition of LSD1 through the use of a specific small molecule inhibitor, GSK-LSD1, decreased vimentin expression in osteosarcoma cells [128]. Gupta et al. have also shown that histone H3 phosphorylation in high glucose conditions is associated with the hypomethylation of the vimentin gene and its upregulation in breast cancer cells [129]. The loss of BRG1, a key subunit of the SWI/SNF chromatin remodeling complex, is associated with the up-regulation of vimentin in primary tumors [130]. The expression of vimentin is also indirectly regulated by the enhancer of zeste homolog 2 (EZH2), a methyltransferase, and the core catalytic subunit of polycomb repressive complex 2. EZH2 represses ephrin type-B receptor 3 (EphB3) expression via lysine 27 residues of histone H3 trimethylation (H3K27me3) modification in gastric cancer cells [131]. Decreased EphB3 expression promoted the expression of vimentin.

MicroRNAs (miR) are epigenetic modulators involved in different diseases and are responsible for affecting the protein levels of target mRNAs. It has been documented that the expression of vimentin is regulated by several miRs such as miR-146b [132], miR-146a [133], miR-143 [134], miR-210-3p [135], miR-30a [136], miR-1275 [137], and miR-17-5p [138]. For example, miR-210-3p promotes the sustained activation of NF-κB signaling via targeting TNFα induced protein 3 interacting protein 1 (TNIP1) as well as a suppressor of cytokine signaling protein 1 (SOCS1), both being two negative regulators of NF-κB signaling, resulting in EMT and migration of prostate cancer cell lines [135].

Long non-coding RNAs (lncRNAs) can act as key cis- or trans-regulators in a variety of biological processes. Mutations in lncRNAs are associated to the development of several diseases, especially cancers and neurodegenerative disorders [139]. However, the functions and molecular mechanisms of

most lncRNAs still remain elusive. Interestingly, a lncRNA named vimentin-antisense 1 (VIM-AS1) has been found as being transcribed from the vimentin gene locus and as an regulator of vimentin expression [140]. Additionally, vimentin expression is regulated by another lncRNA called AGAP2-antisense RNA 1 (AGAP2-AS1). The expression of vimentin, VIM-AS1 and AGAP2-AS1 in 78 breast cancer samples were significantly down-regulated compared with non-cancerous tissues [141]. Huang et al. have identified a lncRNA-Dreh that is downregulated by the hepatitis B virus X protein and acts as a tumor suppressor in the development of hepatitis B virus-associated hepatocellular carcinoma [142]. The lncRNA-Dreh is capable of binding with vimentin, which was demonstrated by an RNA pull-down experiment, can further repress the expression of vimentin, and possesses the ability to change the normal cytoskeleton structure. The increased expression of Dreh through gene transfer allows the reversal of the malignant phenotype of hepatocellular carcinoma [142]. Another vimentin associated lncRNA, LINC01546, was identified by Tian et al. as being directly induced by Akt/Stat3 signaling in lung adenocarcinoma [143]. LINC01546 acts as a potent pro-metastatic molecule due to its ability to directly bind to vimentin and competitively nullify Trim16-depedent vimentin polyubiquitination and degradation. As a result, targeting LINC01546 or vimentin stability to reduce their levels could be a therapeutic approach for lung adenocarcinoma [143]. Moreover, lncRNA FTX has been shown to directly interact with miR-215 and suppressed miR-215 expression whilst also binding to vimentin, resulting in reduced phosphorylation levels on Ser83 (Ser82 when omitting methionine starting amino acid) of vimentin in colorectal cancer cells. Reduction of lncRNA FTX can inhibit colorectal cancer cells growth and distant metastasis *in vivo* [144]. On the other hand, in gastric cancer cells, lncRNA LINC00675 interacts with vimentin in a manner that enhances its phosphorylation levels on Ser83, resulting in the collapse of vimentin filament and a subsequent reduction in cell metastasis [145].

## 3. Post-translational modifications of vimentin

Proteomic advances highlight the immense complexity and regulatory potential of IF protein post-translational modifications. Post-translational modifications regulate IF function, structure and localization [4,31]. Most studies of post- translational modifications in IFs concentrate on investigating phosphorylation and its downstream effects. Vimentin is phosphorylated by a variety of kinases, including p21-activated kinase (PAK), cAMP-dependent protein kinase A (PKA), protein kinase C (PKC), Rho-associated protein kinase (ROCK), Calcium/calmodulin-dependent protein kinase II (CaMKII), RAC-alpha serine/threonine-protein kinase (Akt1), polo like kinase 1 (Plk1), mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP-KII), cyclin-dependent kinase 1 (Cdk1), cyclin-dependent kinase 5 (Cdk5) and Aurora B. Main phosphorylation sites on the vimentin molecule are summarized in **Table 1** and **Figure 2**. It should be noted that the large majority of phosphorylation studies were evenly performed on murine and human vimentin whereas other studies employed rat and dog cells. Fortunately, protein sequence alignment showed that almost all sites of PMT were conserved among all the species studied (human, green monkey, mouse, rat, hamster, dog, and cow). Among all

PMT sites, only three serine were lost in cow sequences, two in hamster, and one in pig. With regards to the two main species used in the studies (human and mouse), all PMT sites were perfectly conserved. Phosphorylation of vimentin plays an impactful role in vimentin dynamics during mitosis. Mitotic-associated phosphorylation of vimentin causes filament disassembly through the phosphorylation of Ser55 by Cdk1 [146,147], Ser82 by Plk1 [147], Ser71 and Ser38 by ROCK [148], and Ser72 by Aurora B [149]. Additional kinases also mediate vimentin dynamics, such as PAK and PKA. PAK phosphorylates Ser25, Ser38, Ser50, Ser55, Ser65 and Ser72 of the vimentin N-terminal [150–152] while PKA facilitates the phosphorylation of Ser38 and Ser72 [153]. Phosphorylation of vimentin on these sites impairs the assembly of vimentin filaments. Furthermore, the phosphorylation of vimentin regulates processes underlying cell motility in physiological conditions as well as in pathological conditions, including cancer. Phosphorylation of Ser38 by Akt1 increases cancer cell motility [154], and the phosphorylation of Ser6 and Ser33 by PKC is associated with the trafficking of integrin to the plasma membrane through vesicles [155]. Interestingly, vimentin phosphorylation does not always impair its assembly. None of the following phosphorylations of Ser38, Ser50, Ser55 and Ser82 by MAPKAP-KII affects vimentin assembly [156], suggesting that vimentin can serve as a phosphate sink. In addition, PKA- and Cdk5-mediated phosphorylation is involved in the secretion of vimentin. The secreted vimentin dimer is modified by PKA-mediated phosphorylation of Ser418, Ser429, Thr457 and Ser458 [153,157], while the secretion of vimentin in neutrophils is associated with the phosphorylation of Ser56 (Ser55 when omitting methionine starting amino acid) by Cdk5 [158].

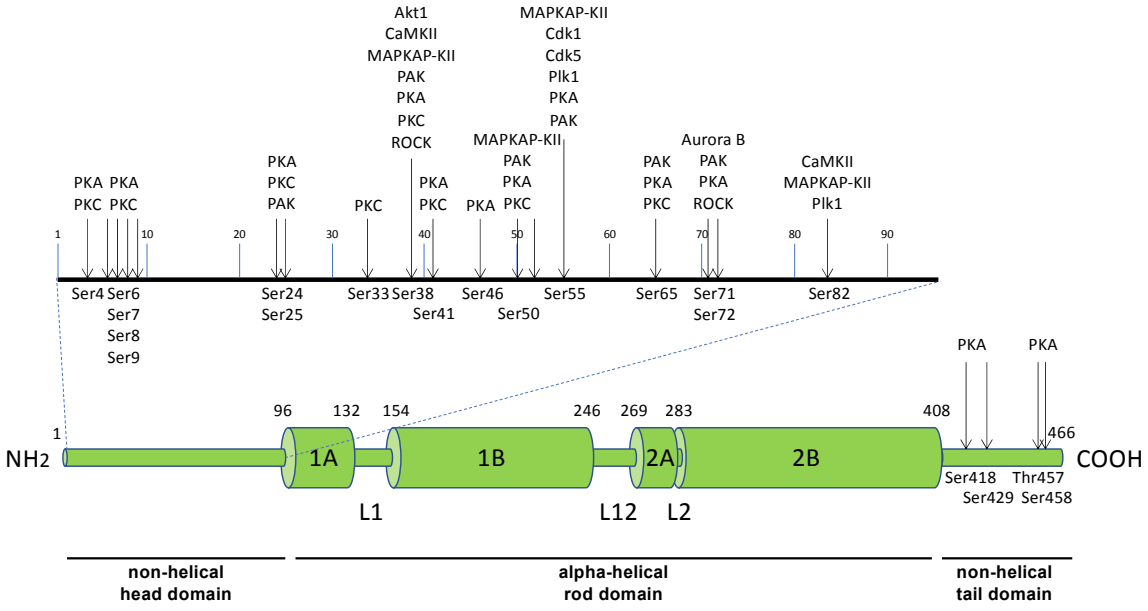


***Figure 2. Main phosphorylation sites described in the vimentin molecule, classified according to their position.*** *Vimentin is formed by a non-helical head (amino acid position from 1 to 95), a central alpha-helical rod (coil 1A, coil 1B, coil 2A and coil 2B) divided by linkers (L1, L12 and L2) (amino acid position from 96 to 407) and a non-helical tail (amino acid position from 408 to 466) domain.*

***Table 1. Main phosphorylation sites described in the vimentin molecule, classified according to the kinase involved.***

| Position | Kinases | Ref |
|---|---|---|
| Ser4, Ser6, Ser7, Ser8, Ser9 | PKA, PKC | [153,155,159] |
| Ser24 | PKA, PKC | [159] |
| Ser25 | PAK, PKC | [150,159] |
| Ser33 | PKC | [148,159] |
| Ser38 | CaMKII, MAPKAP-KII, PAK, PKA, PKC, ROCK | [148,150,153,155, 156,159,160] |
| Ser39* | Akt1 | [154] |
| Ser41 | PKA, PKC | [153,159] |
| Ser46 | PKA | [159] |
| Ser50 | MAPKAP-KII, PAK, PKA, PKC | [150,156,159,161] |
| Ser55 | MAPKAP-KII, Cdk1, Plk1, PKA | [146,147,156,157] |
| Ser56* | Cdk5, PAK | [151,152,158] |
| Ser65 | PAK, PKA, PKC | [150,159] |
| Ser71 | PKA, ROCK | [148,153,161] |
| Ser72 | Aurora B, PAK, PKA | [149,150,153,161] |
| Ser82 | CaMKII, MAPKAP-KII, Plk1 | [147,156,160,162] |
| Ser418, Ser429, Thr457, Ser458 | PKA | [153,157] |

*Numbering omits methionine starting amino acid. Note that in some papers methionine is counted as a first amino acid (see *). Ser39 and Ser56 are the same amino acid as Ser38 and Ser55, respectively.* ***Akt1****, RAC-alpha serine/threonine-protein kinase;* ***CaMKII,*** *Calcium/calmodulin-dependent protein kinase II;* ***Cdk1,*** *cyclin-dependent kinase 1;* ***Cdk5,*** *cyclin-dependent kinase 5;* ***MAPKAP-KII,*** *mitogen-activated protein kinase-activated protein kinase-2;* ***PAK,*** *p21-activated kinase;* ***PKA****, cAMP-dependent protein kinase A;* ***PKC****,* protein kinase C*;* ***Plk-1****, polo like kinase 1;* ***ROCK****,* Rho-*associated protein* kinase.

In addition to the phosphorylation of vimentin, the citrullination [163,164], ADP-ribosylation [165], AMPylation [166], glycosylation as well as O-GlcNAcylation [167,168], glycation [169], S-glutathionylation [170], sialylation [171], sumoylation [172], ubiquitination [173] and malondialdehyde adducts [174] of vimentin have been identified (**Table 2**). Citrullination is characterized as an important modification of extracellular vimentin. It takes places in both physiological and pathological conditions [175]. This enzymatic modification is catalyzed by peptidyl arginine deiminases, which convert arginine within a specific protein to citrulline within another protein. The immune system may attack citrullinated proteins, resulting in the development of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. Citrullination turns vimentin into an antigen in rheumatoid arthritis [176] as well as an antigen

for anti-tumor immunity [177]. In addition, citrullinated vimentin is implicated in the development and progression of lung fibrosis [178], retinal injury [179], dendritic cell transdifferentiation into osteoclasts [180] and neurodegenerative diseases [181]. SUMOylation of vimentin is important for its disassembly. Non-SUMOylatable vimentin mutants expressed in cells possess a reduced level of migration [172]. ADP-ribosylation of vimentin by bacterial SpyA is identified *in vitro* and ADP-ribosylation of head domain Arg residues results in the inhibition of vimentin filament formation [165]. Glycosylation of the vimentin head domain is required for vimentin filament assembly, cell migration and intracellular pathogen replication [167]. S-glutathionylation plays a role in the dynamic rearrangements of vimentin IF in response to changes in cellular redox status. The longitudinal assembly of unit-length filaments into extended filaments is inhibited by the S-glutathionylation of Cys328 on vimentin. However, S-glutathionylation of preformed vimentin filaments leads to their fragmentation to smaller oligomeric species [170]. Lysine residues exhibited predominant vimentin glycation, specifically at linker regions [169]. Vimentin glycation causes its rigorous redistribution into a perinuclear aggresome. The modified vimentin by glycation and the oxidative adduct malondialdehyde can be found in aged or replicative senescent fibroblasts [169,174,182]. Recently, RING finger protein 208 (RNF208), an estrogen-inducible E3 ligase, has been shown to target soluble vimentin to facilitate proteasomal degradation of vimentin in breast cancer cells. RNF208 specifically polyubiquitinated the Lys97 residue through interaction with the Ser39 (Ser38 when omitting methionine starting amino acid) residue of phosphorylated vimentin, which exists as a soluble form [173].

***Table 2. Main post-translational modifications of the vimentin protein, apart from phosphorylation. The types of modifications are indicated with their position in the molecule.***

| Type | Position | Ref |
|---|---|---|
| Citrullination | Arg3, Arg11, Arg12, Arg22, Arg27, Arg44, Arg49, Arg63, Arg144, Arg380 | [163,164] |
| ADP-ribosylation | Arg44, Arg49, Arg63, Arg303, Arg449 | [165] |
| AMPylation | Tyr52 | [166] |
| Glycosylation | Thr33*, Ser34*, Ser39*, Ser49*, Ser55* | [167,168] |
| Glycation | Lys139*, Lys143*, Lys168*, Lys262*, Lys313*, Lys445* | [169] |
| S-Glutathionylation | Cys328* | [170] |
| Sialylation | Ser7*, Thr33*, Ser34* | [171] |
| Sumoylation | Lys439*, Lys445* | [172] |
| Ubiquitination | Lys97* | [173] |
| Malondialdehyde adducts | Cys328* | [174] |

*Numbering omits methionine starting amino acid. Note that in some papers methionine is counted as a first amino acid (see *).*

## 4. Vimentin is present on the cell surface

### 4.1. Non-convention localization: cell surface / extracellular vimentin

Vimentin was originally identified as an intracellular IF protein in many cell types. Immunofluorescence staining and ultrastructural studies investigating the intracellular distribution of IFs have demonstrated the proximity of these cytoskeletal structures to plasma membranes. It has been revealed that non-helical N-terminus vimentin interacts specifically with negatively charged phospholipids, in addition to forming strong ionic relationships between both reactants [183]. At the intracellular surface of the plasma membrane the vimentin IF network is capable of connecting to integrins through its interactions with synemin and vinculin or through plectin, and modulates the adhesion strength of cells to their substrate [54,184].

The non-intracellular distribution of vimentin has been reported from over two decades ago. In 1993, through the use of monoclonal antibodies, Evans et al. [185] identified a vimentin-like associated molecule on rat natural killer cells by monoclonal antibody MoAb 5C6 and demonstrated the ability of this protein to function as a receptor since the anti-vimentin monoclonal antibody can inhibit cytotoxicity. Ten years later, the notion indicating the presence of extracellular vimentin gained extensive support through novel experiments. For example, vimentin has been identified as one of the 19 major detergent-resistant membrane skeleton proteins mediating neutrophil signaling [186] and as the major binding protein of secreted phospholipases A2 that are found at high levels in inflammatory fluids of patients with autoimmune diseases. In conjunction with heparan sulfate proteoglycans, vimentin contributes to the enhanced binding of secreted phospholipases A2 to apoptotic primary T lymphocytes [187]. Vimentin was further identified at the surface of plasma membranes or secreted into the extracellular environment by various antibodies.

### 4.2. Vimentin was identified at the surface of plasma membranes by various antibodies

The presence of cell surface vimentin has been demonstrated using different monoclonal antibodies (MoAb) such as MoAb 5C6, MoAb SC5, MoAb 7G10, MoAb 84-1, MoAb 86C, MoAb 9H4 and MoAb PAL-E. It has been detected on the surface of several different cell types, including endothelial cells, activated macrophages and lymphocytes, natural killer cells, platelets, apoptotic neutrophils, senescent cells, Sezary lymphocytes and different cancer cells. The presence of cell surface vimentin in these diverse cells raises the question regarding the role of this form of vimentin and its potential involvement in cytotoxicity, phagocytosis, immunity, senescent cell clearance as well as in viral infection as a possible co-receptor for viruses. In fact, anti-vimentin auto-antibodies were first identified during the 1980s in patients with Waldenström macroglobulinemia complicated with peripheral neuropathy [188,189], patients with angioimmunoblastic lymphadenopathy [190], and patients with the CREST Syndrome and systemic lupus erythematosus [191]. The ability of these auto-antibodies to recognize cell surface vimentin was not been tested at that time.

***MoAb 5C6***. MoAb 5C6 specifically binds to fish, rat and human natural killer cells and inhibits cytotoxicity. Evidence is presented indicating the presence of a vimentin protein on transformed rat natural killer cells that may act as an antigen binding receptor to initiate target cell lysis [185].

***MoAb SC5***. MoAb SC5 specifically recognizes vimentin on the extracellular plasma membrane of circulating malignant Sezary lymphocytes in Sezary syndrome, a leukemic form of an epidermotropic cutaneous lymphoma [192]. The MoAb SC5 recognition site is located in the N-terminal and the beginning of the coil-coil rod domain. The SC5 detects vimentin both in the cytoplasm of circulating lymphocytes as well as at the cell surface of normal T lymphocytes following activation, suggesting that vimentin might correspond to an intracellular protein in normal T lymphocytes and that its surface membrane expression increases rapidly after activation [193,194]. Vimentin was found on the cell surface of apoptotic neutrophils, conveying the possibility that such cells may contribute to the development of auto-antibodies directed against cytoskeletal proteins. This condition is commonly observed in several inflammatory diseases [195]. Furthermore, the extracellular form of vimentin on the cell surface of apoptotic neutrophils is cleaved by membrane-type matrix metalloproteinase 6, therefore abolishing monocyte recruitment but stimulating phagocytosis, which is not a property of full-length vimentin. As a result, membrane-type matrix metalloproteinase 6 regulates neutrophil and monocyte chemotaxis, and through generating “eat-me” signals upon vimentin cleavage, potentially increases phagocytic removal of neutrophils to resolve inflammation [196]. Through the use of two MoAbs, MoAb SC5 and MoAb V9 directed against the beginning of coil-coil rod and the C-terminus of the vimentin protein, respectively, Steinmetz et al. demonstrated that these two domains of vimentin have been detected on the surface of several different prostate cancer cell lines LNCaP, PC3 and DU145 derived from lymph node, bone or brain prostate metastases, respectively [197].

***MoAb 7G10***. MoAb 7G10 detects vimentin both on the surface and in the intracellular region of MARC-145 cells, a porcine reproductive and respiratory syndrome virus-susceptible cell line. This antibody possesses blocking activity against porcine reproductive and respiratory syndrome virus. Vimentin bound to porcine reproductive and respiratory syndrome virus nucleocapsid protein and anti-vimentin antibodies showed blocking activity against this virus, suggesting that vimentin is part of the porcine reproductive and respiratory syndrome virus receptor complex [198].

***MoAb 84-1***. The anti-vimentin MoAb 84-1 reacts specifically with cell surface vimentin. This antibody is used to isolate circulating tumor cells. Through the use of MoAb 84-1, cell-surface vimentin was detected in circulating tumor cells of peripheral blood samples collected from metastatic breast [199], colorectal and prostate [200,201] cancer patients as well as from pancreatic ductal adenocarcinoma [202]. Furthermore, through the use of MoAb 84-1, cell-surface vimentin-positive and CD133-negative cells were isolated from primary liver tumor cell suspensions [203]. These cells have stem-like properties with the presence of stem cell markers Sox2 and Oct4 as well as EMT phenotypes, proven by the presence of Twist and Slug in the nucleus. In contrast, cell-surface vimentin-negative and CD133-

positive cell populations do not have any EMT phenotypes.

***MoAb 86C***. This antibody acts against cell surface vimentin in a manner that simultaneously induces apoptosis and inhibits spheroid formation in glioblastoma cells *in vitro*. The presence of this antibody in glioblastoma cells causes the rapid internalization of vimentin, which negatively impacts glioblastoma cell viability. This phenotype is characterized by an increase in caspase-3 activity, signifying the apoptosis activation [204].

***MoAb 9H4***. The anti-vimentin MoAb, the IgM clone MoAb 9H4, recognizes senescence-associated cell-surface antigens after immunizing BALB/c mice with senescent mouse lung fibroblasts. This antibody recognizes vimentin having a post-translational modification on cysteine 328 by the oxidative adduct malondialdehyde. Senescent cells identify and secrete an oxidized form of membrane-bound vimentin, and such cells may be recognized by humoral innate immunity due to the presence of membrane-bound malondialdehyde-vimentin. This latter form of vimentin presumably contributes to senescence eradication mechanism, which occasionally becomes impaired with age and leads to senescent cell accumulation [174].

***MoAb PAL-E.*** The MoAb PAL-E reacts specifically to a secreted form of vimentin from blood endothelial cells and activated macrophages. The PAL-E antibody was identified almost 35 years ago through the injection of human melanoma lymph node metastases into mice [205]. The MoAb PAL-E was suggested to be one of the first molecular markers that distinguishes blood and lymphatic endothelial cells, but it was only in 2004 that Xu et al. [206] identified the PAL-E-recognized protein as a secreted form of vimentin using protein purification and mass spectrometry analysis of tryptic peptides.

### 4.3. Vimentin can be secreted or released into the extracellular space

The presence of extracellular vimentin has been demonstrated by a monoclonal antibody MoAb 5C6 [185]. Evans et al. demonstrated that a specific vimentin protein present on transformed rat natural killer cells can be an antigen binding receptor that is responsible for initiating lysis of target cells. Through the application of an anti-vimentin antibody on non-permeabilized activated human macrophages, Mor-Vaknin et al. found that these cells secrete vimentin into the extracellular space via the classical endoplasmic reticulum/Golgi pathway [207]. In order to be secreted in active macrophages, vimentin must first undergo phosphorylation, as demonstrated by both the enhancement of vimentin secretion through the treatment with the phosphatase inhibitor okadaic acid and decreased secretion of vimentin by the treatment of the specific PKC inhibitor. This observation is consistent with the fact that vimentin is a substrate for PKC. Furthermore, the anti-inflammatory cytokine interleukin-10 decreases secretion of vimentin by inhibiting PKC activity. In contrast, the pro-inflammatory cytokine TNFα can trigger the secretion of vimentin. Extracellular vimentin has been suggested to be involved in two significant functions of activated macrophages: bacterial killing and the generation of oxidative metabolites [207].

In response to pro-inflammatory signaling pathways, activated macrophages secrete vimentin that might interact with bacteria and soluble factors that favor bacterial killing. Vimentin is also secreted by astrocytes [208,209]. Furthermore, it has been reported that vimentin is required for efficient Type III secretion system translocation of effectors by Shigella flexneri and other pathogens that use the Type III secretion system; namely, Salmonella Typhimurium and Yersinia pseudotuberculosis [210].

As described above, an endothelial cell-specific antibody MoAb PAL-E [206] identifies a secreted form of vimentin on the cell surface of specific blood endothelial cells and activated macrophages. PAL-E-positive vimentin is not a direct product of an endothelial cell-specific mRNA transcript, but rather is the result of cell-specific post-translational modification. Evidence directly favors PAL-E recognition of a secreted vimentin dimer that is further modified by phosphorylation. The N-terminal domain of vimentin has been shown to mediate the association with lipid membranes and may further facilitate its secretion through association with the endoplasmic reticulum. In addition, the C-terminal of vimentin contains a di-acidic motif (Asp-X-Glu) utilized by certain proteins for export from the endoplasmic reticulum to the Golgi, but the functional significance of these sequences for vimentin secretion is still unknown.

It has been reported that extracellular vimentin can function as a ligand of insulin-like growth factor 1 receptor and promotes axonal growth by activating the phosphorylation of insulin-like growth factor 1 receptor. End of the rod domain (residue number 330-407) in vimentin are the most suitable binding sites for insulin-like growth factor 1 receptor [211]. Moreover, secretion of citrullinated vimentin is not only an early marker of autoimmune diseases such as rheumatoid arthritis [176,212,213] but also of an antigen for anti-tumor immunity [177]. In addition, citrullinated vimentin is implicated in the development and progression of lung fibrosis [178], retinal injury [179], and neurodegenerative diseases [181].

Yu et al. have shown that extracellular vimentin influences the initiation of adaptive immune responses by modulating activation of human dendritic cells, the most effective for priming of naïve T cells. Extracellular vimentin may block the adaptive immune response by decreasing lipopolysaccharide-induced secretion of pro-inflammatory cytokines whilst also promoting the secretion of anti-inflammatory cytokines in dendritic cells [214].

Vimentin can be secreted in extracellular vesicles, including exosomes, found in bodily fluids that play a pivotal role in regulating cell-cell communication and several diverse biological processes [215–217]. Soluble vimentin was detected at higher levels in the sera of colon cancer patients, suggesting that vimentin might be a potential biomarker in colon cancers and an antigen for tumor vaccination in an autologous set-up for colon cancers [218]. Mellgren et al. has reported that the externalization of certain proteins can occur in cells suffering plasma membrane damage and subsequent repair. Several major proteins (caldesmon-1 and vimentin), endoplasmic reticulum proteins (ERp57, ERp5, and HSP47), and

nuclear proteins (lamin C, heterogeneous nuclear ribonucleoprotein F, and nucleophosmin-1) were exposed to cell surfaces damaged by scratching. Following this exposure, they either undergo degradation or internalization a few seconds to several minutes after damage. However, vimentin was an exception to this phenomenon as it was detectable on the cell surface for at least an hour after injury [219]. Furthermore, Walker et al. have reported that vimentin, released into the extracellular space following injury, binds to the cell surface of the mesenchymal leader cells located at the edge of the wound. This extracellular and cell surface-associated vimentin mediates wound closure in the native matrix environment and plays a role in transitioning these cells to a myofibroblast phenotype in profibrotic environments [220]. Adolf et al. have demonstrated that exosomal vimentin positive particles released from astrocytes mediate binding and internalization of Clostridium botulinum C3 transferase in astrocytes and neurons, and promote axonotrophic effects of Clostridium botulinum C3 after spinal cord injury [221].

## 5. Vimentin serves as a receptor or ligand

The fact that vimentin was found to be located on the cell surface of the cell raises the question of cell surface vimentin's role. The data from various experiments suggest that cell surface vimentin could serve as a receptor/co-receptor or ligand for endogenous proteins such as von Willebrand factor (vWF) as well as for exogenous proteins such as bacterial and viral proteins.

### 5.1. Vimentin on platelets and endothelial cells serves as an adhesive receptor for Willebrand factor (vWF)

The interaction between platelet receptor glycoprotein Ibα and vWF facilitates the tethering/translocation of platelets to sites of vascular injury. Vimentin is present on the extracellular surface of platelets and endothelial cells. The interaction of vimentin with the A2 domain of active vWF has been demonstrated through the use of the competitive A2 domain of vWF and an anti-vimentin antibody [222]. The addition of purified A2 domain inhibits the binding between the active form of vWF and vimentin, whereas an anti-vimentin antibody inhibits the platelet adhesion to wild-type vWF (containing A1-A2-A3 domains) protein, collagen, and fibrinogen under high shear stress. In comparison to wild-type mice, platelets from vimentin knock-out mice were characterized by reduced flow-dependent adhesion to both collagen and purified murine vWF under shear stress [222]. This is consistent with the observation that tail bleeding time in vimentin knock-out mice was higher than that of wild-type mice [223].

### 5.2. Vimentin mediates bacterial invasion or killing

It has been shown that the absence of vimentin protects neonatal mice from Escherichia coli K1-induced meningitis [224]. Vimentin is required for meningitic Escherichia coli K1 invasion and polymorphonuclear leucocyte transmigration through the blood-brain barrier. Vimentin constitutes a primary receptor required for the Escherichia Coli K1 IbeA virulence factor [225]. The binding sites of

the IbeA-vimentin interaction have been identified in the 271–370 residue region of IbeA and the vimentin head domain [226]. Vimentin is present in lipid rafts of endothelial cells [227]. The binding of IbeA virulence factor to its vimentin receptor and co-receptor PSF (PTB (polypyrimidine tract-binding protein)-associated splicing factor) at the cellular membrane rafts triggers vimentin phosphorylation at Ser82 by CaMKII through α7 nAChR-mediated calcium signaling, nuclear translocation of NF-κB and ERK signaling, favoring the bacterial invasion [224,225,228]. In addition, cell surface vimentin interacts also with BspC, an antigen I/II family adhesin of Streptococcus agalactiae (Group B Streptococcus), and is critical for the pathogenesis of Group B Streptococcus meningitis [229].

The internalin family proteins InlF possess a specific role in the colonization of the brain by Listeria monocytogenes. The binding of InlF to host cell surface vimentin facilitates Listeria monocytogenes invasion of host cells. In the absence of vimentin, Listeria monocytogenes colonization of the brain was severely compromised in mice, highlighting the importance of surface vimentin in pathogen adhesion and internalization [230]. In addition, surface vimentin is required for stiffness-dependent adhesion of Listeria monocytogenes to host cells [231]. Increased activity of focal adhesion kinase (FAK) in host cells, when cultured on a stiffer matrix, is associated with an increase of surface vimentin, favoring the Listeria monocytogenes adhesion.

Human natural killer cells used the NKp46 receptor to lyse Mycobacterium tuberculosis strain H37ra-infected monocytes. Immunoprecipitation of natural killer cells extract with anti-NKp46 antibody identified vimentin as a ligand for the NKp46 receptor on natural killer cells [232]. Immunofluorescence staining indicated the significant upregulation of vimentin expression on the surface of infected monocytes relative to uninfected cells. Anti-vimentin antiserum inhibited natural killer cell lysis of infected monocytes, suggesting involvement of cell surface vimentin in the binding of NKp46 to Mycobacterium tuberculosis H37ra-infected mononuclear phagocytes.

### 5.3. Vimentin serves as a receptor/co-receptor for viruses

Vimentin has been identified as an important mediator for the different stages (virus adhesion, entry, replication and release) of viral infection [29,32,119,233]. Vimentin expression is quickly induced in response to viral infection [90,91]. It has been reported that cell surface vimentin is involved in the cell entry of several viruses and vimentin has been proposed as a receptor or co-receptor for viral proteins [234]. Furthermore, it has been shown that cell surface vimentin is critical for the cell entry of SARS-CoV1 [234] and SARS-CoV2 virus-like particles [235]. SARS-CoV1 virus-like particles enhanced the expression of cell surface vimentin [234]. Vimentin has direct contact with SARS-CoV spike proteins [234,235]. Yet, it remains unclear as to which specific domain of vimentin plays the role of interaction with viral spike proteins. Moreover, whether vimentin binds to angiotensin-converting enzyme 2 receptor directly or merely arranges in close proximity must be further investigated.

Evidence that viral binding to surface vimentin can facilitate internalization and infections has been demonstrated for other viruses such as Japanese encephalitis virus [236,237], Cowpea mosaic virus [238], Chandipura virus [239], porcine reproductive and respiratory syndrome virus [198], Dengue virus [240] and Enterovirus EV71 [241]. The interaction between Enterovirus EV71 viral envelope protein 1 and vimentin has been reported [241]. Either soluble vimentin or an anti-vimentin antibody could inhibit the binding of EV71 to vimentin on the host cell surface [241] or cause a decrease in Chandipura virus infectivity to Neuro-2a cells [239].

### 5.4. Vimentin serves as a binding site for polysaccharides and RNA

By using artificial biomimicking glycopolymers, Ise et al. have shown that type III IF proteins such as vimentin and desmin possess N-acetylglucosamine (GlcNAc)-binding lectin-like properties on the cell surfaces of various vimentin- and desmin-expressing cells such as cardiomyocytes and vascular smooth muscle cells. The interaction between vimentin and GlcNAc as well as GlcNAcylated proteins is mediated by its alpha-helical rod 2 domain [242]. This GlcNAc-binding activity was used to efficiently isolate mesenchymal stem cells by using GlcNAc-bearing polymer-coated dishes [242], and to deliver genes or drugs to target cell surface vimentin-expressing cells and tissues by using GlcNAc-conjugated agents [243–245]. The GlcNAc-bearing polymer-coated liposomes via intravenous administration delivered drugs into the injured vessel walls but not at the contralateral (uninjured) vessel walls of mice [246]. Since nonparenchymal cells, such as hepatic stellate cells in liver, express vimentin or desmin, and the adhesion of the nonparenchymal cells to GlcNAc-coated dishes take place more quickly than on collagen-coated dishes. They found that GlcNAc can maintain hepatic stellate cells in a quiescent state during a long-term culture [247]. The interaction of surface vimentin with O-GlcNAc-modified proteins has also been considered as a way to be involved in the clearance of apoptotic cells [248]. The O-GlcNAc-modified proteins from apoptotic cells interact with the surface vimentin of neighboring phagocytes to induce the phosphorylation of Ser71- or Ser38 of vimentin by ROCK and PKC, leading to the disassembly of vimentin filaments, and favoring in turn the recruitment of tetrameric vimentin to the cell surface [244,248]. The affinity of vimentin alpha-helical rod 2 domain for lipid bilayers, including transmembrane domains [242,249], could facilitate the migration of tetrameric vimentin from the cytoplasm to the exterior of the membrane. Furthermore, this mechanism for the clearance of apoptotic cells was observed in the phagocytic engulfment and clearance of apoptotic footplate cells in mouse embryo development [248].

Acute inflammation is initiated by leukocyte P-selectin glycoprotein ligand-1 (PSGL-1) binding to P-selectin on inflamed endothelium and platelets. Since GlcNAc is a moiety present in PSGL-1, Lam et al. tested if vimentin binds to PSGL-1 and influences the interplay between platelet P-selectin and PSGL-1 on leukocytes. They have shown that vimentin binds to P-selectin via its rod domain but not PSGL-1 in a calcium-independent way [250,251]. Vimentin binds P-selectin at or near the PSGL-1 binding site in order to inhibits P-selectin-PSGL-1 interactions. The recombinant human vimentin

blocks neutrophil adhesion to platelets and endothelium under venous shear stress and diminishes inflammation and acute lung injury in endotoxemic mice [250,251].

In addition, cell surface vimentin seems play an important role in Schwann cell migration and in peripheral nerve regeneration in nerve injury. Vimentin functions as a receptor for the lncRNA BC088259 that is upregulated following sciatic nerve injury. The mechanism underlying the interaction between BC088259 and vimentin remains to be explored [252].

## 6. Conclusion and perspectives

Multiple functions have been attributed to vimentin at the cellular level, including maintenance of stemness, proliferation, differentiation, adhesion, migration and invasion. Using vimentin knockout mice, it has been shown that the absence of vimentin expression leads to deficiencies in physiological processes, such as mammary gland development, angiogenesis, vascular stiffness, steroidogenesis, immunity response and inflammatory reaction, glial development, myelinization of peripheral nerves and wound healing. The expression profile of vimentin is unique in the IF family. It is mainly expressed in precursor cells before being replaced by other IF members during cellular differentiation, with the exception of its co-presence with other IF members in some mesenchymal-derived cells such as endothelial cells, smooth muscle cells and platelets in adult animals. The remarkable feature of vimentin is its re-expression during dedifferentiation processes and pathological conditions, such as EMT, cancerous progression, pathogen infection as well as in most cells in cell culture. The activation, modulation or repression of vimentin expression is controlled both at the promoter level, a promoter with a set of activating and inhibiting elements such as the regulating sites of NF-κB, AP-1, Sp1, Sp3, PEA3, H4TF1, ZBP-89, ZBP-99, Stat1α and Stat3, and either directly or indirectly at the epigenetic level, such as through DNA and histone methylation, chromatin modifications, miR and LncRNAs. Moreover, proteomic advancements highlight the vast complexity and regulatory potential of PTMs, which are involved in extracellular localization of vimentin and exert specific functions in cells and tissues. Uncovering a deeper understanding of regulatory mechanisms of vimentin expression will be valuable in creating strategies to modulate the intracellular and extracellular vimentin levels, and ultimately develop biotherapies for disease treatment.

It has been suggested that the vimentin possesses both mechanical and non-mechanical function in filamentous or non-filamentous forms (for review see) [29]. In addition to intracellular vimentin, the presence of extracellular vimentin on the cell surface or in the extracellular environment has been involved in many physiological and pathological processes, such as the clearance of apoptotic footplate cells in mouse embryo development, cancer and traumatic tissue injury, bacterial or viral infection, rheumatoid arthritis, multiple sclerosis, aging and senescence, innate and adaptive immune responses and thrombosis. The functions of extracellular/cell surface vimentin in these processes and underlying mechanisms are still to be explored. Extracellular/cell surface vimentin could be a novel therapeutic

target for several diseases or could be used as an approach for drug delivery via targeting cell surface vimentin.

Most data are concerned with the involvement of extracellular/cell surface vimentin in pathological conditions, giving the impression that extracellular vimentin is a marker of diseases or a consequence in response to the development of diseases, while its implication in physiological conditions is not generally investigated. This could be linked to the availability of antibodies capable of solely recognizing extracellular vimentin and the fact that higher levels of intracellular vimentin than that of extracellular vimentin could hinder the study of the latter. Many studies focus on vimentin knock-out mice in order to clarify the role of extracellular vimentin in the pathogenesis of diverse diseases. It would be interesting and useful to investigate the role of vimentin in the conditional tissue or cell-specific knock-out mouse model to avoid the adaptation effect and mutual influence between tissues. Although it has been suggested that changes from filament to non-filamentous structure, mostly including only 4-12-mers, are needed to expose vimentin to the cell surface [253], the mechanisms implicated in the cell surface recruitment or secretion remains elusive. Are there different forms of extracellular vimentin and does each possess a specific function? What type of PTM (such as citrullination, oxidation, glycosylation, O-GlcNAcylation, phosphorylation etc.) or proteinase digestion is required for the extracellular localization of vimentin? Are certain PTMs specific to particular pathologies? What are the signaling pathways induced by extracellular vimentin? These questions are significant areas of investigation for future studies.

**Contributors**

DP, AL, SK, OA and ZL developed the idea, wrote the draft and are the guarantors of the article jointly.

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**Conflicts of Interest**

None.

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Figure 1



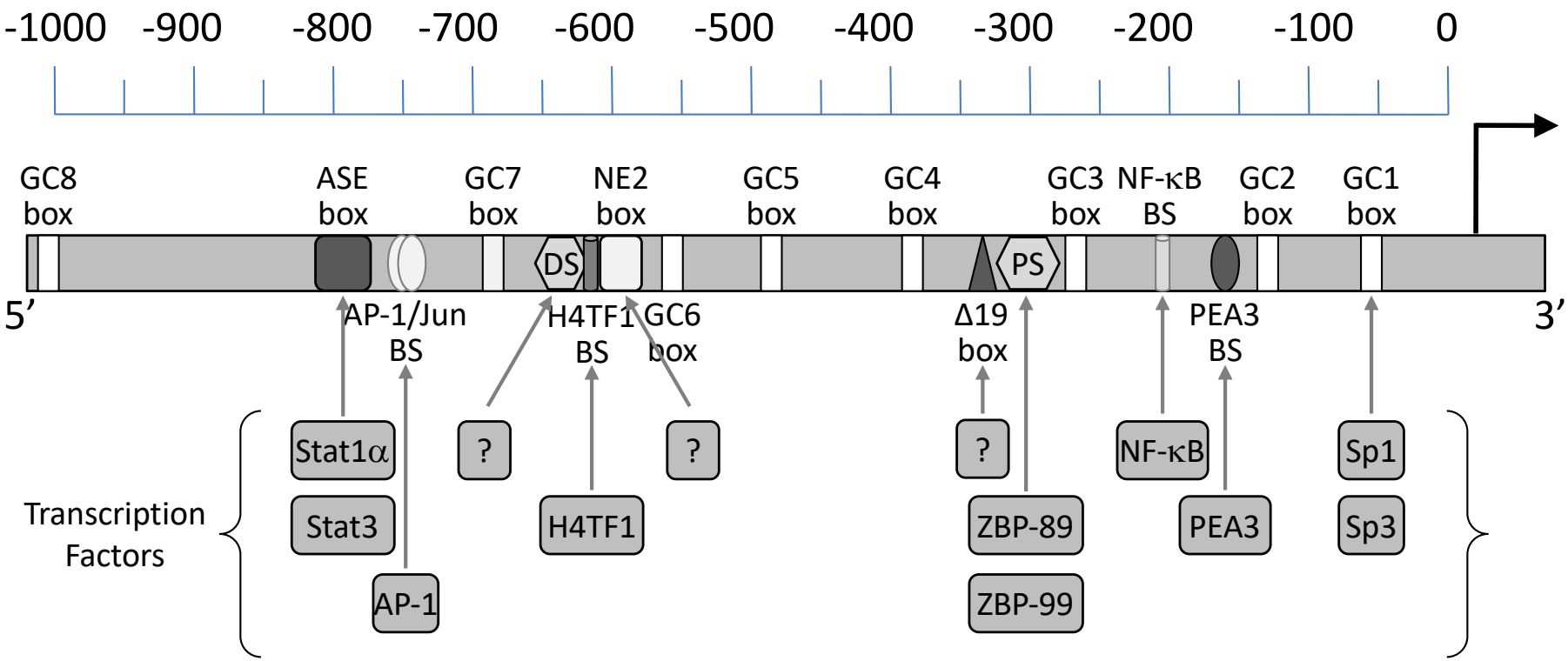

Figure 2