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Vimentin takes a hike – Emerging roles of extracellular vimentin in cancer and wound healing

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Abstract

Vimentin is a cytoskeletal protein important for many cellular processes, including proliferation, migration, invasion, stress resistance, signaling, and many more. The vimentin-deficient mouse has revealed many of these functions as it has numerous severe phenotypes, many of which are found only following a suitable challenge or stress. While these functions are usually related to vimentin as a major intracellular protein, vimentin is also emerging as an extracellular protein, exposed at the cell surface in an oligomeric form or secreted to the extracellular environment in soluble and vesicle-bound forms. Thus, this review explores the roles of the extracellular pool of vimentin (eVIM), identified in both normal and pathological states. It focuses specifically on the recent advances regarding the role of eVIM in wound healing and cancer. Finally, it discusses new technologies and future perspectives for the clinical application of eVIM.

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Introduction

Vimentin belongs to the intermediate filament (IFs) protein family, which is a large group of cytoskeletal elements expressed in a context- and tissue-specific fashion [1]. IFs are resilient proteins that are also dynamically modified and exchanged, which allows the cell to adapt quickly to environmental changes to endure stressful conditions [2]. This way, although widely studied for their structural properties, these proteins are important for various signaling pathways and cellular processes ranging from cell growth and proliferation to migration and differentiation [3,4]. Although vimentin knockout (Vim−/−) mice were first reported to develop without obvious phenotypes [5], it is now well established that these mice have serious defects and are severely comprised when challenged with different types of stresses [6]. Moreover, a recent report described the first human vimentin mutation, a heterozygous missense mutation with a severe phenotype involving multiorgan failure [7,8]. Hence, it is clear that vimentin is important for many processes that go beyond structural support.

Vimentin is characteristic of mesenchymal cells, which have enhanced migratory capabilities. In this context, it is widely used as a marker of epithelial-to-mesenchymal transition (EMT) [9,10], a process during which epithelial cells gain mesenchymal properties and increase vimentin expression [11]. This process favors cell migration and is, therefore, a crucial step in wound healing and cancer metastasis [9,12]. Importantly, vimentin is critical for EMT in both wound healing and cancer development [13], likely due to active engagement with the cellular signaling machinery [14–16].

Although most studies focus on intracellular vimentin, increasing evidence shows that vimentin can be secreted to the extracellular environment to exert functions such as receptor activation [17,18] and host-cell-pathogen interaction [19,20]. Shorter and non-filamentous forms of vimentin can be found on the cell surface or secreted to the extracellular environment either as a soluble form or as a vesicle-transported protein [21,22]. Overall, it is still unclear how these forms are secreted to the extracellular space, but recent evidence suggests the involvement of the unconventional protein secretion pathway, specifically type III [23]. This pathway does not rely on signal sequences and uses secretory organelles as a means to secret proteins and other cargo [24]. Notably, vimentin is found in

extracellular vesicles as well [25,26], which are believed to be secreted via this same pathway. Similarly to endogenous vimentin, eVIM is often associated with inflammation, cell activation, senescence, apoptosis, stress, and injury [18,25–29] (Table 1). Recent advances in the field point to a critical role of eVIM in enhancing wound healing and inflammatory responses [25–27]. However, eVIM can also have harmful effects as it promotes tumor growth and improves host infection by both viruses and bacteria [30–32]. Thus, this review explores the role of eVIM in cancer and wound healing and its potential future in vimentin-mediated therapies.

Release of eVIM and its post-translationally modified forms

Extracellular release of vimentin is favored by inflammatory signaling that lead to post-translational modified forms of vimentin, through phosphorylation or citrullination, that disassemble vimentin filaments before their export out of the cell. This process proceeds by protein kinase C (PKC) and by pro-and anti-inflammatory cytokine signals. While anti-inflammatory cytokine interleukin-10 (IL-10) inhibits PKC activity and vimentin secretion, the pro-inflammatory cytokine tumor necrosis factor α (TNF-α) enhances its secretion [73,74]. Vimentin is expressed in a polarised manner on the surface of activated macrophages and is subsequently released in a fragmented form [75]. Vimentin secretion occurs by oxidized low-density lipoproteins (oxLDL)/CD36 interaction [27,54]. Release of citrullinated vimentin is observed during neutrophil and macrophage activation [55,76], as well as chronic inflammation. This can lead to autoimmune responses to citrullinated vimentin in diseases, such as rheumatoid arthritis, fibrosis, and tumor progression [77–79]. Interestingly, extracellular citrullinated vimentin has been shown to stimulate fibroblast invasion and fibrotic tissue remodeling, an effect not seen with vimentin in its unmodified form alone [76]. Taken together, these studies suggest that autoantibodies that react with citrullinated vimentin could have anti-fibrosis and anti-tumor effects, potentially leading to the development of new vimentin-based therapies.

Extracellular vimentin and the extracellular matrix

eVIM can interact with cells in three main ways (Figure 1). The first and most commonly reported is as a cell surface-bound protein. Cell surface vimentin has many functions, including facilitating cell–cell binding, binding soluble factors, and as an attachment factor for different pathogens [21]. Second, soluble eVIM may be internalized by receptor cells, where it elicits specific cellular responses [25,26]. A third way is through modifying the cell interaction with the extracellular matrix (ECM) [76,80,81]. The presence of eVIM alone is enough to facilitate cell attachment, migration, and motility by a mechanism involving GlcNAc-containing structures [80]. The rod II domain of vimentin is localized at the surface of the cells and binds to GlcNAc-bearing polymers [82]. Unlike surfaces coated with collagen or fibronectin, cells on vimentin-coated surfaces do not form large focal adhesions, stress fibers, or perform cell proliferation, but can exert traction stresses at the same order of magnitude [76]. Moreover, eVIM could interact with fibrinogen to facilitate fibrin formation and abnormally high levels of eVIM may enhance fibrin clot formation in patients with systemic inflammation [81]. Together, this work suggests eVIM may serve as a ligand for cell adhesion that stimulates cell migration and cell contractility [76]. Still, many aspects of eVIM and its influence on cell migration and cell-ECM interactions remain to be understood [80,82].

Extracellular vimentin in cancer

Vimentin's role in cancer progression has been the subject of several recent reviews [12,83], as cytoplasmic vimentin expression is associated with increased tumor aggressiveness and poor prognosis [12,83]. However, in contrast to cytoplasmic vimentin, the role of eVIM in cancer development is only starting to be understood. It was previously reported that vimentin binds to IGF1R (insulin-like growth factor 1 receptor) and promotes axonal growth [18]. Moreover, treating MCF-7 cells with human vimentin led to a significant increase in cell proliferation and migration [29], showing that vimentin could exert similar functions to IGF1 in cancer. eVIM binds to the surface of colon cancer cells and leads to beta-catenin accumulation in the nucleus, suggesting the involvement of Wnt signaling [42]. Notably, treatment with exogenous vimentin led to increased vimentin expression and EMT-related genes, which enhanced cancer cell migration [42]. Although it is unknown how eVIM leads to Wnt signaling activation in cancer cells, it is predicted that eVIM could directly bind to the Ryk receptor. Nevertheless, the molecular mechanisms triggered by eVIM remain largely unknown. Thus, vimentin-driven outside-in signaling could emerge as a new field in cancer research. As eVIM can inhibit the adaptive immune system [84], it is interesting to speculate that this feature is important for the immunosuppressive capacity of tumor microenvironments.

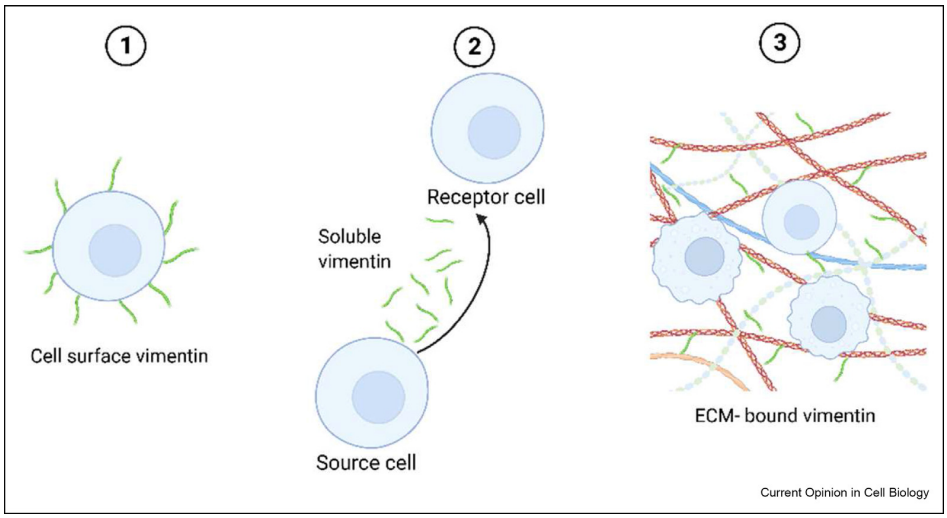
Vimentin has also been found in the serum of cancer patients. Intriguingly, in a cohort of 152 patients, vimentin was found to be overexpressed in hepatocellular carcinoma tissue samples. Circulating vimentin was detected in the serum by ELISA with high specificity and sensitivity [68]. Another study using 48 pancreatic cancer patient samples showed cell surface vimentin can be used as a marker to identify circulating tumor cells [32]. Proteomics approaches showed that vimentin is a potential marker of colon cancer from serum samples [85]. Similar results were obtained with gastrointestinal

Table 1

Cell sources, forms and modifications, and respective functions of eVIM.

Source	Modification	Function	Reference
Astrocyte	Cell surface vimentin, Circulating vimentin, Citrullinated, Exosomal	Specific indicator for the reactive astrocytes under abnormal neurological conditions, facilitator of axonal growth, promotes wound healing	[18,29,33,34]
Cancer cells	Cell surface vimentin, Circulating vimentin, Exosomal vimentin, proteolyzed	Specific marker of activated Sézary Cells, transformation of cancer-favorable macrophages, indicator of circulating tumors, metastasis, promotes cancer exosome release, Wnt Signaling activation, and cancer cell invasion, potential molecular target for cancer therapy	[32,35–45]
Endothelial cells	Cell surface vimentin, Circulating vimentin, Disulfide-dimerized	Formation of new blood vessels, attenuates inflammation, blocks neutrophil binding, promotes platelet binding, internalization by endothelial cells through interaction with CD44, pathogens invasion through interaction with virulence factor, promotes angiogenesis	[17,46–50]
Mesenchymal cells	Cell surface vimentin, Exosomal vimentin	EMT marker, promotes wound healing and determines the fate of wound healing by mediating the transition of mesenchymal leader cells to myofibroblasts	[25,26,28,51,52]
Monocytes/Macrophages	Surface vimentin Circulating vimentin	Expressed on the surface of infected monocytes, mediates the lysis of infected cells as a ligand for NKp46, bacterial killing, generation of oxidative metabolites, pathogen trapping	[27,53]
Neutrophil	Cell surface vimentin, Circulating vimentin, Citrullinated	Expressed by apoptotic neutrophils and activated neutrophils to neutralize pathogens during the innate immune response and NETs formation Antigen for apoptotic T-cells	[54,55]
Platelet	Surface vimentin	Attenuates inflammation through blocking P-selectin-PSGL-1 interactions and decreases leukocyte adhesion to endothelial and platelet monolayers contributes to stroke pathology by the formation of von Willebrand factor string, expressed on the surface of activated platelets and platelet microparticles to regulate fibrinolysis	[56,57]
Senescent Fibroblasts	Circulating vimentin Surface vimentin oxidized, malondialdehyde-modified	Expressed on the surface of senescent cells and consequently released into the blood, malondialdehyde-modified vimentin can be used as a non-invasive biomarker for monitoring age-related illnesses	[58]
T-lymphocyte	Cell surface vimentin	Specific marker of activated Sézary Cells, exposed on the surface of apoptotic T cells and promotes arachidonic acid metabolism	[37,59]
Pathogen-induced, several cell types	Cell surface vimentin Secreted vimentin	Co-receptor for virus internalization in DENV, Enterovirus, SARS, Cytomegalovirus porcine reproductive and respiratory syndrome virus, Japanese encephalitis virus, cowpea mosaic virus Restrictor factor in HPV infection	[19,30,60–67]
Hepatocytes	Secreted vimentin	Hepatocellular death, non-alcoholic steatohepatitis	[68,69]
Multiple	Cell-surface vimentin	Autoantigen in autoimmune diseases including idiopathic pulmonary disease and systemic lupus erythematosus; autoantigen in cardiac transplant	[70–72]

Figure 1



eVIM can interact with cells in three ways: (**1**) as a cell surface-bound protein, (**2**) as a soluble extracellular protein that can be internalized by receptor cells, and (**3**) through modification of the cell's interaction with the extracellular matrix.

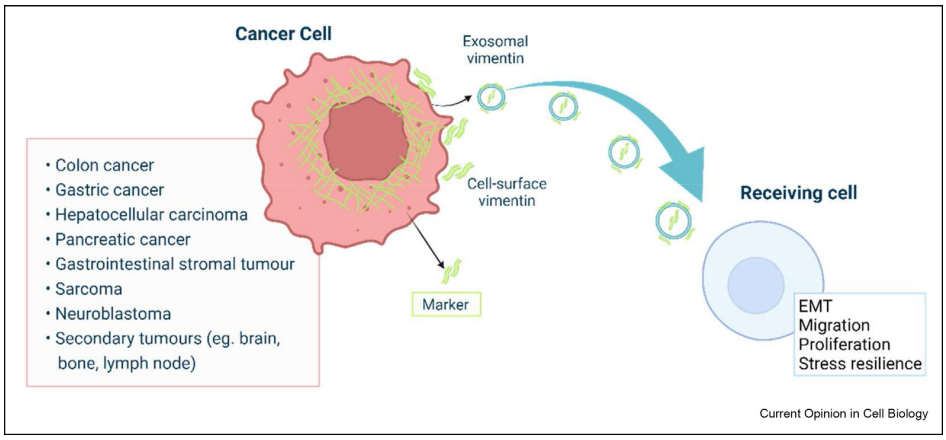
stromal tumors [39], neuroblastoma [39], and pediatric sarcomas [86]. Although these do not elaborate on the effects and mechanisms of action of eVIM, these studies provide strong evidence that eVIM is important in cancer. Interestingly, an antibody against cell-surface vimentin increased the sensitivity to temozolomide, a chemotherapeutic agent used with glioma stem cells [87]. This way, combining existing therapies with eVIM-targeting compounds could yield promising results in cancer therapy. Notably, in gastric cancer patients, circulating tumor cells positive for cell-surface vimentin correlated with a poor response to treatment and decreased survival [88]. Moreover, this form of vimentin served as a marker for stem-like hepatocellular carcinoma cells [89]. This is important as these cells possessed EMT-like phenotypes, and were, therefore, more aggressive. This way, eVIM may contribute to, not only stem-like phenotypes but also increased migratory and invasive capacities, which are important for cancer progression. These aspects, together with the previous observations on increased cell proliferation via IGF1R signaling [18,29], highlight the harmful effects of eVIM in cancer. Notably, eVIM contributes to immune suppression [84] and acts as an immune checkpoint molecule [23]. Despite having pro-angiogenic properties similar to VEGF, eVIM also inhibits leukocyte—endothelial interactions. As a result, targeting eVIM may also represent a promising anti-angiogenic immunotherapy approach for cancer treatment [23]. Together, these observations highlight eVIM plays a role in multiple cancers (Figure 2) and suggest that combining vimentin-binding molecules with existing therapies could improve patient survival.

Despite the diverse role of eVIM in cancer progression, we note that eVIM is relevant for other diseases as well. For example, vimentin is secreted upon hepatocellular death and is implicated in non-alcoholic steatohepatitis [69]. Furthermore, secreted vimentin is implicated in coronary heart disease [73]. Importantly, antibodies against vimentin are found in cardiac transplant patients [71,90], patients with idiopathic pulmonary disease [72], and systemic lupus erythematosus patients [70], highlighting its role in autoimmunity. Moreover, cell-surface vimentin serves as an antigen for apoptotic T-cells [59] and presents on apoptotic neutrophils [59]. Together, these studies point to the role of eVIM in autoimmunity. Thus, although outside the scope of this review, these studies are important to keep in mind as it is clear that the roles of eVIM in disease are not restricted to cancer. Insights into the molecular mechanisms underlying these findings could also contribute to improving our understanding of eVIM functions in tumor progression, especially considering how these diseases are associated with immune function.

Extracellular vimentin and wound healing

Wound healing is a dynamic and complex process that involves sequential but overlapping phases including hemostasis, inflammation, mesenchymal cell differentiation, proliferation, and migration, angiogenesis, re-epithelialization and synthesis, cross-linking, and collagen fiber alignment [91]. A characteristic feature of the Vim−/− mice is that they have severely compromised wound healing and display a wide variety of phenotypic abnormalities [6], that are linked to defects

Figure 2



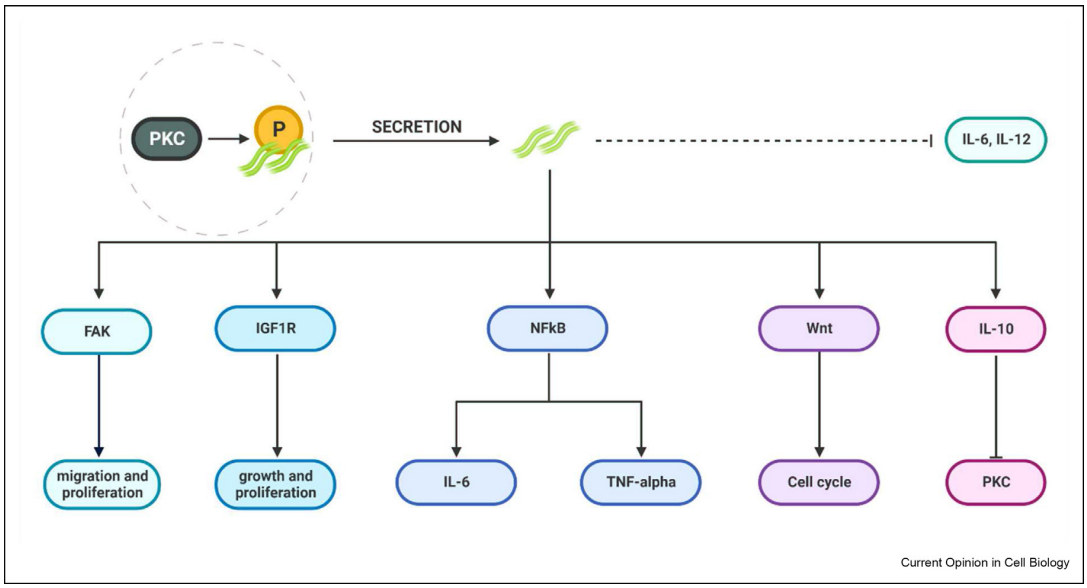
Roles of the eVIM pool in cancer. Extracellular vimentin is a pool of vimentin found outside of cells. It includes cell surface, circulating, and vesicle-bound vimentin (exosomal vimentin). eVIM presents itself as a considerably smaller variant compared to the full-length filaments found within cells. In cancer, eVIM promotes tumor growth and metastasis by facilitating cancer cell migration and invasion. Additionally, it has been shown to stimulate angiogenesis, the process of creating new blood vessels to nourish tumors. Moreover, eVIM interacts with other proteins within the extracellular matrix, such as fibronectin and laminin, contributing to enhanced cancer cell adhesion and survival. eVIM can be also found not only in serum from patients with different cancer subtypes but also at the cell surface in circulating cancer cells, serving as a marker for these conditions.

in wound healing and tissue regeneration [13,51,92–94]. Thus, vimentin is one of the main IF proteins necessary for wound healing. eVIM, in specific, plays significant roles in this process and contributes to various diseases related to impaired wound healing, including fibrosis, atherosclerosis, lupus erythematosus, and pulmonary sarcoidosis [18,29,51,56,70,72,95–97]. For example, eVIM is considered a damage-associated molecular pattern (DAMP) that can be up- and down-regulated during pro- and anti-inflammatory conditions, respectively [97]. eVIM can also block the secretion of pro-inflammatory cytokines IL-6 and IL-12 by dendritic cells and enhance the secretion of the anti-inflammatory cytokine IL-10 (Figure 3), which suggests eVIM suppresses the proinflammatory adaptive immune response [84]. Furthermore, eVIM mediates focal adhesion kinase activation and NF- B signaling, promoting the release of pro-inflammatory cytokines such as TNF-α and IL-6 (Figure 3) [74], which are important for the inflammatory phase of wound healing. In this context, eVIM secreted by activated macrophages contributes to immune function by acting as a pro-inflammatory factor, aiding in killing bacteria and promoting the generation of oxidative metabolites [27]. This way, eVIM has a positive effect on wound healing and participates in both innate and adaptive immune functions.

A well-studied example of the role of eVIM in wound healing relates to neural injuries. Upon spinal cord injury, neuron-intrinsic mechanisms significantly promote axonal growth and synapse formation to restore electrophysiological neuron activity [98,99]. Vimentin expression and secretion from astrocytes acts as a neurotrophic factor, enhancing axonal growth and functional recovery. This eVIM interacts with insulin-like growth factor 1 receptor, promoting axonal growth [18,33]. Intriguingly, exosomal vimentin from astrocytes may mediate attachment and uptake of *Clostridium botulinum* C3 transferase after spinal cord injury [34].

Upon injuries and during healing processes, eVIM functions both as a receptor for different types of ligands, such as N-Acetylglucosamine (GlcNAc) and CD44 [46,82], and as a ligand for various receptors such as P-selectin [17] and, as mentioned above, IGF-1R [18]. In addition, eVIM plays an important role in angiogenesis in the central nervous system during injury, as vimentin deficiency in vascular endothelial cells prevents proper angiogenesis [100]. Following injury, vimentin is released into the extracellular space and attaches to the cell surface of mesenchymal leader cells located at the wound edge to define their fate. Here, vimentin plays a dual role in wound repair by directing the collective closure of the injured epithelium wounds, or by differentiating mesenchymal leader cells to myofibroblasts that can induce fibrosis [51]. Notably, recombinant vimentin treatment reduces acute lung injury. This is achieved by reducing leukocyte adhesion to the vascular endothelium and by blocking neutrophil adhesion to P-selectin-coated surfaces [17]. This way, eVIM dampens acute inflammatory responses during wound healing. It is worth mentioning that eVIM also participates in hemostasis. The Von Willebrand factor

Figure 3



Different signaling pathways triggered or affected by extracellular vimentin. eVIM can trigger or affect various signaling pathways involved in cell migration, epithelial–mesenchymal transition (EMT), inflammatory response, and immune regulation. eVIM can activate FAK (Focal Adhesion Kinase), a pivotal regulator of cell adhesion, migration, and survival. FAK activation by eVIM can promote cell migration and invasion in cancer cells. Additionally, eVIM interacts with IGF1R (Insulin-like Growth Factor 1 Receptor) to stimulate axonal growth and can be regarded as a novel ligand of IGF1R that facilitates axonal growth in a manner analogous to IGF1. Moreover, eVIM activates Nuclear Factor Kappa B (NFKB), a transcription factor that governs the expression of genes implicated in inflammation, immunity, and cell survival. Activation of NFKB by extracellular vimentin can induce the production of mediators involved in inflammatory responses within resident cells. Furthermore, eVIM activates the WNT pathway—a signaling cascade governing cell proliferation, differentiation, and migration.

(VWF) is a multimeric glycoprotein that contributes to hemostasis and angiogenesis during wound healing by promoting adhesion and aggregation of platelets and slow release of growth factors to the wound site, respectively [101]. eVIM interacts with VWF during VWF string formation, binding to its A2 domain [56] and promoting platelet adhesion [102]. On the other hand, surface vimentin on activated platelets localizes and stabilizes vitronectin and activates Plasminogen Activator Inhibitor 1 (PAI-1) complexes to inhibit epithelial repair and promote fibrosis [57,103–105]. Finally, while sustained senescence contributes to impaired wound healing, transient senescence is necessary for wound repair, promoting fibroblast activity and differentiation during early wound healing stages and preventing excessive fibrosis [106,107]. Notably, senescent primary human fibroblasts express cell surface vimentin, which suggests a role of eVIM in mediating senescence [58]. The engagement of eVIM in both beneficial and detrimental roles, contingent on the context and timing, suggests its intricate participation in wound healing. However, it remains unclear how disparate effects occur. Further investigations into the underlying molecular mechanisms and structural aspects of eVIM promise to unveil new insights into its diverse effects.

Concluding remarks

Vimentin is a multifunctional IF protein with many key roles in both structural and regulatory intracellular processes, including cell signaling, cellular integrity, organelle positioning and function, cell resistance to stress, cancer development, and metastasis. In addition, vimentin now emerges as an important extracellular protein with many non-mechanical roles. eVIM appears at the cell surface in an oligomeric form or can be secreted by different cells in soluble and vesicle-bound forms. eVIM is involved in biological functions in the extracellular milieu, such as cell activation, inflammation, stress, senescence, and apoptosis. Similarly, to intracellular vimentin, the functional diversity of eVIM depends on its different inherent properties, including structural plasticity and signal transduction roles regulated by biochemical, mechanical, and spatiotemporal cues. Cell-type-specific post-translational modifications, location, interactions, and vimentin expression levels can affect its functions. Based on vimentin's pleiotropic characteristics and its functional diversity in physiological and pathophysiological conditions, eVIM could be considered a relevant molecular target in theragnostic applications. Undoubtedly, further studies are needed to determine the mechanical and structural

modifications required to generate vimentin that is compatible with extracellular release. Further information is urgently needed on the molecular and cellular mechanisms underlying the biogenesis, trafficking, and secretion of extracellular vimentin. Finally, it will be interesting to determine which of the observed effects are specifically generated by vimentin and to what extent the effects are dependent on vimentin-associated proteins. Several advanced novel technologies may facilitate this development. For example, gene-editing methods to study the specific effects of individual post-translation modification sites on vimentin's assembly state, employing advanced 'omics' technologies at a single cell level, and designing new molecules for selective targeting of vimentin.

Editorial disclosure statement

Given the role as Guest Editor, John Eriksson had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Patrick Lusk.

Declaration of competing interest

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

Data availability

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

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